pharma's almanac

A NICE INSIGHT SUPPLEMENT

Q4 2016 EDITION

GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS

THE ROLE OF INNOVATIVE TECHNOLOGIES

GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS
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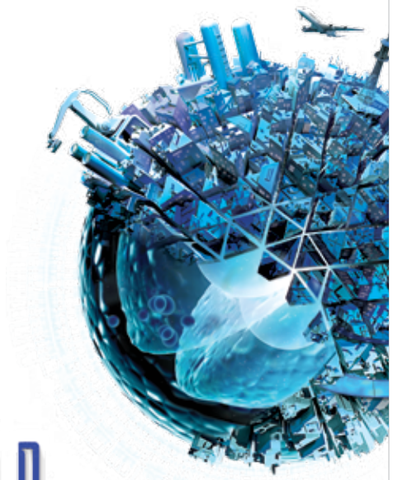

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→ **A NOTE FROM THE EDITOR**

SHAPING THE CONVERSATION – BRINGING VOICE & VALUE

→ BY **GUY TIENE**, NICE INSIGHT

Originally born of a discussion about our Nice Insight research (now going into our eighth year) and how we could align our customers' voices in an open forum, we published our first supplement under American Pharmaceutical Review in the spring of 2015.

As of this print issue, we have had the honor of bringing 66 industry-contributing company articles and 35 Nice Insight research reports and pieces to press in six supplements, now celebrating a first full calendar year in print. So, "wow," content is certainly in high demand, and we have been thrilled and delighted to help bring so much to the conversation.

Growing both organically, being challenged to stretch the limits of content in our heavily technical realm, and strategically, to build a viable content enterprise, our editorial guidelines are simple:

[1] Be informative and fact-based
[2] Speak from experience and knowledge
[3] Address current needs and advances in the industry

The entire Nice Insight team has shown outstanding dedication to Pharma's Almanac in providing the research our pharma-biotech sponsors are looking for, especially regarding outsource resources, to meet the challenges and opportunities of today's market.

Likewise, supplier company contributions to the dialogue have been compelling and insightful, sharing many diverse aspects of the global supply chain. Thank you! You are the true thought leaders who are shaping the conversation.

Among the many things we have learned about the demands of you, our pharma-biotech customers – who we support in bringing experimental, novel, reformulated and proven medicines to patients – is that there is an expectation to come to the table with innovation of every kind.

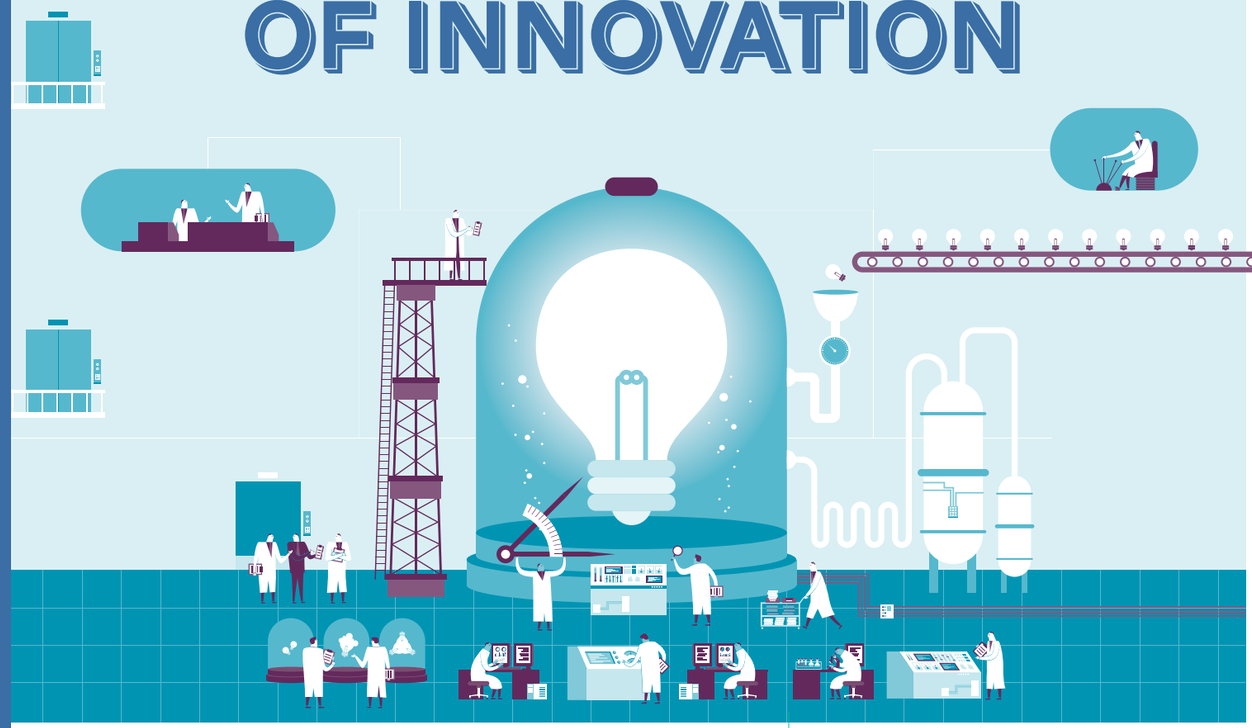
Whether advances in targeted drug screening, advances in chemical synthesis, continuous manufacturing, greater downstream processing, better capsulation technology, cold chain solutions or automated clinical trials/data management, or more partnership-minded service, at-risk deal structuring, dedicated manufacturing capacity, accelerated analytical services and more, this is the time to step up and be part of the emerging new age of healthcare solutions.

Nice Insight has enjoyed providing content to many editorial and media partners, and we hope to continue to do so – there is so much to share and learn. It has been exciting to see the rise of the content movement that covers everything from global regulatory alignment to advances in discovery possibilities and expanded efficiency in manufacturing of both small- and large-molecule compounds.

With this printing, we have also evolved our digital platform to engage more individuals in Nice Insight's Content Community through the launch of www.PharmasAlmanac.com. Please join us online for even more content-driven insights, discussion and learning.

We welcome you to enjoy this issue of the Pharma's Almanac supplement! P

A FOUNDATION OF INNOVATION



BY **CYNTHIA A. CHALLENER, Ph.D.**, **STEVE KUEHN** AND **ANDREW WARMINGTON, Ph.D.**, NICE INSIGHT

Innovation is at the heart of the pharmaceutical industry. Researchers develop innovative approaches to understanding biological processes, including the identification of potential new targets for which novel drug substances are developed. New technologies are continually being introduced to improve the efficiency and productivity of discovery, development and manufacturing activities. And all the while, the goal is to provide safe and effective medicines to patients in need.

In this last Pharma's Almanac of 2016, we look at recent notable innovations in the pharmaceutical industry, from discovery to packaging. Nice Insight editors and industry experts weigh in on key trends in innovation and strategies for success in the future. You will also find added news and trends sections, information about our online debut and other new Nice Insight offerings.

In this issue's Industry Leader Insight article, Unither Pharmaceuticals General Manager Kevin Haehl highlights the need for patients, caregivers, payers, governments and the pharmaceutical industry to work together to reduce the cost of poor patient adherence.

The benefits of implementing continuous downstream bioprocessing are outlined by Michelle Najera, Ph.D., a Development Scientist, Downstream Process Development, with CMC Biologics.

Virtual Panelists explore the deal-structuring shift in the pharmaceutical market from an investor perspective, as reported by Andrew Ferraro, a Biopharma Investment Contributor with Nice Insight.

How dynamic supply chain demands are driving innovation in global healthcare is the focus of the feature story.

For Nice Insight, Emilie Branch, Strategic Content Manager, reports on recent news from the pharma industry in the new "This Just In" section, while in the debut "Trends Trading" column, Boobalan Pachaiyappan, Ph.D, Market Research Manager, focuses on drug discovery with a review of two promising orphan drugs. Andrew Warmington, Ph.D., the new Executive Content Director, reports on Nice Insight's Content Community, PharmasAlmanac.com, which is now live.

Haig Armaghanian, Managing Consultant and Josh Dunn, Division Lead, Strategy & Execution, Nice Consulting, provide perspectives on drug pricing strategies and practices.

Guy Tiene, Strategic Content Director with Nice Insight, discusses industry expert opinions on how packaging differentiation equates to brand loyalty in a Virtual Panel, and in an *In Conversation* piece, he shares insights from Uwe Harbauer, Senior Vice President of the Pharma Business Unit of Bosch Packaging Technology, on how equipment supplier/pharma company relationships have changed over time.

The importance of equipment redeployment for achieving cost efficiency in manufacturing operations is outlined by Adam Covitt, Vice President of Federal Equipment Company.

Robert E. Chew, PE, President of Commissioning Agents, Inc., highlights the advantages afforded by the ability to secure commercial-scale GMP capacity on demand.

In this issue's Roundtable, industry leaders discuss the state of serialization, the impact of FDA's new focus on quality culture, and new technologies that have had significant impact on their businesses.

Biologics contract manufacturers must do much more than offer their partners additional capacity, reports Janice Graff, Director of Finished Product Sales & Business Development, Americas, GlaxoSmithKline and KaShauna Rohlehr, Program Manager, GlaxoSmithKline Biopharmaceuticals.

Philippe Dartiguelongue, Industry Quality Director at Servier, discusses how taking a holistic approach that brings people, processes and policies together creates an efficient, agile QA/QC culture.

Formulation development capabilities are no longer sufficient for CDMOs, according to Ed Scholtz, Ph.D., Vice President of R&D for UPM Pharmaceuticals; achieving product commercialization is also a must.

Stephen Munk, CEO of Ash Stevens, discusses the need for CDMOs with specialized, small-volume manufacturing capabilities as the industry moves towards a more personalized and precise approach to treating disease.

With many new drug products requiring fermentation and specialized chemical technologies, BioVectra's Vice President of Business Development, Heather Delage, says that carefully selecting manufacturing partners is increasingly important.

Patient-centric parenteral drug development strategies are the focus of an article by Marga Viñes, Business Development Manager and Oriol Prat, Director of Contract Manufacturing with Grifols.

Guy Villax, Chair of pharmaceutical industry consortium RX-360 and CEO of Hovione, describes the work conducted by the organization and its value.

Magdalena Mejillano, Executive VP and General Manager of CMC Solutions and Lijun Duan, Associate Director of Analytical Development at BioDuro, discuss the changing analytical services market and the new standalone services offered to support its (bio)pharma partners.

In an *In Conversation* piece with Nigel Walker, Founder of That's Nice LLC and Nice Insight, Capsugel President and CEO Guido Driesen discusses key trends driving drug development, and recent acquisition activity at the company.

Cynthia A. Challener, Ph.D. speaks with Icagen CEO Richie Cunningham, Douglas Krafte, Chief Scientific Officer, and Anil Nair, Director of In Silico Drug Discovery, on how in silico approaches are impacting pharma.

Syed T. Husain, Chief Commercial Officer of Alcami, stresses the importance of supply chain management and security as pharmaceutical supply chains become increasingly complex.

Carlton Winters, Director of Drug Product Development and Eunice Costa, the Group Leader of Inhalation and BioPharmaceuticals for Hovione Portugal, elucidate dry-powder inhalation formulation manufacturing.

Nigel Walker, Founder of That's Nice LLC and Nice Insight, looks at recent pharma innovations.

Nice Insight researchers Govindra Singh and Kshitij (TJ) Ladage describe their ongoing efforts across the pharma supply chain as our yearly surveys are initiated.

Nigel Walker, Founder of That's Nice LLC and Nice Insight, introduces Nice Symposium, a unique industry think tank and interactive approach designed to enable supply chain partners and their customers to explore real solutions to pharmaceutical industry needs. P

We hope you find this latest edition of Pharma's Almanac enjoyable and educational. Let us know your thoughts at PharmasAlmanac.com.

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VIRTUAL PANEL

PHARMACEUTICAL PACKAGING: DIFFERENTIATION EQUATES TO BRAND LOYALTY

→ BY **GUY TIENE**, NICE INSIGHT

NICE INSIGHT'S VIRTUAL PANELISTS SHARE THEIR THOUGHTS ABOUT THE INTEGRAL ROLE THAT SAFER, SIMPLER AND SMARTER PACKAGING PLAYS IN A COMPOUND'S SUCCESS.

Of the upwardly climbing global pharmaceutical packaging market, which was valued at close to $52 billion in 2014 and is expected to reach upwards of $80 billion by 2020,[1] plastic bottle and parenteral containers are the top two segments, respectively. The combined sectors accounted for 36% of the market in 2014. However, it is blister packaging, closures and labels that are expected to witness the fastest growth through to 2020. Driving this growth are the industry's demands for packaging that is increasingly sophisticated, integrated and consumer-friendly. Safety is another leading concern, both from the standpoint of package/drug compatibility and from a supply chain perspective. Currently, counterfeiting accounts for annual losses estimated at $75 billion.[2] To address these issues, drug manufacturers are demanding a variety of value-added services, making packaging as important as the drug it is tasked with protecting.

CHILD-RESISTANT VS. SENIOR-FRIENDLY PACKAGING

Although it may seem that all proofing-packaging is sufficient, the need for child-resistant (CR) packaging can clash with senior-friendly packaging. Packaging companies must resolve this paradox, creating a package that children cannot open but older adults can. CSP Technologies Inc. designs, engineers and manufactures child-resistant/senior-friendly containers. "It isn't easy to engineer these solutions given the inherent challenge of finding the proper balance required," says Craig Voellmicke, Vice President, Business Development, CSP. "Many of our customers want the consumer to be able to open the package using only one hand to make the package as user-friendly as possible. We have met and exceeded our customers' expectations by providing user-friendly CR packaging solutions while ensuring the fit, form and

IT ISN'T EASY TO ENGINEER CHILD-RESISTANT/SENIOR-FRIENDLY SOLUTIONS GIVEN THE INHERENT CHALLENGE OF FINDING THE PROPER BALANCE REQUIRED.

Craig Voellmicke — CSP Technologies Inc.

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Marketing Director, Pharmaceuticals, Bemis Healthcare Packaging

Craig Voellmicke
VP, Business Development, CSP Technologies Inc.

> OUR MATERIAL SCIENTISTS PARTNER WITH PHARMACEUTICAL COMPANIES TO UNDERSTAND THE INTERACTION BETWEEN THE DRUG AND THE PACKAGE.
>
> Georgia Mohr – Bemis Healthcare Packaging

function of the package is consistent with their brand equity and overall value proposition, while staying within budgetary constraints."

The importance of child-resistant packaging goes beyond the primary container. Bemis Healthcare Packaging offers a line of flexible foil laminations with increased puncture and tear resistance, which can be incorporated into child-resistant packaging. "In addition to primary packaging, we have taken the additional precautions of designing a child-resistant, self-seal, disposable pouch for the safe disposal of transdermal patches and inhalers to help prevent accidental exposure to highly toxic drugs," says Georgia Mohr, Marketing Director – Pharmaceuticals, Bemis Healthcare Packaging.

AUTHENTICATION AND SERIALIZATION

Counterfeiting is no shrinking matter. The issue is defined by the World Health Organization (WHO) as a major problem in all pharma markets globally. In order to remain ahead of the game, anti-counterfeiting solutions (AC) are needed. An innovation from SCHOTT Ampoules AC includes colored rings, laced with luminescent nanoparticles inside their ink. These rings are indistinguishable from normal rings, which are often and easily counterfeited. A small detector, however, reveals the presence of the nanoparticles and confirms the authenticity of the product. "In this way doctors and patients, as well as retailers, pharmacies and customs authorities, are able to quickly establish whether a drug is genuine," explains Christopher Cassidy, VP Sales & Marketing – North America, SCHOTT Pharmaceutical Packaging. "A multitude of combinations – ampoule shape and size, type of glass as well as color, shape and number of identification rings or dots, including luminescent particles – make it easier for manufacturers to protect their products against counterfeiting."

> DOCTORS AND PATIENTS, AS WELL AS RETAILERS, PHARMACIES AND CUSTOMS AUTHORITIES, ARE ABLE TO QUICKLY ESTABLISH WHETHER A DRUG IS GENUINE.
>
> Christopher Cassidy — SCHOTT Pharmaceutical Packaging

Countries like China and Brazil already have implemented track-and-trace procedures, yet serialization will not be required in the U.S. until next year, with the EU to follow. By February 2019, all prescription drugs for sale in the EU will need to be serialized and to have tamper-proof features that clearly distinguish an original from a counterfeit. Yet, some industry insiders claim that many companies are not that far along in their serialization programs.

One company that is taking the regulations seriously is Bespak, which works with its sister company, Aesica, to offer a comprehensive serialization solution across all packaging locations. "Having serialization incorporated into packaging is spreading," says Steve Kaufman, Global Business Development Lead, Bespak. "Our colleagues have developed a flexible and scalable module that enables them to meet the serialization requirements of a wide range of countries." The module is capable of high-resolution printing at fast line speeds, with an advanced communication protocol for remote operation and high-speed serialization.

Additionally, as an increasing number of high-value injectable biologics enter the market, Bespak is collaborating with pharmaceutical partners to look at options that address their packaging needs. "Some autoinjectors and self-injection devices are now being embedded with anti-counterfeiting and anti-tampering solutions and specially designed labels," says Kaufman.

> SERIALIZATION INCORPORATED INTO PACKAGING IS SPREADING.
>
> Steve Kaufman — Bespak

"Difficult-to-reproduce holograms are being embedded in designs to dissuade potential counterfeiters."

Bemis also offers a fleet of security and authentication features that can be built into the packaging products it supplies to healthcare companies. All print-related technologies can be applied via rotogravure or flexographic printing processes. Technologies are available for primary packaging systems, secondary packaging systems and labeling. Security features verify authenticity throughout product distribution, including the point of sale, explains Mohr.

Constantia Flexibles International GmbH has developed a range of overt and covert solutions. One of the most secure overt features is security foil. Involving a rolling mill and engraving technology, this represents a barrier that is very difficult for counterfeiters to overcome, and it is also one of the most affordable security solutions for primary packaging, says Dr. Pierre-Henri Bruchon, Executive Vice President Pharma, Constantia Flexibles International GmbH, a manufacturer of flexible packaging and labels. Covert features are made possible using security graphics. "These are complex print designs that are extremely difficult to reproduce without expert printing technology and knowledge."

UNDERSTANDING THE DRUG/PACKAGE RELATIONSHIP

As drug products are manufactured, packaged and stored, they come into direct contact with packaging systems. Such contact may result in interactions between the drug product and its packaging system. For example, minute glass flakes might detach from the inner surface layers of pharmaceutical vials during a drug's shelf life. This phenomenon is known as "delamination." It is rare and only occurs under certain circumstances, but still poses a danger for patients if glass flakes are injected into the bloodstream.

SCHOTT, a parenteral packaging supplier, launched a new generation of pharmaceutical vials that keep the risk of delamination under control. "We optimized the hot-forming process in a way that the inner glass surface of the vials is more homogeneous and thus chemically very stable and less susceptible to delamination," explains Cassidy.

Bemis' focus is on issues of solubility and diffusion in relation to the drug/packaging interaction. "Our material scientists partner with the pharmaceutical companies, not only to understand the interaction between the drug and the package, but to develop a package format that is consumer friendly with sustainable features," explains Mohr. "Drawing on our material science expertise, our scientists take a theoretical, analytical and practical application approach to understanding the solubility and diffusion characteristics with many drugs and excipients. Through these advanced modeling techniques, we have developed a strong understanding of drug solubility and diffusion into the packaging/drug contact layer."

Packaging integrity can also include headspace management. CSP, for example, integrates Activ-Polymer™ technology into primary packages, which control moisture, oxygen and other gases that can affect the stability and shelf life of a given compound, while minimizing product impurities. "We can injection-mold the polymer technology into components for drug delivery devices (e.g., dry-powder inhalers, or large-molecule transdermal drug delivery systems) and we can extrude the technology into a film that can be heat-staked onto foil substrates to absorb moisture and/or oxygen to protect transdermal patches," explains Voellmicke.

> ADDING DIGITAL PRINTING ALSO ALLOWS THE DATA ON EVERY INDIVIDUAL UNIT TO BE READ AND EXPLOITED IN ORDER TO ENSURE THAT THE PATIENT IS TAKING THE RIGHT DRUG AND RECEIVING THE RIGHT DOSE, AT THE RIGHT TIME.
>
> Dr. Pierre-Henri Bruchon — Constantia Flexibles International GmbH

IMPROVED PATIENT COMPLIANCE

And sometimes a drug and its packaging can work together to improve patient compliance and treatment efficacy. Pharmacy benefit manager Express Scripts estimates that prescription nonadherence costs the country roughly $330 billion annually.[3] Products that combine a drug or biologic with a device, such as drug-eluting stents and drug delivery systems, can offer valuable approaches for treating disease. The number of product categories and individual product offerings in the drug-device combination market has grown to be relatively large. According to BCC Research, sales of drug-device combination products reached $22 billion in 2014 and the market is expected to grow to $31 billion in 2019.[4]

The biotech industry is particularly interested in drug-device combination products such as autoinjectors, pen injectors and wearable injection devices, because these drugs tend to be highly viscous and require high dosing. While some companies have device and packaging capabilities internally, others outsource to companies like Bespak. "With the push towards self-administration, packaging has become an integral factor," says Kaufman. "We offer a range of autoinjector devices powered by our patented compact energy source, delivering drugs at high viscosity and high volumes."

As medical devices become more sophisticated and sensitive, using packaging that protects the high-value device and still appeals to consumers is critical. Constantia Flexibles developed Safemax for this purpose. The deep-draw aluminum container not only protects against moisture and gas ingress, but features customer-friendly foil lidding that is easy to open. Adding digital printing also allows the data on every individual unit to be read and exploited in order to ensure that the patient is taking the right drug and receiving the right dose, at the right time, says Bruchon.

As proper drug delivery becomes increasingly critical going forward, pharmaceutical and biopharma packaging must remain patient-centric by being safer, simpler and smarter. Novel packaging is likely going to be a key differentiator between companies. Manufacturers should keep in mind that the right packaging has the potential to increase brand loyalty and ultimately improve market sales. P

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Having worked at That's Nice from 2000 to 2006 as Business Director for many life science accounts, **Guy**'s new role involves the deployment of strategic content across marketing communications and thought leadership. Guy holds a master's degree from Columbia University in New York City.

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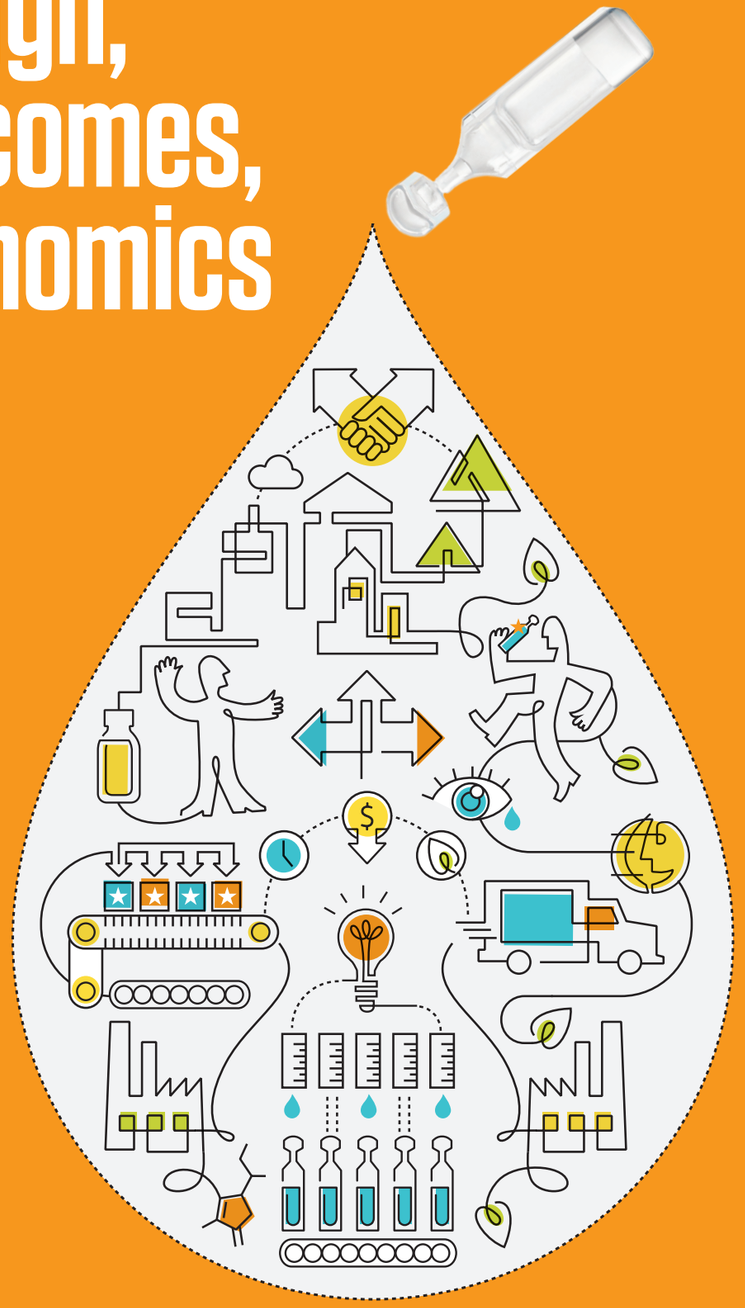
Better Design, Better Outcomes, Better Economics

→ BY **KEVIN HAEHL**, UNITHER PHARMACEUTICALS



The problem of American patients not adhering to their medication as directly prescribed is a $290 billion burden to our economy. The growing cost of healthcare is increasingly in focus; it is time for patients, caregivers, payers, governments and the pharmaceutical industry to work together to reduce this waste.

With the advent of another presidential election cycle, we are caught up in a familiar debate about the cost of healthcare. Naturally, the pricing of pharmaceuticals is front and center – even more so than in previous campaign years – due to the recent media firestorm surrounding the exorbitant price increases of some generic medications. But there is another issue, one depriving the U.S. healthcare system of billions of dollars, which is not being addressed in an open forum.

This problem is poor medication adherence, which occurs when patients do not take their drugs as they are designed. It should come as no surprise that this creates tremendous waste – not only from expensive drugs going unconsumed, but also from societal costs associated with poor patient outcomes.

According to the New England Healthcare Institute (NEHI), estimates by several prominent government and nongovernmental organizations, including the World Health Organization (WHO), Centers for Disease Control (CDC) and the National Institutes for Health, medication nonadherence generates as much as $290 billion in direct – but avoidable – costs in the U.S.[1] Though nonadherence contributes a third of the $750 billion that the National Academy of Medicine (NAM) estimates is the total for excess costs in healthcare, neither Republicans nor Democrats addressed this issue during the 2016 election cycle. Cost and access to healthcare remain paramount, but lawmakers are missing the opportunity to bring attention to nonadherence and propose measures to reduce this waste, which contributes to the spiraling cost of health insurance coverage.[2]

HEALTHCARE STILL NOT AFFORDABLE

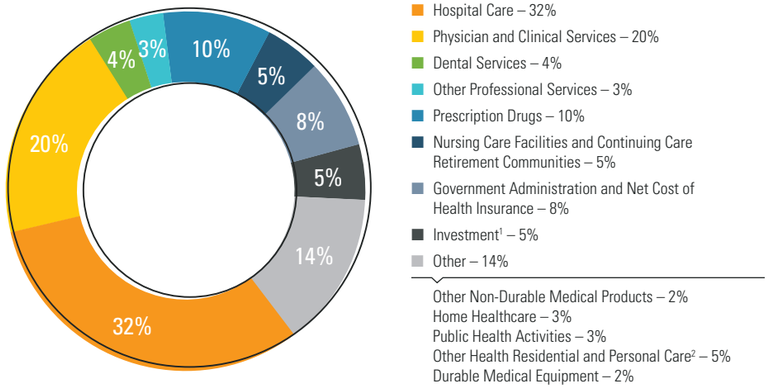
According to a 2015 report on healthcare costs, the Department of Health and Human Services' Centers on Medicare and Medicaid Services (CMS) found "U.S. healthcare spending grew 5.3 percent in 2014, reaching $3.0 trillion or $9,523 per person. As a share of the nation's Gross Domestic Product, health spending accounted for 17.5 percent."[3] The NAM report "Best Care at Lower Cost: The Path to Continuously Learning Health Care in America," notes healthcare spending has increased at a greater rate than the economy for "31 of the past 40 years."[4] The growth in healthcare costs has also led to stagnation in income for America's working-class families. The NAM explained that, even though income has increased by 30% since about 2004, the gain has been essentially wiped out by the 76% increase in healthcare costs associated with traditional modes of healthcare delivery.

Critically, the NAM report also finds that these models are generating costly unintended consequences, the result of paying clinicians and healthcare organizations to administer services and therapies "without a specific focus on patient health and value," which has contributed to waste and inefficiency. The report concludes that these costs will surpass maintainable limits, noting: "The growth rate of healthcare expenditures is unsustainable, with waste that diverts major resources from necessary care and other priorities at every level – individual, family, community, state, and national."

The overall contribution of drug prices to the rise of healthcare costs remains a source of ongoing debate. CDC figures from 2014 reveal prescription drug costs represent 9.8% of national health expenditures.[5] Recent drug cost studies find drug prices are rising, especially among specialty drugs. Healthcare data company Truveris said prescription drug prices rose more than 10% in 2015, a number representing some $2 billion in higher costs to consumers.[6] Generic drugs haven't been immune either, with double- and triple-digit price increases for certain classes of generics or ones affected by supply disruptions. Further, it's likely that the advent of biosimilars won't brake biopharmaceutical prices much either, as development costs remain similar for both NMEs and biosimilars.

Some six years after its inception, it is not clear if the Affordable Care Act (as currently written) will remain law. But whatever may emerge post-Obamacare, reducing the economic burden of nonadherence must become a central focus of legislators as they consider improvements going forward.

THE NATION'S HEALTH DOLLAR ($3.0 TRILLION), CALENDAR YEAR 2014, WHERE IT WENT



1 Includes Noncommercial Research (2%) and Structures and Equipment (4%).
2 Includes expenditures for residential care facilities, ambulance providers, medical care delivered in nontraditional settings (such as community centers, senior citizens centers, schools and military field stations), and expenditures for Home and Community Waiver programs under Medicaid.

NOTE: Sum of pieces may not equal 100% due to rounding.
SOURCE: Centers for Medicare & Medicaid Services, Office of the Actuary, National Health Statistics Group.

PROPER PHARMACEUTICAL USE IS CRITICAL

The leading causes of death include heart disease, cancer, lung disease, stroke and Alzheimer's, and according to 2012 CDC data, approximately half the population (117 million people) live with at least one chronic disease.[7] Government data shows seven of the top 10 causes of death in 2010 were the result of chronic diseases, with heart disease and cancer responsible for nearly 48% of all deaths. Arthritis is the most common cause of disability; according to CDC, some 53 million U.S. adults suffer from this painful disease.

This trend toward treating increasingly elderly patients with multiple chronic conditions is not likely to abate, as many of the world's developed and fast-developing economies increase their uptake of pharmaceuticals. Unfortunately, chronic diseases tend to have chronic costs. This includes expenses associated with the corresponding drug treatment. Payer systems are focused on managing these costs and continue to put pressure on the pharma industry to suppress drug prices, unrelated to the economics associated with developing and manufacturing pharmaceuticals or to the benefits of the drug.

"Because ongoing use of prescription medication is a key component of treatment for chronic conditions," says Roebuck, et al., in "Medication Adherence Leads To Lower Health Care Use And Costs Despite Increased Drug Spending," ensuring patients take drugs as prescribed for them "is a matter of great importance to policy makers, insurance plan sponsors, physicians, and patients." Study authors confirmed that patients who adhere to their medication regimens enjoy better health outcomes and explained that compliant patients "make less use of urgent care and inpatient hospital services, compared to patients with similar medical conditions who are not adherent."[8] Regardless of the evidence, in spite of how much can be gained, the WHO reports average medication compliance rates in developed countries are just 50%.

Research and real-world experience confirms that when drugs, however effective clinically, reach consumers, their therapeutic value can be diminished dramatically – largely because they are not taken as prescribed. For instance, patients with chronic vascular disease who adhered to their medication underwent less hospitalization and emergency-department use.[8] Indeed, improving medicine adherence has the best potential to cut healthcare costs in the short term.

According to the paper "Adherence and Healthcare Costs," an increasing number of private payers are implementing "value-based insurance designs," to encourage adherence.[9] For example, "The Medicare Modernization Act" of 2003 mandated Medicare Part D prescription drug plans to include medication therapy management (MTM). MTM is intended to advance medication adherence through patient education, conducting comprehensive reviews of a patient's drug regimens and monitoring the efficacy and safety of medication therapies.[10] Also for consideration is the introduction of the ACA's 5-Star rating system, which puts MTM in the spotlight.

FEE FOR SERVICE — ON ITS WAY OUT

As with most aspects of healthcare, a variety of financial incentives and payment models are in use. However, most of these models tend to pay clinicians and healthcare organizations without a specific focus on patient health and value, which contributes to the nonadherence issue. Most current systems pay healthcare providers in a "Fee-for-Service" (FFS) model. This means that for any service you undergo, you pay separately for what you have received.[11] The argument is that this FFS model is depleting the healthcare system, as the emphasis is on volume. This translates to a cost, represented by an individual; one who is ill is actually more valuable than someone who is healthy, which can potentially result in doubling of services, unnecessary services or tolerance of nonadherence to drug regimens.

To move past FFS, public and private healthcare payers are experimenting with new provider payment models and other alternatives for care. These new models include patient-centered medical homes, accountable care organizations (ACOs) and episode-based payment plans that are designed to slow the pace of spending growth and achieve better healthcare quality. According to *Health Affairs*, "20 of the 33 quality measures to which Medicare ACOs are accountable are related to the safe and effective use of medications."

A NEW APPROACH TO PRODUCT DEVELOPMENT

Perhaps no other sector of the economy has contributed more to improving the world's health and well-being than the pharmaceutical industry. If the industry lives and breathes on quality by design, why is the crucial step of adherence by the patient often overlooked? It's time to seek further innovation and consider the human element in formulation, with the question, "How will the product be used in the real world?" For the sake of patients and the industry, more attention must be paid to how well products perform in the hands of the users, which requires innovating across all fronts to improve the ease of use for medicines as prescribed. Fortunately, that work has already begun.

Pharmaceutical manufacturers have also responded to the social and economic factors driving the fight against poor prescription medication adherence. R&D spend is shifting away from blockbuster business models to more patient-centric product strategies that address the pharmacokinetic and pharmacodynamic characteristics of the different first-in-class, generic and OTC drugs in their portfolios. Similar to a consumer technology company studying user interfaces and device form factors, drug developers are working on drug form and dose frequency, as well as dose administration/delivery complexity to remove barriers to efficacy, mitigate patient issues post-approval and generate better patient outcomes.

The NEHI study uncovered a number of key design principles for medication-adherence interventions, including patient-centered methods using direct patient contact to tailor the overall intervention to meet patient preferences and address that person's readiness to adhere. New England Healthcare Institute analysts also suggested forming a holistic view of the patient based on a complete understanding of the person's medical condition, as well as full accounting of all their prescriptions. It is at this intersection that physicians, pharmacists and caregivers can all play a primary role in intervening with patients to improve their adherence and better outcomes overall.[12]

Simplifying medication dosing regimens and improving a given medication's relative ease of use is now well understood to be primary strategies for improving adherence behavior. Combination therapies or new/alternative therapies that treat multiple conditions can help ease dose frequency

WHY DOSAGE FORM MATTERS PROTECTING THE ELDERLY

IMPACT IN THE U.S.

90%

of people receiving Medicare took medications, with half of them taking five or more drugs.[1]

15%

of the elderly population are affected by dysphagia (difficulty swallowing), which can lead to nonadherence.[2]

One/Day **80%** Four/Day **50%**

On average, adherence drops significantly when medications must be taken four times per day (80% for one/day to 50% for four/day).[3]

40%

Up to 40% of nursing home admissions can be attributed to nonadherence.[4]

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EASY-ACCESS AND PORTABLE CONTAINERS, INCLUDING SINGLE-UNIT DOSE FORMATS, HAVE PROVEN TO DELIVER A POSITIVE IMPACT, ESPECIALLY WITH ELDERLY PATIENTS.

UNITHER OFFERS A COMPREHENSIVE RANGE OF SINGLE-USE DOSAGE FORMS AND DELIVERY SYSTEMS THAT HELP MITIGATE ADHERENCE ISSUES AND SUPPORT EFFECTIVE PATIENT-CENTRIC THERAPIES.

or dose complexity. Extended-release formulations can have a similar impact, reducing dose frequency because one dose lasts longer.

Packaging can also play an effective role in supporting adherence. Easy-access and portable containers, including single-unit dose formats, have proven to deliver a positive impact, especially with elderly patients. Unit-dose medication delivery is popular both in the U.S. and Europe because it helps prevent under- and overdosing and similar medication errors. This is especially true for elderly or impaired patients who may have trouble navigating medication regimens across several multiple-dose packages. Single-dose packaging helps accurately administer drugs and therapies because they hold only a single dose of a drug and are meant to open only once.

Most dosage forms can be packaged as unit doses, including oral, topical and parenterals. Blister and pouch packaging for OSDs are common, as are pre-filled syringes and cartridges for parenterals. Squeeze tubes and blow-fill-seal containers effectively deliver topical, oral and sterile formulas, such as ophthalmic and respiratory agents.

DEVELOPMENT, EDUCATION AND COLLABORATION

The need to improve medication adherence is abundantly clear, and the answers are becoming so. Study after study confirms that the closer the industry gets to the patient the better; health outcomes improve and so does the cost profile to payers. The pharma industry is being compelled to demonstrate its social value even more strongly than ever before. Rather than waiting for legislation or market forces to act, the industry must be proactive to better serve their ultimate customers – the patients – by collaborating closely to drive initiatives across three broad fronts:

[1] Increased investment and innovation to design and deliver therapeutically efficient, patient-centric products that are easier to use safely and correctly in the real world.
[2] Comprehensive consumer education programs to drive medication adherence, with pre- and post-approval studies to determine why failures occur.
[3] Collaboration among stakeholders (manufacturers, regulators, academia, providers, payers, patient advocates and governments) to institute models that reward therapeutic efficiency and value outcomes, rather than services delivered.

Technologies that support easy-to-use dosage and packaging forms are readily available; CDMOs like Unither Pharmaceuticals have been introducing successful solutions to the industry for years. Unither offers a comprehensive range of single-use dosage forms and delivery systems that help mitigate adherence issues and support effective patient-centric therapies. These forms are proven to be a convenient, affordable way for patients to consume single doses of liquid and semi-liquid medicines, as well as patient-friendly respiratory and orally digestible dose formulations. These and other innovations allow Unither to support its customers' patient-centric drug development plans, including the shared goal of combatting poor drug compliance.

It is imperative that the healthcare industry, payers and governments act deliberately to address this multi-dimensional and highly complex issue. Better medication adherence saves lives and has the potential to cut billions of dollars in waste from the system. Although it is likely the current structure of U.S. health insurance policy and law will change, its final form has yet to be determined and may be years away. Regardless, all stakeholders need to take bold steps, both to ensure this critical aspect of healthcare policy is not ignored and that valuable pharmaceuticals are taken as intended to deliver the best outcomes for patients. P

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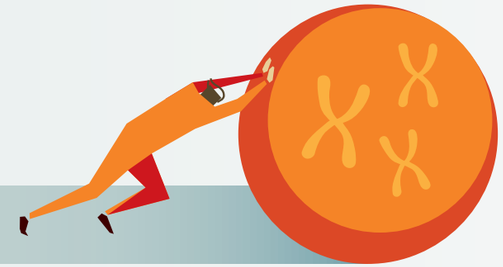
NICE INSIGHT OVERVIEW

A LOOK AT RECENT PHARMA INDUSTRY INNOVATIONS

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

Success in the pharmaceutical industry is integrally linked with innovation. Advances in chemistry, biology, biochemistry, genetics and engineering are essential for both the discovery and manufacture of novel medicines. Innovative drug delivery and packaging technologies are also needed to ensure that complex large and small molecules in the pharma pipeline today are formulated into high-quality, safe and efficacious drug products. Representative examples of recent industry innovations are highlighted below.



ADVANCING API SYNTHESIS

Small-molecule drugs continue to dominate the marketplace and the drug pipeline despite growing demand for biologics. Advances in combinatorial chemistry are, in fact, leading to the discovery of novel, highly complex and efficacious active pharmaceutical ingredients (APIs). At the same time, there is a significant push to employ synthetic routes that are not only feasible at production scale, but also cost efficient, atom economical and more environmentally friendly.

One response of both sponsor companies and contract manufacturers is expanded use of flow chemistry and microreactor technology to achieve process intensification. Often this approach leads to reduced costs while increasing throughput and yields, and in addition, enabling the use of hazardous processes that are not possible to perform under batch production conditions. Lonza, for instance, has invested in a multi-million CHF facility for continuous flow and microreaction technology in Visp, Switzerland and developed its own proprietary Flowplate® Microreactor Platform.

Advances in catalyst technologies continue unabated as manufacturers seek more efficient routes to complex intermediates and drug substances. As the number of commercially available enzyme and transition metal catalysts expands, the development of more economical and sustainable processes for API production is more commonplace.

New chemocatalyst technologies include chiral transformations such as Grignard addition reactions, processes for the formation of natural and non-natural amino acids and their derivatives, and reactions that afford fluorinated compounds. The scope of asymmetric hydrogenations, C-H insertions and carbon-carbon coupling reactions are enabling the preparation of new chiral intermediates, including those that contain quaternary carbons.[1,2] Attention is also being paid to ligand design, the reclamation and reuse of homogeneous catalysts, immobilization of catalysts on solid supports and encapsulation of toxic complexes without loss of selectivity and reactivity.[3]

Biocatalysts have numerous advantages for pharmaceutical manufacturers looking to implement "greener" processes. They not only proceed with high efficiencies and selectivities, they often mediate transformations that result in complex structures that would take multiple steps with conventional chemistry. These reactions also typically proceed at or near room temperature in water with minimal byproduct formation and emissions generation, generally without the need for expensive and toxic metals.[4]

As importantly, advances in genetic engineering have led to the identification of an ever-increasing number of enzymes that can be used to accomplish chemical conversions that are difficult, or not possible, with conventional catalysts. These enzymes are being carefully engineered using a number of state-of-the-art techniques (site-specific mutagenesis, directed evolution and computational *de novo* design) to have the structures and other properties that allow their production and use on a commercial scale.[5]

Recent examples of new enzyme-catalyzed reactions include reductive coupling of ketones with amines for protection and deprotection steps, imine reductases that reductively couple ketones with amines for the convergent synthesis of secondary and tertiary chiral amine drug targets, enantiospecific synthesis of primary amines and secondary alcohols, as well as the preparation of asymmetric sulfoxides. There are no chemocatalyst alternatives for many of these transformations, according to Jim Lalonde, Senior Vice President of R&D with Codexis in a recent *Pharmaceutical Technology* article.[6] »

> "ADVANCES IN CATALYST TECHNOLOGIES CONTINUE UNABATED AS MANUFACTURERS SEEK MORE EFFICIENT ROUTES TO COMPLEX INTERMEDIATES AND DRUG SUBSTANCES.

> WHILE SOME LARGE PHARMA COMPANIES ARE INVESTING IN MANUFACTURING CAPABILITIES FOR CELL THERAPIES, MANY, ALONG WITH MOST SMALLER AND EMERGING FIRMS, ARE SEEKING SUPPORT FOR LARGE-SCALE CELL THERAPY PRODUCTION FROM OUTSOURCING PARTNERS.

Other new reactions for which enzymes are being developed include the direct hydroxylation of unactivated C-H bonds, the direct synthesis of amides, the regiospecific glycosylation of hydroxyl groups and the site-specific conjugation of proteins.[6]

Many drug companies are also exploring the preparation of deuterated versions of existing APIs to extend the lifetimes of currently marketed products facing patent expiry. Replacement of hydrogen atoms with deuterium can lead to slightly different properties and allow novel formulations for new indications. Johnson Matthey is one CDMO that is developing this specialized expertise.[7]

ACCELERATING VACCINE DEVELOPMENT

Serious diseases, including AIDS and malaria, continue to challenge vaccine manufacturers. The diversity of viruses and the need to identify the relevant antigen in order to determine an appropriate production method complicates the issue.[8] The focus is consequently on gaining a greater understanding of which vaccine antigen features impart resistance to viruses.

The Ebola outbreak in 2014 underscored the significant need for accelerating vaccine development. It also created the incentive for vaccine manufacturers and regulators to find ways to move from phase I to phase III in months and be ready to achieve full-scale manufacturing of an approved vaccine. For instance, Janssen Vaccines – part of the Janssen Pharmaceutical Companies of Johnson & Johnson – received the 2016 Facility of the Year Award for Project Execution for its "Fast Track Refurbishment for Ebola Vaccine Production" from the International Society of Pharmaceutical Engineers (ISPE).

The company took the daring approach of running parallel accelerated manufacturing scale-up and clinical development programs, including the simultaneous refurbishment of an existing production facility and the technology transfer and optimization of the process, according to Dirk Redlich, Vice President and Global Head of Technical Development for Janssen Vaccines, in a recent *BioPharm International* article.[8] He noted that successful scale-up of vaccine production can be attributed to the relentless effort of Janssen employees, the intensive collaboration between all parties involved in the project and the in-depth knowledge that the company has of its technology. The result: production (and freezing) of 2.4 million doses of its vaccine regimen.

The use of advanced processing capabilities, including high-throughput and single-use technologies, also contributed to the project's success. The development of chromatography-based purification processes and the use of microcarriers for cell growth are also improving vaccine production.[9] Continuous processes for vaccine manufacturing are under development and expected to accelerate production startup once proof of concept has been established, according to Sangeetha Sagar, Assistant Vice President for R&D with Sanofi Pasteur, who commented in the same article.[8]

Several innovative technologies for vaccine production that have the potential to more rapidly provide vaccines in response to pandemic situations are currently being worked on. Cell culture, synthetic DNA, virus-like particles, chimeric antigens, recombinant protein nanoparticles and subunit vaccines are all examples of alternatives to traditional egg-based vaccine manufacturing, which typically is a many-months-long process.[10]

Recently, researchers at the University at Buffalo, The State University of New York, reported the development of a pneumococcal disease antigen comprising a bacterial core electrostatically coated with a cationic polymer.[11] The design results in natural adjuvant properties and allows passive and active targeting of antigen-presenting cells plus *in situ* antigen production and consolidation within the bacterial component of the vector, eliminating the need for dedicated antigen production and purification prior to vaccination, according to the authors. The easy-to-formulate hybrid vector was successfully tested against a range of clinically relevant *Streptococcus pneumoniae* strains; the results compared to those for several traditional vaccine formulations.

Other interesting work includes the production by researchers at the University of California, San Diego School of Medicine, of a properly folded malaria parasite protein (Pfs25) in algae typically used for biofuel production.[12] Algae is advantageous because it is inexpensive, easy to work with and environmentally friendly. Most importantly, when combined with an immune-boosting cocktail suitable for use in humans, the algae-produced protein generated antibodies in mice that nearly eliminated mosquito infection by the malaria parasite.

SOLVING DRUG DELIVERY CHALLENGES

Both the highly complex small-molecule and biologic drugs on the market today present significant challenges to formulators in terms of drug delivery. According to Kline & Company, 40% of currently marketed drugs and 80% of pipeline candidates have low solubility (Class III/IV according to the Biopharmaceutical Classification System.)[13] In addition, effective technologies for the targeted delivery of protein-based drugs have yet to be developed. CDMOs with specialized capabilities in solubility, bioavailability enhancement and targeted delivery are therefore well positioned for success.

Choice of a specific technology is molecule-dependent. Whether the compound is to be administered as a solid, liquid, parenterally or via inhalation also influences the decision. Extensive experience in formulating solutions for poorly soluble APIs is therefore a real competitive advantage. Fortunately the available range of drug delivery technologies is expanding and now includes the formation of salts or co-crystals, particle manipulation, the use of lipid-based carriers and the generation of amorphous dispersions.[14]

Cryogenic spraying, which includes spray freezing onto cryogenic fluids, spray freezing into cryogenic liquids, spray freezing into vapor over liquid and ultra-rapid freezing, is an example of a newly introduced particle engineering technology. The low-temperature process yields nanocrystals of APIs with significantly enhanced surface areas.[14]

CAR-T CELL THERAPIES MOVING FROM THE CLINIC TO THE PATIENT

There are over 500 companies involved in cell therapy technology, according to Jain PharmaBiotech.[15] Some of the most promising therapies are based on adoptive cell transfer using T cells (T lymphocytes) harvested from patients and then genetically engineered to have chimeric antigen receptors (CARs) that recognize specific proteins (antigens) on tumor cells.

Recent developments have focused on increasing the safety of CAR-T cell therapies (to avoid cytokine release syndrome and on-target, off-cancer toxicity) and address the challenges associated with the large-scale manufacture of cells as therapeutic products.[16] Solutions to the safety problems include the incorporation of safety switches that allow for destruction of the cells in the event of severe toxicity; the development of bispecific CAR-T cells that deliver activating signals upon binding to desired tumor cells and inhibitory signals upon binding to healthy cells; and CAR-T cells for which activity is modulated using small-molecule drug inducers.

Juno Therapeutics has licensed Streptag technology from the Fred Hutchinson Cancer Research Center, which is used to select T-cells with the appropriate CAR protein, allowing highly pure cell samples that when expanded are more potent and have better regenerative capabilities within patients.[17]

With respect to manufacturing challenges, Novartis, which was the first health-care company to initiate phase II CAR-T therapy trials across the U.S., Europe, Canada and Australia, has reported the successful transfer of cell processing technology from the University of Pennsylvania to the company's cell manufacturing center in Morris Plains, NJ.[18]

The appropriate cell expansion technology for a given therapy will depend on the type of product (small-scale autologous or large-scale allogeneic), with 2D culture processes likely for the former and 3D processes using microcarriers expected for the latter.[16] Closed, disposable systems provide the needed flexibility and low cost. Automation of the production process, particularly for patient-specific autologous products, will be crucial for minimizing space and cost while increasing consistency.

While some large pharma companies are investing in manufacturing capabilities for cell therapies, many, along with most smaller and emerging firms, are seeking support for large-scale cell therapy production from outsourcing partners. There are only a few firms focused on this sector – newly formed Brammer Bio, WuXi PharmaTech (which is building its third cGMP cell-therapy production facility in Philadelphia, Pennsylvania), PCT and Lonza.[16]

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ADVANCING PATIENT-CENTRIC PARENTERAL DRUG STRATEGIES

→ BY **MARGA VIÑES** AND **ORIOL PRAT**, GRIFOLS

Parenterally administered drugs will remain the delivery option of choice, especially in the era of biologics, but their ultimate success therapeutically and commercially hinges on how well these drugs can be integrated into a patient-centric continuum of care.

For the foreseeable future, therapies delivered via parenteral routes will dominate advancements in healthcare and patient outcomes. Regulators, governments, health systems and – most importantly – patients are all stakeholders, linked by dependence on the safe, reliable and abundant supply of sterile liquid drugs. There is little dispute that this sector of pharmacopeia represents a tremendous growing opportunity for drug innovators and owners. But bringing a parenteral product to market successfully, then sustaining its long-term commercial and therapeutic success, is extremely challenging, requiring a broad and all-encompassing strategy well integrated into the patient-centric continuum of care. Industry leaders are very deliberately pursuing these strategies, but increasingly not without involving the intense and strategic collaboration of contract manufacturing and development organizations.

Not widely available until the 1950s, intravenously (IV) administered medications have become a central feature of modern healthcare. Most major categories of biopharmaceuticals and biologics – and most vaccines, antibiotics, immunotherapies and similar therapeutic IV-delivered substances like plasma and saline – are parenterals. Spanning the continuum of care, parenterals are delivered to caregivers and patients in a broad array of primary packaging and administration regimes. Primary packaging and dosage forms are also following major patient-centric trends, and innovation here is introducing new complexities for both manufacturers and consumers.

INFUSION OR INJECTION?

Intravenous infusion is the most common parenteral delivery method, providing an immediate therapeutic effect by delivering medication directly into the bloodstream. Small-volume parenterals (less than 100 mL) and large-volume parenterals (100 mL or greater) are both specified by the millions for the continuous or intermittent infusion of drugs and therapeutic fluids. Caregivers and patients encounter these forms across the continuum of care.

Admixtures are generally dried and most often lyophilized drug products packaged primarily in glass vials or ampoules. In the case of many large-molecule drugs, including antibiotics, a lyophilized admixture of the drug is reconstituted and placed into an IV solution by a nurse or by a compounding pharmacist or some other medical personnel. When added into solution in this manner, the margin for human error looms large. It's not surprising that with admixture-based dosing regimens, the opportunity for error is present throughout all stages of the process – from preparation and dose calculation through to infusion. Intrinsically error-prone already, many healthcare systems access IV therapies through compounding pharmacies, which have generated a significant history of medical error introduced in the admixture formulation process.

In a 2001 report, a five-year FDA study found that the most common medical errors resulting in patient death were administering an improper dose (40.9%).[1] These errors can be exacerbated in a situation where multiple steps, like administering admixtures, is required. The more compli-

> IT'S NOT SURPRISING THAT WITH **ADMIXTURE-BASED DOSING REGIMENS,** THE OPPORTUNITY FOR ERROR IS PRESENT THROUGHOUT ALL STAGES OF THE PROCESS.

cated the solution, the greater the margin for error. In 2010, a six-week-old infant died because a PN solution the infant was receiving had 60 times the amount of sodium than was supposed to have been prescribed. In 2007, a preterm infant received a 1,000-fold overdose of zinc, which was entered incorrectly into an automated PN compounder – a total of six staff members missed it.[1]

Compounded admixture IVs were not primarily regulated by the FDA because they are generally customized combinations of already-approved drugs. The FDA had ordinarily given oversight authority to state pharmaceutical boards, but who can forget the October 2012 incident involving a compounding pharmacy in Massachusetts releasing 17,000 vials contaminated with meningitis that subsequently caused several patient deaths? Incidents caused by unsafe or unsanitary practices in the making and distributing of parenterals or custom IVs – by outsourced compounding agencies or by in-house compounding pharmacies – led to the FDA's passing of the Compounding Quality Act that regulates those agencies outsourcing medicines.[2]

Complicated admixture procedure was at the heart of it. The Institute for Safe Medication Practices 2009 study "The State of Pharmacy Compounding Survey" found that 30% of hospitals had experienced a patient event attributed to an admixture-related compounding error over a period of five years. Among the study's conclusions: the use of premixed IV solutions could have reduced such life-threatening or damaging incidents.[3,4]

GREAT RISK, GREAT REWARD

The world's major health systems and drug-developing leaders are spending billions to help bring new (or high-demand or supply-challenged) injectable and infusible therapeutics to the market. The demand for premixed solutions is also therapeutically led. Premixed IV solutions, for example, are the preferred mode of delivery for antibiotics globally and a market segment growing exponentially. According to one study, the world's consumption of antibiotics has risen ~36% since 2000.[5] Pain management and cardiac medications (both very popular therapeutic categories) are most often delivered intravenously, contributing to the demand for a safer, more reliable premixed solution.

To support these initiatives, drug owners are prompted to adapt their business models and frame them to meet the realities and risks associated with parenteral drugs. For an increasing number of companies, seeking technically and operationally superior contract-service partners to deliver capacity and resources is becoming a key component of their patient-centric strategy and the fastest path to market.

Overall design of the premixed fill, package material, and the functional attributes of the IV bag are integral to patient-centric

GRIFOLS:

Types Of Containers

Grifols Partnership is specialized in developing and manufacturing high-quality sterile solutions and lipid emulsions in a wide range of containers made from a variety of materials in different sizes to suit every need in both the human and veterinary markets.

Glass bottle: Naturally inert material, totally transparent and recyclable. Available sizes: 100 mL, 250 mL and 500 mL.

Glass vials: Available sizes 5ml to 50ml.

Polypropylene bag: Totally PVC-free. Excellent drug compatibility, very flexible and transparent material. Available sizes: 100 mL, 250 mL, 500 ml and 1000 mL.

product strategies. Grifols, which has a 75-year history developing plasma-derived medicines, provides a knowledge base and a source for design wisdom to create parenteral vessels intended to support successful healthcare and patient outcomes.

Plastic primary packaging for parenterals has been supplanting glass for decades and its positive attributes regarding pharmaceutical delivery and aseptic process benefits are well documented. Packaged in flexible bags, Grifols Partnership premixed solutions deliver a fixed dose in 50 mL to 1 L containers. These bags are terminally sterilized to assure sterility and safety. It is this specific dose feature that guarantees the patient receives an accurate dose while eliminating the potential for waste. Another example of the benefits of premixture versus admixture delivery strategies is that reasonable dosage limits are likely to encourage healthcare providers to write more cost-effective orders. Another advantage of premix bags involves shelf life and logistical capabilities — admixtures must be used between 24 and 48 hours — whereas premixed formulations can have a shelf life as long as two years.

GRIFOLS PARTNERSHIP PARENTERAL STRATEGY LEADER

It is well established that parenteral drugs and therapeutic fluids require highly controlled, sterile process environments to be manufactured correctly and to current GMP standards. Processing parenteral drugs is extremely challenging and any review of drug recalls over the past 10 years will confirm this. Safety and quality in aseptic processing requires a tremendous focus on both process and understanding of process technologies, as well as an extremely well-integrated and -aligned quality system backing it up.

It is a complex and costly undertaking to advance a parenteral drug product. To achieve market and therapeutic success, a range of specific requirements is mandatory. This includes category expertise, integrated and aligned resources, advanced and automated aseptic processing systems, operational excellence and a thorough understanding of the market dynamics that effect parenteral drug markets. In 2007, Laboratorios Grifols was one of the first companies in Europe to obtain authorization for parametric release for its two EMA- and FDA-certified production plants covering more than 15,000 m² in Barcelona and Murcia, Spain. Parametric release is a guarantee that the product has attained the desired quality and is based on the information collected during the manufacturing process in compliance with the specific demands of the Good Manufacturing Practices (GMP). This recognition was received thanks to the rigorous quality system at Grifols, which guarantees the sterility of the product without the need to carry out additional sterility tests.

CDMOs with experience in meeting regulatory specifics globally, as well as those well versed in parenterals through the product's lifecycle, will be the ones most qualified to provide the strategic counsel required to attain market success. Grifols Partnership is uniquely qualified in this case and any strategy that involves attaining or sustaining market and patient success for a parenteral therapy will benefit from the association. P

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Marga Viñes holds a degree in pharmacy and an MBA in pharmaceutical management from the University of Barcelona. She has more than 15 years' sales and marketing experience in the pharmaceutical industry and healthcare business, defining and implementing marketing strategies for international and domestic markets. In addition, she has nine years' experience in the field of strategic marketing and business development in the contract manufacturing business on an international level.

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SUPPLY CHAIN MANAGEMENT AND THE IMPORTANCE OF SECURITY OF SUPPLY

→ BY **SYED T. HUSAIN**, ALCAMI

As global demands rise, supply chains are becomingly increasingly complex. Of course, with this increased complexity comes increased risk of error and, more significantly, increased risk of supply disruptions and drug shortages. In order to prepare for the possibility of unforeseen events affecting the supply chain, contingency plans are a priority. Alcami's innovative Protect Your Brand™ is a key example of this type of security service, offered through an outsourcing partner.

According to the FDA, 64% of all reported drug shortages are caused by quality issues (37% manufacturing, 27% delays/capacity) and another 27% are due to raw materials, so it's not surprising that the 2016 Nice Insight CDMO Outsourcing Survey showed quality as the most important factor when selecting a new outsourcing partner.[1,2] When a shortage occurs, companies face profit losses, damage to their reputation in the market and possible regulatory action, while patients – including those with chronic or life-threatening illnesses – are left without medication as healthcare providers scramble to find replacements when possible. In recognition of the risks associated with drug shortages and the importance of maintaining a sound supply network, many sponsors are actively pursuing contingency plans. Similarly, companies producing drugs via reliable single-source supply networks are looking for zero-commitment, dual-supply protection options – a strong CDMO can become a valuable part of these strategies.

One such CDMO is Alcami, the alliance of AAIPharma Services and Cambridge Major Laboratories. Following the 2013 merger, Alcami became a leading provider of integrated chemistry, manufacturing and controls (CMC) services and, in October 2016, launched its new Protect Your Brand™ service to help pharmaceutical and biopharmaceutical companies alike establish a reliable dual-source supply chain. When dual supply is paired with innovative logistics solutions, the industry appears poised to continue minimizing the effects of drug shortages; however, risks in the supply chain continue to demand attention – management and partnership remain critical in the effort to keep operations moving.

CONTINGENCY PLANNING AND THE IMPORTANCE OF LOGISTICS

Contingency planning isn't new to the pharmaceutical or healthcare industry. In fact, according to the Eighth UPS® Pain in the Chain Survey, published in 2015 and focused specifically on the healthcare and life sciences industry, contingency planning was categorized as an area that needs attention, with the report noting that "unplanned events have impacted [6% of] healthcare supply chains in the last 3-5 years."[3] Regardless of this impact, only 60% of respondents to the survey viewed contingency planning as important. However, with global demands pressuring pharmaceutical companies to increase production volumes while continuing to speed development and drive costs down, contingency planning is only growing in importance. As production technologies become more advanced and sponsors continue to explore outsourcing options, including those in the emerging markets, many supply chains are becoming more complex than ever and the potential for both production and logistics issues is increasing.[4]

According to FedEx, "Finished pharmaceutical products represent about 4% of the total value of imported goods in the American import portfolio," and Ireland, Germany and Switzerland "[were] responsible for 46% of US pharmaceuticals import values in 2015."[5] With that volume relying so heavily on global logistics, it's critical for pharmaceutical manufacturers to understand how these goods are moving and, more than anything, what happens when shipments get stuck in customs or otherwise held up in transit. Just as many companies have found the value in establishing partnerships for outsourcing drug development and production, logistics partnerships are also beneficial.

Research from LogiPharma states, "66% of respondents indicated they currently outsource at least some part of their distribution and order fulfillment operations, and 67% outsource transportation management."[6] Logistics partners can help here by increasing supply chain visibility, offering import and export expertise, and providing specialized transportation and storage in the event of delays. FedEx, for example, recently opened a cold chain facility with approximately 1,000 square meters of temperature-controlled storage in Memphis, the largest port of entry in the US. However, logistics are only part of the problem facing the industry. Pharmaceutical and biopharmaceutical companies must also ensure that production proceeds as planned and, when it doesn't, that measures are in place to minimize downtime and, ideally, prevent shortages.

DUAL SUPPLY AND THE CONTINUED RISKS OF PARENTERAL DRUGS

Though drug shortages have decreased overall, to just 44 shortages reported to the FDA in 2014 – an admirable number following the spike in 2011 that brought 251 – the changing global supply chain and continued growth of biopharmaceuticals are keeping this risk relevant; of the 44 shortages reported in 2014, 68% were injectables, only a modest improvement since 2011.[2] Due to the comparatively shorter shelf life, specialized and costly storage

ENGAGING A CDMO PARTNER CAN PROVIDE MUCH-NEEDED PEACE OF MIND, **BUT SELECTING THE RIGHT PARTNER IS KEY**.

requirements (e.g., temperature sensitivity) and sterile production requirements associated with biopharmaceuticals, quality problems frequently lead to shortages as many of these drugs are produced in an almost "as needed" manner. Further, in 2015 many existing biopharmaceutical companies were estimated to be operating at near capacity, while larger CDMOs were similarly estimated to be approaching capacity for both microbial fermentation (81%) and mammalian cell culture (71%).[8]

Though many pharmaceutical companies with legacy products may have significant inventory on hand or may be able to produce and store large quantities of the necessary API to weather production/supply chain issues, newer medications and biopharmaceuticals often cannot benefit from the same supply.[7] However, even the most minor excipients can change product characteristics and, as a result, require everything from preformulation analysis to regulatory-filing requirements, meaning that even those companies that might turn over inventory only twice a year are at risk if production delays occur.[9]

To make matters worse, supply chain preparedness issues typically span the entire chain, from sourcing to fill-finish, and these challenges are further magnified when dealing with biopharmaceuticals and parenteral medications in general. From 2002 to 2013, the demand for sterile injectables increased by 39% while the number of generic medications in this category increased by 57%.[8] With many legacy products likely to experience lower yields due to advanced technologies not being implemented on those lines and many generics manufacturers unlikely to feel any incentive to invest in manufacturing/infrastructure improvements due to smaller profit margins, the shortage risks in this area are still very relevant.[8]

Opening lines of communication along the entire supply chain – including suppliers, wholesalers, CDMOs and group purchasing organizations – can help by allowing companies to better forecast supply chain needs and possibly predict shortages in advance.[8] Contract development and manufacturing organizations are also uniquely positioned to help ensure the continued integrity of a supply chain. Engaging a CDMO partner can provide much-needed peace of mind, but selecting the right partner is key. More specifically, selecting a partner with capabilities that span both upstream and downstream processes for complex drug development and production – including sterile production and fill-finish operations – can allow companies to meet global demands and safeguard against the most likely shortages. Alcami has extensive capabilities and the capacity to provide analytical testing, development, prototyping and reformulation services for APIs with both oral-solid and parenteral- dose finished products.

PROTECT YOUR BRAND™

In addition to its industry-leading integrated offerings for both drug-substance and drug-product development, Alcami officially launched a service that can help ease the process of establishing a dual supply, at CPhI Worldwide in Barcelona in early October: Protect Your Brand™. Though Alcami strives to prevent production disruptions from occurring at any of its global facilities – three of which just completed FDA inspections with zero observations (Germantown, WI, Charleston, SC and Wilmington, NC) – the company also recognizes that unforeseen events can and have occurred across the globe and that all companies need backup. Protect Your Brand™ is a convenient, "no strings attached" – meaning no long-term contracts or commitment – dual-supply option that allows for the tech transfer and validation of drug substance and/or drug products in advance of potential production needs.

Even if drug shortages continue to become less frequent over the coming years, supply chain management and contingency planning will remain important. From unforeseen global disasters that can affect materials, supplies and shipments, to manufacturing challenges that halt production, a contingency plan can help reduce loss and ensure that operations return to normal as quickly as possible. When paired with its global presence and existing manufacturing expertise, Alcami and its new Protect Your Brand™ program combine to form a reliable partner capable of offering peace of mind in a supply chain with an increasing number of moving pieces. P

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Syed Husain, the commercial leader for Alcami, leverages in-depth experience in sales, business development, marketing and operations for the development and manufacture of small molecules, antibody drug conjugates, peptides and large molecules covering drug substance and drug product. Syed earned a BS in chemical engineering from New Jersey Institute of Technology in 2003 and an MBA from Cornell University in 2009.

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MEETING UNMET PATIENT NEEDS WITH SMALL-VOLUME APIS

→ BY **STEPHEN MUNK**, ASH STEVENS

At the invitation of *Pharma's Almanac*, Dr. Stephen Munk, CEO of Ash Stevens, discusses the need for CDMOs with specialized, small-volume manufacturing capabilities that will support the industry as it moves towards a more personalized and precise approach to treating disease.

Personalized medicine, precision medicine, evidence-based medicine and patient-centered outcomes research dominate the landscape today and are driving the need for significant change in manufacturing strategies. Pressure is mounting to accelerate the development and commercialization of novel drugs with greater efficacy than current treatments, while also increasing their quality and safety. Competition from generics/biosimilars is also growing, and the age of the blockbuster is passing.

Fortunately, advances in personalized and precision medicine are creating numerous opportunities to improve the quality of life for patients with unmet medical needs. Greater understanding of diseases mechanisms and genetics, combined with innovative manufacturing technologies, is leading to the development of novel treatments and diagnostic tools. Increasingly potent, targeted therapies are, in particular, attracting attention due to their greater efficacy at lower doses and with reduced side effects.

FDA provides strong support for the rapid development of these novel drugs through the use of Fast Track and Breakthrough Therapy Designations and Accelerated Approval and Priority Review processes. These designations are attributed to drug candidates with good preclinical and/or clinical data demonstrating novel mechanisms of action, or that the therapies are more efficacious than the currently available standard of care. The Orphan Drug designation, meanwhile, provides advantages to drugs intended for the treatment of a disease affecting less than 200,000 US citizens and encourages the development of small-volume products. These special designations therefore provide tremendous benefit for both patients and the advancement of the scientific community's understanding of underlying disease mechanisms and therapeutic interventions.

The shift to personalized medicine and growing interest in orphan drug development has created a need for contract development and manufacturing organizations (CDMOs) that have capability for small-volume manufacturing of very specialized drug substances, including highly potent active pharmaceutical ingredients (HPAPIs). Technical competence in the validation of production processes and analytical methods, often under accelerated timelines, to ensure preparation of a complete regulatory package for filing, is essential.

AWARENESS OF PROCESS SAFETY ISSUES

With increasing pressure to deliver faster turnaround times and lower manufacturing costs, there is impetus to deemphasize the need for comprehensive process safety evaluations and accept greater safety risks. Inattention to process safety can, however, lead to devastating consequences. To conduct safe manufacturing processes, an effective process safety strategy and process safety management system are needed within a culture that emphasizes safety.[1]

Prior to acceptance, proposed projects must be evaluated to determine whether the capabilities of the CDMO are compatible with the capabilities and staffing of the CDMO, and only those projects for which suitable facilities, equipment and skilled personnel are available should be accepted. From a process safety perspective, once a project is initiated, both theoretical and experimental analyses must be conducted to determine the thermodynamic and kinetic properties of all materials involved in the process and the process itself, both under normal and worst-case scenario conditions.

IMPLEMENTING ADVANCED QUALITY INITIATIVES

Many Life Science companies developing drugs are looking to apply the principles of Quality by Design (QbD) to their manufacturing processes to better comply with current regulatory guidelines for QbD with the anticipation that QbD will become a requirement at some point in the future.[2]

FDA guidelines provide a structured framework anchored in statistical methods to provide accurate understanding and control of pharmaceutical manufacturing processes. Implementing QbD services can be expensive for CDMOs, requiring new equipment, statistical support and the training and/or hiring of personnel. Although QbD remains a guideline and not a regulatory requirement, the momentum is in the direction of more QbD work for CDMOs as drug developers try to get out ahead of the regulatory curve.

For Ash Stevens, the early adoption of a QbD approach has contributed to the company's extensive track record for commercialization of APIs and continues to facilitate accelerated approvals. The use of a practical qualification strategy also enables Ash Stevens to efficiently validate the processes it develops following QbD principles.[3] Appropriate preparation and planning ensures that all central issues are identified and surprises during validation are minimized. Experience with the latest guidelines also means that Ash Stevens can address the issues of importance to the various regulatory agencies.

FACILITATING PROCESS DEVELOPMENT

While initial laboratory syntheses are focused on making enough of an API as fast as possible for preclinical testing, process development focuses on multiple aspects for process improvement. Effective process development and optimization is most efficient when integrated with scale-up and cGMP manufacturing operations. CDMOs with integrated capabilities from early-stage drug substance development through commercial manufacturing can potentially effect a smoother transition from the laboratory to commercial manufacturing, streamlining the process, reducing complexity and building process knowledge. These benefits are particularly realized when key stakeholders, such as process chemists and engineers working on the project, transition with the process through the various stages of scale-up to ensure the tech transfer proceeds seamlessly.

ACCELERATED CAPABILITIES

Drugs with Fast Track or Breakthrough status place even more pressure on a CDMO to rapidly scale processes to expedite the delivery of potential new therapies to patients. Here especially, a well-integrated team of engineers and process chemists are essential to bringing the process online and meeting accelerated timelines.

In general, scale-up must be achieved without changing the manufacturing

Ash Stevens Expands Piramal Pharma Solutions Portfolio

In August, 2016, **Ash Stevens was acquired by PEL Pharma Inc, a subsidiary of Piramal Enterprises Ltd India,** adding to its significant capabilities for the manufacture of highly potent and other specialty APIs to PPS' portfolio of contract development and manufacturing services. PPS now has three local facilities to support the North American market, including the recently acquired Coldstream Labs' fill-finish site in Kentucky, the Torcan plant in Toronto for the production of complex, high-value APIs and Ash Stevens' Michigan facility for manufacturing HPAPIs.

As part of PPS, Ash Stevens contributes to a highly differentiated platform of services that facilitates the development of strategic partnerships and creates synergies with PPS' existing antibody-drug conjugates and injectables businesses. PPS and Ash Stevens also share common core values and have a customer-focused approach, and there are several areas where as a combined organization we can create real value for our customers. Becoming part of a company with such a diverse portfolio and a track record of growth and investment in the pharmaceutical services sector represents an exciting opportunity for both our customers and our employees.

process used for the production of preclinical/toxicity testing quantities, in order to avoid any delay in the initiation of clinical trials. It is therefore important to improve the efficiency of the laboratory process with respect to process cycle times, waste minimization and yield.[4] Increasing the productivity of kilo-scale processes for clinical trial material can also be an important factor for accelerating the development of a Fast Track drug.

It is also important to recognize that because the timelines are reduced, clinical trials involve fewer patients and the quantity (number of batches) of manufactured material that is subjected to testing is fewer. As a result, there is generally less time to gather full information about how the process can potentially impact product API quality, which can present challenges when it comes to qualification of process performance as regulatory agencies do not permit a less well-developed CMC section of the NDA. At the same time, the margin of error is much slimmer than what is acceptable for a standard drug candidate. CDMOs must work closely with the drug sponsor and FDA to identify and mitigate any potential issues before they arise.

Experience with the development of comparability data that can be used to relate initial analytical data, with data obtained using validated methods developed for process performance qualification and specification determination, is very important. The use of a QbD approach and early determination of critical quality attributes can help ensure that analytical methods developed under accelerated conditions still allow for the demonstration of process and product control.

HPAPI EXPERTISE

HPAPI manufacturing requires much higher investment in specialized facilities and equipment than CDMOs, which provide traditional API manufacturing services. These CDMOs must also be prepared to adopt, improve, and/or implement new protocols, equipment, training and technologies to meet the ever-rising bar for risk reduction and regulatory compliance in HPAPI manufacturing. Continuous improvement is essential to sustaining safe operations, mitigating risk and attracting client opportunities.[4]

CONCLUSION

Finding a CDMO that can meet all of the above criteria can be a real challenge. To date, Ash Stevens has received fourteen FDA manufacturing approvals for innovator APIs, including four Fast Track projects. With a business model predicated on providing the safest and highest quality work product possible, while meeting delivery obligations on budget and on time, combined with the ability to provide expert regulatory and analytical support for all phases of drug development and commercialization, Ash Stevens has developed a reputation as a reliable full-service CDMO with the capabilities needed to manufacture specialized small-volume APIs, including highly potent and other complex drug substances under traditional and highly accelerated timelines.[4] P

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Dr. Stephen Munk has been with Ash Stevens Inc. since 1997, serving as President since 1998 and CEO since 2001. He is experienced in drug discovery, development and manufacturing, both as a scientist and as a manager. Prior to joining Ash Stevens, Dr. Munk worked at Allergan, Inc. as a drug discovery scientist and subsequently as the co-team leader of the adrenergic drug discovery team. Under Dr. Munk's stewardship, Dr. Munk is also an Adjunct Professor of Chemistry at Wayne State University and has served on the Board of Directors of MichBio.

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DESIGNING EFFECTIVE DRUG FORMULATIONS: KEYS TO SUCCESSFUL PROOF OF CONCEPT SERVICES

→ BY **ED SCHOLTZ, PH.D.**, UPM PHARMACEUTICALS

Increasing API complexity has created a need for innovative formulation solutions. To rapidly reach the formulation proof of concept stage, pharmaceutical companies frequently rely on outsourcing partners with extensive formulation development experience. Because the goal is commercialization, however, many sponsors prefer to work with contract development and manufacturing organizations (CDMOs) that can readily scale those proven formulations.

A comprehensive understanding of the properties of a drug substance – its solubility in solvents and buffer systems, compatibility with excipients, stability under different physiological conditions, solid-state characteristics, basic physicochemical properties, etc. – is necessary to select the most effective drug-delivery system and develop an optimal drug formulation, particularly for challenging and complex compounds that suffer from poor solubility or are highly potent. Preformulation studies offered as part of proof-of-concept services are designed to fully characterize the API and determine the dosage form and drug delivery system that will provide a safe, stable drug product with high efficacy.

Thorough preformulation studies can, however, be quite costly. Drug manufacturers are seeking service providers that can apply extensive experience with a broad array of compounds/chemistries to the design of comprehensive preformulation studies that include only relevant tests, as well as the selection of appropriate formulation technologies with the greatest potential for success.

Outsourcing to CDMOs that can take a project from the proof of concept stage all the way through to commercialization, thus eliminating the risk, time and cost associated with technology transfer and the need to manage multiple suppliers, is also increasing. Preferred service partners also continually invest in new equipment and facilities, provide dedicated project management support with personalized service, offer real manufacturing flexibility and focus on meeting customer milestones.

A STRONG DEVELOPMENT HISTORY

UPM Pharmaceuticals was founded as a formulation development company and has been providing development services for over 15 years. The company focuses on solid and semi-solid formulations and has extensive experience with many different types of APIs and solid/semi-solid dosage forms.

Once a project contract has been approved, UPM forms a dedicated project team that meets with the customer to understand the project goals and gather any available information on the API. These teams consist largely of scientists with Ph.D. or MS degrees that are extremely knowledgeable and focused on formulation science. They identify the analyses required to determine additional necessary information, and based on the obtained results, excipients and formulation/delivery technologies are suggested to the client.

Comparability studies using material prepared in minibatches (50- to 100-g scale) are then performed. Head-to-head comparisons of formulations that have different ingredients (except the API) help to quickly identify stable formulations. Throughout this process there is close cooperation between the analytical and development groups, which allows for the engineering of the optimum formulation that can be directly scaled to GMP clinical and commercial production.

CONTINUED INVESTMENT

Ongoing provision of innovative drug development and manufacturing solutions requires continual investment in advanced technologies, equipment and facilities. Recognizing the need of pharmaceutical customers for more rapid and cost-effective proof of concept services combined with GMP production capabilities, UPM moved from its original location in Baltimore, Maryland to a previous Pfizer manufacturing site in Bristol, Tennessee and invested over $12 million to expand production suites and modernize the facility, plus over $1 million to create a Solids Formulation R&D Facility.

The R&D facility includes a GLP laboratory with dedicated small-scale, state-of-the-art equipment identical to that used for GMP production of clinical and commercial material, allowing for easy scale-up. Capabilities include wet and dry granulation, particle size reduction, encapsulation, bi-layer tableting, granules and coating. HEPA filters, down-flow hoods, glove boxes, soft enclosures, advanced personnel protective equipment and a gowning room enable the handling of highly potent compounds. Three analytical laboratories for raw material, test method development, and in-process material and product testing provide support to the development lab. The facility also includes a dedicated R&D raw material warehouse and space for in-process material (with refrigerator/freezer capability and airflow, temperature and humidity controls) and equipment storage. Onsite maintenance support reduces the risk of equipment failure and project delays.

ONGOING PROVISION OF INNOVATIVE DRUG DEVELOPMENT AND MANUFACTURING SOLUTIONS REQUIRES **CONTINUAL INVESTMENT** IN ADVANCED TECHNOLOGIES, EQUIPMENT AND FACILITIES.

DIRECT SCALABILITY

The new Solids Formulation R&D Facility offers UPM clients several advantages. First, very small batches using 50 to a few hundred grams can be processed in the mini-scale equipment, allowing a large number of runs to be performed without consuming large quantities of expensive API that may be in limited supply. Secondly, because the equipment is the same as that used for clinical and commercial manufacturing, scale-up is facilitated, leading to both time and cost savings.

UPM's trademarked BREVI-BATCH® processing platform for solid dose mini-scale R&D formulation development targets batch sizes of 100 – 500 grams, a much smaller scale than typically found in R&D formulation development laboratories. In addition, the equipment is designed for easy setup, use and cleanup, and is small enough to allow processing of highly potent compounds under containment conditions.

During the formulation development process, approximately 10 mini-batches are run, with scalability and the availability and cost of raw materials considered from the initial formulation design stage.

UPM'S TRADEMARKED **BREVI-BATCH® PROCESSING PLATFORM** FOR SOLID DOSE MINI-SCALE R&D FORMULATION DEVELOPMENT **TARGETS BATCH SIZES OF 100 – 500 GRAMS,** A MUCH SMALLER SCALE THAN TYPICALLY FOUND IN R&D FORMULATION DEVELOPMENT LABORATORIES.

Notably, in some cases, batches can be run using as little as 25-50 grams of API. Use of the BREVI-BATCH® processing platform allows UPM customers to reduce the cost and time required to successfully complete the formulation development and proof of concept stages – increasing the likelihood of commercializing effective and innovative medicines and getting them to patients sooner.

DEDICATED PROJECT MANAGEMENT

Effective project management is essential for achieving the smooth progression of a project through the proof of concept stage, onward through clinical material production, and ultimately into commercial manufacture. At UPM, project managers are selected not only for their technical knowledge and expertise, but also the ability to effectively communicate and collaborate. Managers adopt an ownership approach and, along with the entire project team, stay with a project from the kickoff meeting through formulation development, proof of concept and all the way to commercialization.

MANUFACTURING FLEXIBILITY

UPM recognizes that the drug development process is unpredictable and the unexpected should always be expected. Accordingly, we have built in flexibility for addressing the challenges that arise. With daily scheduling meetings, UPM is able to quickly respond to changing client and market needs. We also have the operational capability to respond to unexpected manufacturing issues.

Technical flexibility is also essential for developing effective, safe, robust formulation solutions for the challenging drug candidates moving through the pharmaceutical pipeline today. UPM has extensive experience in drug delivery technologies that are appropriate for solid and semi-solid dosage forms. For those clients that wish to run phase I studies using capsules containing neat API, we have substantial capability for meeting their needs with four specialized filling machines. In our R&D facility, we also have a small-scale packaging line for bottles and can perform manual packaging processes for the production of 10-20 bottles for various studies. Plans are in place to install a small-scale blister packaging line as well.

PERSONALIZED SERVICE

Along with manufacturing flexibility, personalized service is highly valued by pharmaceutical companies looking for innovative formulation solutions for their complex and challenging APIs. Although a smaller CDMO, UPM is closer to larger, integrated service providers, offering not only proof of concept services, but also clinical and commercial manufacturing support – but with the personalized, responsive service of a well-funded, family-owned organization that emphasizes customer service and satisfaction.

In fact, UPM customers are treated like family too, with project teams operating as extensions of their businesses. Both team leaders and team members take a high interest in projects. Face-to-face interactions are a key component of our relationships with our pharmaceutical partners. President and CEO James E. Gregory is accessible to clients and very engaged with the business and concerned about meeting customer needs for the rapid development of high-quality, cost-effective, innovative formulations and delivery solutions.

MEETING MILESTONES

While clients recognize that formulation development and scale-up to clinical and commercial manufacturing rarely proceeds without some unexpected challenges, they still expect projects to be completed on time. The most successful CDMOs offering proof of concept services have a track record of consistently meeting client milestones on time and within budget. UPM is one such service provider. We focus on deliverables: meeting customer milestone timelines, such as for producing high-quality, on-spec clinical supply materials and completing regulatory filings. That means performing the work that needs to be done to move projects forward as rapidly and smoothly as possible.

UPM's dedicated team of technical and manufacturing experts have nurtured projects starting from the proof of concept stage, clearly demonstrating our extensive expertise in early-stage formulation development and commercial production for solid and semi-solid oral dosage drugs, including immediate and controlled release products. P

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Dr. Scholtz is responsible for UPM's Research and Development Division. He also personally manages numerous formulation and development projects. Prior to joining UPM, Dr. Scholtz enjoyed 22 years working in various sophisticated scientific and management positions for Merck & Company. These positions included site automation compliance, worldwide quality assurance, manufacturing division regulatory compliance, and pharmaceutical R&D leadership on large, complex, new-product formulation/process development project teams. He received his BS degree in pharmacy from the University of Pittsburgh, an MS in pharmaceutical sciences from the same institution, and his Ph.D. in industrial and physical pharmacy from Purdue University.

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CAPSUGEL'S TRANSFORMATION

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

That's Nice checked in with Guido Driesen to inquire about Capsugel's ongoing transformation, the brand's latest service offerings and drug development in general.

Q1 Most industry followers know Capsugel for its leadership in hard capsules, but your company has become much more than that, hasn't it?

It absolutely has. Throughout our history, Capsugel has been at the forefront of innovation in hard capsules and polymer science, and we have built great relationships with customers in the biopharmaceutical and consumer health and nutrition industries. Over the past few years, we saw several opportunities to offer our customers even more – to complement our capsule engineering know-how and establish ourselves as a leading global provider of technology platforms for the design, development and manufacture of a wide range of innovative dosage forms. During that time, we have made four strategic acquisitions, invested in enhanced capacity and capabilities and launched new technology platforms – making us an even stronger, more differentiated partner for our customers.

We are also taking steps to develop shared capabilities across our global network so that our customers receive more localized access to our broad range of technologies and services. This includes initiatives currently underway to expand our capabilities in spray-dried dispersion, micro-dosing and specialty polymers across multiple product development sites.

Q2 What are some of the trends driving drug development in general and the role that CDMOs like Capsugel will play in the pharma industry?

The biopharmaceutical industry is continually challenged to accelerate the pace of discovering and developing novel products that will help improve people's lives. That's why our customers are looking to partner with companies such as Capsugel that possess a fundamental understanding of APIs that comes from advancing thousands of drug compounds, predictive models and expert systems for selecting optimal enabling technologies.

Another important challenge is lifecycle management, and we are working with a growing number of generic and specialty companies, as well as larger companies, who are seeking line extensions or product enhancements. This has led to several formulation-driven innovations that are enabling our customers' products to better serve the needs of patients and consumers.

And of course, we continue to see a shift away from blockbuster drugs toward specialized products with smaller volumes and more complex formulations. These innovations require seamless integration from early development to commercial supply.

Q3 What can you tell us about the new corporate brand campaign that Capsugel has launched?

That's Nice and the Capsugel team spent several months gathering insights from customers and partners to better understand their needs and the ways in which they perceive Capsugel as standing apart from other CDMOs. We found that while the Capsugel brand was very strongly associated with capsules, as well as with deep scientific knowledge and product engineering know-how, customers were not always aware of our expanding number of offerings and capabilities in other drug-delivery technologies.

Based on these insights, we recently launched our new brand campaign centered on the theme of "Engineering Medicines to Life." The campaign is designed to amplify Capsugel's position as a differentiated, specialty CDMO partner with the ingenuity, credibility and flexibility to tackle any product delivery challenge in collaboration with our customers. It also brings all parts of our organization under one name, and allows us to use the Capsugel brand to represent our full, integrated offering. P

→ **ABOUT THE PANELIST**

Guido Driesen
President and CEO,
Capsugel

Having joined the company in 1983 and serving as President since 2001, **Mr. Driesen** has led Capsugel through an exciting transformation since becoming its President and CEO, following KKR's acquisition of the company from Pfizer in 2011. His three-plus decades of experience in the pharmaceutical industry includes various leadership roles spanning Operations, Quality, Country GM and Regional VP. He holds a master's degree in engineering from the Catholic University of Leuven, Belgium, and a bachelor's degree in economics.

CAPSUGEL – EVOLVING A STRONG BRAND

→ **REVIEWED**

NEW BRAND POSITIONING FOR **CAPSUGEL**

Capsugel is the type of brand that is not to be trifled with. The company has been around in some shape or form for almost a century. Over the last 30 years, it didn't just become the leader in capsules and encapsulation – it became the leader by some considerable margin. It was owned by Pfizer, and has gone from strength to strength since spinning off five years ago. It manufactures 200 billion capsules a year and serves over 4,000 customers. The majority of people that make or fill capsules do so with Capsugel products on Capsugel equipment. It is respected. To reiterate – it is a powerful brand and changing it should be done lightly.

Therein lies the challenge. Capsugel itself had been visionary and recognized that while its capsule and encapsulation engineering expertise had carved out a very strong business, future opportunities lay in integrating that know-how and the company DNA with formulation services and the ability to design, develop and manufacture dosage forms. A series of acquisitions between 2013 and 2016 provided technology assets and complementary expertise that provided this capability, with strong positions to tackle bioavailability enhancement and targeted delivery.

→ WWW.CAPSUGEL.COM

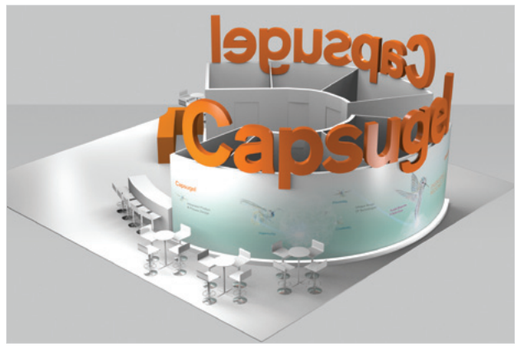
MARKET RESEARCH

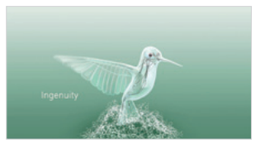
An extensive research project was undertaken – involving internal stakeholders worldwide, customers, and a target audience across the spectrum of traditional and new services – to measure the equity found in perceptions of the Capsugel name, identity, brand associations and acquired brands. The decision was made to stick with the Capsugel name but to develop a strategy to migrate perceptions of the business with new visuals and messaging. When a brand is so strong and so heavily associated with one historical service line, it can require a shock strategy to initially elicit recognition that there's change – before messaging drives absorption of the new positioning.

When a brand is so strong and so heavily associated with one historical service line, it can **require a shock strategy** to initially elicit recognition that there's change — before messaging drives absorption of the new positioning.

STRATEGY

While we saw the need for a quantum shift in perception, we also recognized that messaging had to clarify that Capsugel's expanded offering still embodied the company DNA – science and engineering expertise, ingenuity, credibility and flexibility. We had to be careful with the messaging. So we devised the idea to do the attention-grabbing with evolution in the visual side of the brand.





Capsugel®

BRINGING IT TO LIFE

Conceptually, we had explored the idea of interpretations of incredible engineering in nature. Visuals explored the natural engineering that gives a hummingbird its unique characteristics. This became key art, with the engineered bird emerging from a matrix made up of fragmented chemistry symbols. The tagline, Engineering Medicines To Life, conveys the position of being able to design today's personalized medicines to meet target profiles, while also complementing the image in conveying actually bringing them into existence for the people that need them.

Following rollout into the public domain just prior to and during CPhI 2016, the careful but impactful evolution of the brand continues. There's a new logo and colors, although both show respect for the legacy. Website updates, advertising, booth presence, video, literature, sales presentations and PR all contributed to its launch. This will extend to full implementation – including building signage, packaging and all global marketing – within a year. P

EQUIPMENT REDEPLOYMENT'S STRATEGIC ROLE

BY **ADAM COVITT**, FEDERAL EQUIPMENT COMPANY

In the post-blockbuster era, pharma's major manufacturers are under pressure to increase the cost efficiency of their manufacturing operations and extend the service life of their processing equipment. Equipment investment recovery strategies that include a well-planned and executed redeployment process and the right partners can add flexibility and extend asset utilization across geographically dispersed operations.

Over the last decade and well into the post-blockbuster era, the industry's most prominent drug manufacturers have been working to align their internal manufacturing facilities and equipment to be more flexible and cost effective. Many of the major drug companies are fueling real change in this area, consolidating their plants in one country or rationalizing operations and equipment in a different region to exploit emerging market opportunities or improving economic circumstances. Although CDMOs are playing a more strategic role in pharma's supply chain, most major drug companies continue to field multiple manufacturing sites to bring their core products and class- or market-leading drugs to market.

According to posted statistics on their websites, among the top 10 drug makers listing their manufacturing assets, J&J operates 139 manufacturing facilities, Novartis ~100, Roche 20, Pfizer 55, Sanofi 100 and Merck 58. Pfizer, for example, says its Global Supply Network is aligned to serve 175 markets and provides fast, flexible solutions across the full manufacturing and supply-chain spectrum. The company's global strategy hinges on extending the flexibility and value of their supply chain throughout their network of plants and facilities.

Similarly, excipient and fine-chemical producers serving the pharmaceutical industry field extended manufacturing networks to efficiently supply their customers. BASF North America, a leading excipients manufacturer, says it has approximately 100 production and research and development sites throughout North America and operates Verbund sites in Geismar, Louisiana and Freeport, Texas.

EQUIPMENT COST RECOVERY

Drug manufacturers of the scale described previously are constantly analyzing the value and performance of manufacturing assets to assess their manufacturing network's ability to contribute to the company's overall strategic and commercial direction. Most will agree that the capacity pharma companies like J&J or Novartis operate in a constant state of flux. On a more granular level, the same is true for the processing lines and equipment-processing product on the manufacturing floor.

At commercial scale and across a 50-facility network or greater, the investment in manufacturing technologies is staggering, well into billions in capital and other sunk costs. Manufacturers, or at least their equipment and procurement teams, are seeking better ways to get the most return on capital equipment spend and contribute to the cost-control and investment recovery efforts of the company. All it took to get the equipment investment recovery movement started was one astute person in procurement at a major pharmaceutical company seeking to maximize the return on equipment by offering companies like us this simple premise: "I want to be able to internally redeploy my equipment. If not, I would rather maximize my returns by marketing directly to end users and getting more money for my equipment."

Since then, the idea has caught on, and many of the major industry players are implementing or plan to implement equipment cost recovery initiatives, including Pfizer and BASF North America, who both operate internal programs managed by Federal Equipment Company. A 2016 study on pharmaceutical equipment by Nice Insight surveyed procurement managers and other operations leadership (46% representing large pharma) with equipment-specifying and purchase authority. The study found 69% pursue equipment investment recovery programs. This group also identified reasons equipment becomes surplus, selecting outdated/obsolete or purchasing upgrades as primary reasons (39% and 39% respectively). A similar portion (34%) also cited "Change in production/packaging capability" as another popular reason equipment at their sites has become surplus.[1]

The reality is that there are a range of reasons equipment at one site can become idle and a target for internal transfer to another site. A common scenario is a major pharma manufacturer may be shutting down a line, or is transferring a product line to another site or to a CMO; this creates surplus, idle equipment. For example, a major producer in California has a process line that they have shut down. One of the company's other facilities can use it. Doesn't it make sense that the best possible use of this equipment is to transfer it internally – whether to extend the production of a current product at another plant or introduce a new product at a more strategically located facility?

BETTER COMMUNICATION REQUIRED

Managing extended global supply chains effectively has become a real art as well as a science, and most major pharmaceutical companies have invested heavily implementing enterprise resource planning platforms, automation technologies and the IT infrastructure to interconnect manufacturing facilities – exchanging data across the enterprise and sharing

operational metrics to manage it all. In Federal Equipment Company's experience, while some major pharma companies are quite good at sharing operational data among the facilities in the field, they're often less successful sharing the inventory, availability and location of idle equipment in their manufacturing networks, even though they have established it's the right thing to do. From Federal Equipment Company's point of view, the industry's track record of sharing basic equipment information, applying resources and putting necessary structure and organization to the effort can be improved and suggests that to get the most from an equipment investment recovery effort, companies should engage the experience of companies like Federal Equipment Company to oversee and facilitate the internal transfer or sale of equipment. That means the plant manager in Texas can go to his computer and look for the 1,000-gallon water-for-injection tank he needs, and seeing that there are two idle ones at the plant in Ireland, he places his order and Federal Equipment Company does the rest.

The best possible way to extend a piece of idle equipment's institutional value is to extend the equipment's service life supporting manufacturing strategy elsewhere within the company's manufacturing network. Beyond just inventory, Federal Equipment Company facilitates the entire process, building an inventory database and providing the basic tools and communication channels that plant and processing line managers need to successfully identify, locate and transfer equipment internally. Federal Equipment Company staff creates an internal database, supplies logistics support and provides access to a broad range of technical services from original equipment manufacturers (OEMs). The Federal Equipment Company team also provides mechanical and electrical services to make internal transfers as seamless as possible. Further, commissioning and validation are much faster because all the original data has still been retained.

EQUIPMENT STRATEGY BEYOND COST RECOVERY

An equipment investment recovery strategy can serve to support effective supply-chain strategy and new ways to leverage the value of equipment across a large network of internal plants, as well as those of contract service providers. To extend their supply-chain flexibility and hedge against supply disruption and similar risk, major drug companies often shop their product and process and hire a contract manufacturer to run their products in their facilities. Imagine the benefits if a drug owner had the means to efficiently transfer the processing line over to its contract supplier while retaining ownership – a broad range of risk and associated complexity might be avoided. Another possibility is to effect the transfer of the equipment and its ownership to the CMO and secure credits or other compensation in trade.

NOT A FIT AFTER ALL

Obviously, not every piece of equipment can find a new home internally. Equipment can become functionally obsolete to the owner even though it still functions as designed. For example, a manager may be implementing broad process cost-efficiency strategy and switching from a hard-piped dedicated pressure vessel to a single-use system to meet his objectives. Most pharma manufacturing operations concentrate on making the highest-quality product faster and at the lowest cost. Rarely do operations managers have the time or resources to sell equipment and put in the effort needed to recover as much investment as possible. The value of this service should not be underestimated. The market for used equipment is a multifaceted and dynamic space. Federal Equipment Company's history and reputation in the industry continues to be supported by the close relationships it maintains with all significant pharmaceutical manufacturers. Further, our association with OEMs and other suppliers helps put buyer together with seller quickly and then facilitates the close of these sales with the same services associated with internal transfers.

> THE BEST POSSIBLE WAY TO EXTEND A PIECE OF IDLE EQUIPMENT'S INSTITUTIONAL VALUE IS TO **EXTEND THE EQUIPMENT'S SERVICE LIFE SUPPORTING MANUFACTURING STRATEGY ELSEWHERE** WITHIN THE COMPANY'S MANUFACTURING NETWORK.

For major pharmaceutical manufacturers operating globally diversified manufacturing networks, internal transfer and equipment disposition that supports investment recovery is becoming an attractive standard operating procedure. But to be effective, an internally created equipment-management effort may fall short, unable to secure enough return from the program to justify the effort. An external partner with expertise in all aspects of equipment sale and transfer, like Federal Equipment Company, can offer the resources and experience to field a more effective and lucrative equipment investment recovery strategy. P

→ ABOUT THE AUTHOR

Adam Covitt
Vice President, Federal Equipment Company

Adam has over 19 years of experience in the pharmaceutical and chemical process and packaging industry, with a focus on investment recovery and the purchase and sale of high-end equipment to major pharmaceutical sites and contract manufacturers with a global footprint. Mr. Covitt earned a bachelor's degree from Ohio University in Athens, Ohio.

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IN CONVERSATION

THE IMPORTANCE OF FLEXIBILITY: COMPETITIVE SOLUTIONS IN AN ERA OF INNOVATION

→ BY **GUY TIENE**, NICE INSIGHT

NICE INSIGHT IS IN CONVERSATION WITH UWE HARBAUER, SENIOR VICE PRESIDENT, PHARMA BUSINESS UNIT, BOSCH PACKAGING TECHNOLOGY, TO DISCUSS HOW EQUIPMENT SUPPLIER/PHARMA COMPANY RELATIONSHIPS HAVE CHANGED OVER TIME, INCLUDING THE GROWING IMPORTANCE OF LONGER-TERM, MORE STRATEGIC INTERACTIONS.

The pharmaceutical industry has been experiencing significant change in recent years, and the relationships between equipment suppliers and their pharmaceutical manufacturing customers have not been immune. In this era of innovation, drug makers expect equipment manufacturers to provide much more than pieces of machinery – they expect comprehensive solutions that help support all aspects of manufacturing, from achieving competitive costs and production timelines to meeting regulatory compliance requirements.

NEED FOR HIGHER EQUIPMENT PRECISION AND FLEXIBILITY

In the past, most pharmaceutical manufacturers produced large batch sizes on robust equipment and expected equipment suppliers to meet their very detailed user requirement specifications, according to Uwe Harbauer, Senior Vice President, Pharma Business Unit, Bosch Packaging Technology. A lot has changed since then, not only in terms of drug development, but also regarding project planning, expectations and the role of equipment manufacturers. “We are no longer solely delivering single machines. Our customers expect us to deliver complete solutions that provide much more than mere technical or mechanical expertise,” he explains.

“WE MUST BE ABLE TO ANSWER QUESTIONS SUCH AS ‘WHAT WILL REGULATORY CHANGES MEAN FOR OUR CUSTOMERS’ PRODUCTION PROCESSES?’ ‘WHICH EQUIPMENT NEEDS TO BE MODERNIZED OR UPGRADED?’ AND ‘HOW CAN EXISTING PROCESSES BE IMPLEMENTED WITH NEW GUIDANCE?’”

BOSCH INNOVATION

The power of innovation is one of the major characteristics of Bosch Packaging Technology. As a driver of innovation, we offer pioneering technology. Our portfolio to customers ranges from planning and individual machine design, including all preliminary stages through to service requirements – leading technologies and solutions all the way.

What has driven this important change in the role of equipment suppliers? In part, the need for ever-higher precision and flexibility of equipment. "Smaller batch sizes and different packaging types are required for biopharmaceuticals and personalized medicine. Drug manufacturers expect the same flexibility from their suppliers. In addition, our customers want a partner along their value chain and throughout their projects," says Harbauer.

Moreover, the interconnection of machines, lines, processes and IT is becoming more and more important. He notes that this connectivity and flexibility is easiest to find with a partner that can deliver everything from a single source. "At Bosch Packaging Technology, we recognized this trend at an early stage and have been expanding our portfolio ever since through internal innovation, acquisitions such as Eisai Machinery in 2012, and joint ventures – for instance – with Klenzaids in 2015."

EXPECTATIONS FOR IN-DEPTH KNOWLEDGE

While having specific drug expertise will always remain the key competence of pharmaceutical companies, drug manufacturers increasingly expect their suppliers to have in-depth knowledge about filling, isolating, packaging and the like, as well as which product characteristics demand which type of solution, according to Harbauer. "Our job has evolved from an equipment expert to the role of consultant; we are responsible for finding the optimum solution for a specific product – a role we identify with very well."

For instance, Bosch focuses on knowing the different markets and regions, being up-to-date with all regulatory requirements, identifying new trends and remaining in constant contact with its customers. "Apart from our standard portfolio," Harbauer asserts, "we need to be able to deliver customized line concepts for any kind of pharmaceutical requirement. That's what makes us the ideal partner for all pharmaceutical needs and a true full-range solutions provider."

He adds that next to Bosch's machinery know-how, the company also offers its customers comprehensive pharma services in its laboratories. Customers receive advice and support in formulation development, process design and equipment use. "With a large range of after-sales services such as modernization, maintenance and training, we further support customers to flexibly adapt their existing machines and lines to future market requirements," notes Harbauer.

"Our goal is to support our customers in bringing successful drugs to the market that help save lives. We don't just work with them on a project basis; we care about their pharmaceutical products, the entire lifecycle of their lines, their needs and, in the end, about their success," he continues. As a result, the customer relationship does not stop when Bosch delivers a piece of equipment. The company's focus on Overall Equipment Effectiveness (OEE) is integral to this approach. "The goal is to further achieve systematic optimization for our customers. Every percentage we manage to raise the OEE is a valuable success – and we have achieved this more than once in joint customer projects," he observes.

In fact, Bosch has many long-lasting relationships with its customers, working together on long-term projects that include consulting, planning and development, and expand beyond the scope of implementation. One such relationship is with a leading contract manufacturing organization (CMO). Nearly all of the CMO's equipment is from Bosch, and the two companies have been working closely together for many years. In one joint project, a machine concept to address the scalability of a filling device for liquid pharmaceuticals was developed based on the user experience approach. The equipment was built and then installed and tested at the customer's facility. It is currently used for many different projects, providing highly relevant data and easy scale-up of their operations, according to Harbauer.

EVOLVING WITH THE CONTRACT SERVICES SECTOR

The role of CMOs and contract development and manufacturing organizations (CDMOs) is expanding significantly as drug manufacturers increase their reliance on contract service suppliers throughout the lifecycle of new and existing drugs. "CMOs and CDMOs have experienced tremendous growth as more and more processes are being transferred to their facilities. As a result, they no longer simply fill drug A into packaging B and put this packaging into a folding carton; their equipment requirements are sometimes even more diverse than those of a large drug producer because they have an even larger project variety," Harbauer observes.

> GOVERNMENTS, PAYERS AND PATIENTS ARE LOOKING FOR DRUGS THAT PROVIDE SIGNIFICANT IMPROVEMENTS IN HEALTH AND QUALITY OF LIFE, COMPARED TO EXISTING PRODUCTS, WHILE BEING EASIER AND MORE CONVENIENT TO ACCESS AND ALL AT A LOWER COST.

On the one hand, CMOs/CDMOs require dedicated lines that are tailored exactly to one single customer product. On the other, they also need highly flexible lines that are able to run different products from different customers. "These dual needs demand the highest possible flexibility combined with fast changeover, cleaning and validation times," he says.

SUPPORTING REGULATORY COMPLIANCE

Proactive compliance is key to successful manufacturing operations. Monitoring the regulatory environment and supporting its customers at very early stages of their projects, or even before they start, is an integral part of the company's regular consulting activities, according to Harbauer. He points to the revision of USP General Chapter 1207 on Container Closure Integrity, EU GMP Annex 1, and the different national guidelines on serialization as key examples of newer regulations that are impacting Bosch's customers.

"Knowing the market and regulatory requirements is part of our everyday business," he asserts. "We must be able to answer questions such as 'What will regulatory changes mean for our customers' production processes?' 'Which equipment needs to be modernized or upgraded?' and 'How can existing processes be implemented with new guidance?' By constantly asking ourselves these questions and by participating in discussions and dialogue, we are able to offer our customers solid advice. Our experts know exactly what is happening and can incorporate this knowledge into all projects and equipment developments."

> WHAT HAS DRIVEN THIS IMPORTANT CHANGE IN THE ROLE OF EQUIPMENT SUPPLIERS? IN PART, THE NEED FOR EVER-HIGHER PRECISION AND FLEXIBILITY OF EQUIPMENT.

FACILITATING PATIENT-CENTRIC DEVELOPMENT STRATEGIES

Changing expectations for new drug products are also impacting pharmaceutical industry innovators, contract service providers and equipment suppliers. Governments, payers and patients are looking for drugs that provide significant improvements in health and quality of life, compared to existing products, while being easier and more convenient to access – and all at a lower cost. As a result, patient-centered development strategies are now an important component of most drug development programs. Equipment manufacturers have a role to play here, too.

"Faster time-to-market, easier scale-up, the highest product quality and OEE – these are some of the demands on the agenda when Bosch builds equipment. By offering our customers fast consulting and straightforward solutions, we support them in achieving their strategic goals. With our large base of experts, we are able to deliver specific solutions for high-quality products, for instance with zero product loss, sophisticated containment and isolator technology," states Harbauer.

With respect to the development of patient-oriented medical devices, he notes that Bosch supports its customers through the development of novel technologies, such as those for the assembly of pens and auto-injectors. "The solutions we have provided our pharmaceutical customers enable them to meet patient requirements for safety, convenience and adherence, as well as support them in living healthier lives," Harbauer concludes. P

→ ABOUT THE PANELIST

Uwe Harbauer Senior Vice President, Pharma Business Unit, Bosch Packaging Technology

Uwe Harbauer graduated in mechanical engineering and started working for Bosch Packaging Technology in 2000. He draws on many years of experience as head of sales of the pharma business unit, and as Senior Vice President in charge of customer service, before he took on his current position as Senior Vice President, Pharma Business Unit at Bosch Packaging Technology in Crailsheim, Germany, in 2013.

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INNOVATION

Creating Solutions for Healthcare's Ambitious Agenda

STEVE KUEHN, **CYNTHIA CHALLENER, Ph.D.**, **EMILIE BRANCH**, **CARRIE CAO, Ph.D.** AND **JOHN BRAY**, NICE INSIGHT

Society is increasingly expecting better performance from the world's healthcare systems, public or private. This translates into a demand for better access to more therapeutically effective care at the lowest price possible, with little tolerance for any negative outcomes, especially by the world's regulators and politicians.

Pharmacological supply chains within the industry – including those of drug owners as well as developers; contract research, development and manufacturing organizations; equipment suppliers and more – have ambitious agendas to successfully meet and profitably deliver the social demand for more healthcare value per fixed dollar spent through innovation.

INNOVATION FEATURE PART 1

Automating Drug Discovery's Next Breakthrough

Contemporary, successful drug innovation springs fundamentally from a well-managed R&D effort, one increasingly reliant on automation, robotics and high-throughput analytical tools to identify the highest-potential targets quickly and efficiently.

Drug innovators' ability to create novel life-changing pharmaceuticals relies heavily on a diligent, sophisticated and multidisciplinary discovery process. Scientific advancements in the understanding of the human body and diseases, along with continued adoption of breakthrough technologies like high-throughput screens (HTS), have dramatically transformed the landscape of modern drug discovery. Novel science and technologies are constantly reshaping this field with exciting, innovative research ideas and discovery tools.

HIGH-THROUGHPUT SCREENS AND LABORATORY AUTOMATION

Drug discovery starts by selecting a validated biological target, typically a gene or a protein underlying the disease being studied. The groundbreaking work in understanding the pathogenesis of diseases at a molecular level is often accomplished via academic research laboratories and then published to enrich public scientific knowledge.

Once a target is validated, the search begins for a lead compound – either an organic compound or other drug molecule – which can interact with the target and modify its function. Ideally, the lead molecule will alter the disease course without affecting any off-target molecules. This process involves the generation of lead compounds and cycles of lead optimization, pharmacokinetic profiling and toxicity testing.[1]

High-throughput screens, a critical element of modern drug discovery, are playing a major role in identifying lead compounds. Introduced to the discipline in the mid-1980s, this innovative technology was expanded significantly in the 1990s with an array of technological innovations that allow HTS to screen a large number of compounds (millions) against the drug target in a timely and cost-effective manner.

This array of innovation includes parallel synthesis/combinatorial chemistry (the technique for rapid generation of every possible variant of a parent compound, physically or virtually); automated high-performance liquid chromatography to purify products of combinatorial synthesis; and especially lab automation to improve the efficiency of HTS and streamline the drug-discovery workflow.

With the aid of automated technology and equipment, screening millions of compounds for leads becomes attainable and economical. Lab automation accelerates the speed of performing large-scale sample analysis with a high degree of reproducibility and accuracy, as well as eliminating some of the tedium of manual lab work. A broad range of routine laboratory procedures, such as chromatography, mass spectrometry, and DNA and peptide synthesis, can be conducted by semi- or fully automated instruments.[2]

In addition, automation is critical in achieving assay miniaturization. This has become an important feature of HTS in response to the increasing number of chemical compounds and molecular targets. Miniaturized assays, such as microarrays, shorten the throughput screen time by using small volumes of samples and reagents, while improving screen efficiency and reducing costs.

This technology requires precise liquid handling within the range of microliters or even nanoliters. Through the facility of automation, such small-quantity liquid measurement and dispensing can be accomplished by advanced liquid-handling instruments using robot arms. Some of these instruments offer real-time dispense verification and independent pipetting control, ensuring precise and accurate liquid dispensing. They can also function as an integral part of a fully automated system.[3]

An emerging trend in lab automation is to fully automate drug discovery workflows through "robotic researchers" that apply advanced machine learning and artificial intelligence.

ALL ABOUT EVE

An emerging trend in lab automation is to fully automate drug-discovery workflows through "robotic researchers" that apply advanced machine learning and artificial intelligence. One such system is Eve, a collection of computers connected to instrument automation. Eve combines three separate parts of the drug-screening pipeline into a systemic and integrated process, thus streamlining compound screening, hit validation and analysis. Eve's developer, professor Ross King (University of Manchester, U.K.), believes that the tool will have a lasting influence on the efficacy of drug discovery, given its ability to intelligently respond to a hit with instantaneous analysis rather than after the screening.[4]

The demand for high testing accuracy and reproducibility is the main driver for a robust drug-discovery laboratory automation system market ($4.1 billion in 2014). As well as large testing volumes and new drug-discovery technology adoption, laboratory automation systems cover almost every aspect of the discovery process, including liquid handling, plate readers, dissolution testing, storage retrieval, laboratory information management systems and robotic systems.[5]

COMPUTER-AIDED DRUG DISCOVERY/DESIGN (CADD)

In addition to the traditional experimental approach, computer-aided drug discovery (CADD) forms an important branch of modern drug discovery and is broadly used to facilitate and expedite hit identification, lead selection and optimization. Availability of a variety of databases (i.e., chemogenomics, pharmacogenomics, protein data banks and therapeutics target databases), improved computer processing power and information technology are fundamental to the CADD approach.

CADD can be classified into two broad categories. The first is the structural-based design of new molecules centered on the desired binding to a target. This approach applies the 3D structural information of a target (i.e., a protein) to reverse engineer suitable

SUCCESS RATE OF A DRUG FROM PHASE I TO MARKET APPROVAL

binding molecules through simulated docking. The other is ligand-based design, which focuses on developing new molecules based on known active or inactive ligands against a target through ligand chemical-similarity modeling.[6] A variety of algorithms can be used to facilitate these two approaches.

The most common use of CADD is to perform virtual high-throughput screening over simulated compound libraries by structure-based, ligand-based or combined methods.[7] Another important application of CADD is *de novo* drug design, in which novel compounds are developed from starting molecules with demonstrated activity by adding one functional group at a time or piecing together fragments into novel chemical entities using construction algorithms. In addition, comprehensive algorithms have been used to predict a drug's ADME (absorption, distribution, metabolism and excretion), related properties and potential toxicity. MetaSite software for example (Molecular Discovery Ltd., Middlesex, U.K.), also offers in silico structure modification to improve the metabolism profile of the lead compounds.[7]

PRECISION RESEARCH MODELS FOR BETTER OUTCOME PREDICTION IN HUMANS

One challenge facing drug discovery is to predict an investigational drug's pharmacological and toxicological behavior in humans based on the results of *in vitro* and animal testing. To increase effectiveness, drug innovators must improve their ability to predict failure and reject drug candidates as early as possible.

According to a study led by the Director of Economic Analysis at Tufts Center for the Study of Drug Development, Dr. Joseph A. DiMasi, the success rate of a drug from phase I to market approval is approximately 11.83%.[8] Unacceptable toxicity, lack of desired result and disappointing pharmacokinetics (i.e., ADME) are the main reasons for drug failure.[9] Just a 10% improvement in predicting failures before clinical trials can translate into savings of up to $100 million on development costs.[10]

To meet this challenge, precision research animal models are created by inserting human genetic components into an animal model or by engrafting human cells, tissue or tumor cells to the immunodeficient mice to mimic human organ systems or diseases.[10] Due to their "humanized" features, these models address the species-difference issue that plagues traditional animal models, improving the reliability in predicting human outcomes with respect to effectiveness and safety. Precision research models are commonly employed to mimic an array of human disorders.[10] The hPXR/CAR/CYP3A4/2D6/2C9 mouse is currently the most genetically humanized model available, with 33 human genetic counterparts substituting the mouse's own genes. This model is used in predicting induction and inhibition of human cytochromes and drug-drug interactions.[11]

Another exciting advancement in this area is the emergence of 3D bioprinted human tissue models. The leading technology, exVive3D™, was developed by Organovo for preclinical testing and drug discovery research.[12] The company's first commercial product – exVive3D Human Liver Tissue – is generated by depositing groups of patient-derived living cells in precise layers by a 3D printer. One significant advancement offered by the living 3D liver tissue is a longer functional and stable period compared to standard 2D liver cell cultures.[13] Unquestionably, the 3D bioprinted human tissue models are powerful research tools to assist in understanding a particular disease and treatment. P

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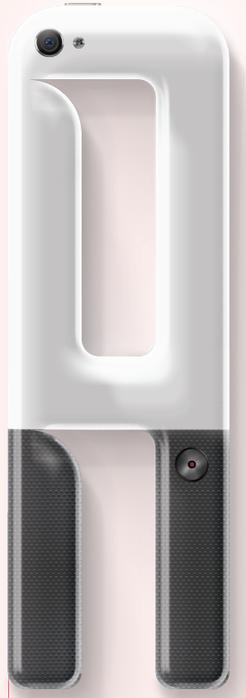
INNOVATION FEATURE PART 2

New Forms of Outreach and Improving Clinical Trial Recruitment and Data Integrity



s the cost of drug development continues to mount in unison with the demand for safer, more cost-effective drugs, the pharmaceuticals market is in need of innovation in clinical trial management and design to keep pace with the demand for more effective trial data.

There's no dispute that total life-cycle costs of developing a drug are high; these costs continue even post-approval, with approximately $312 million in R&D costs required to support drug products after they have been accepted into the market.[1] With clinical trials being one of the largest contributors to these costs, improving trial efficiency and the quality of the data is a priority for the industry as outsourcing trials and related services has proven valuable.

According to the 2016 Nice Insight Clinical Research Outsourcing Survey, 56% of respondents reported spending more than $50 million annually on

In 2013, The Pew Internet Project found that 59% of adults in the U.S. use the internet to search for health-related topics.

outsourcing, with 18% spending in excess of $100 million.[2] Additionally, 76% of respondents reported outsourcing clinical trial services.[2] However, as clinical trials continue to demand an increasing level of competence, with sponsors turning to CROs for trial expertise, there is a competitive imperative among potential outsourcing partners to provide new, innovative solutions to clinical trial challenges, which continues to trouble the industry. One of the most significant challenges occurs before these trials even begin, when researchers attempt to recruit participants – a process that can become costly and time-consuming.

SUPPLEMENTING RECRUITMENT WITH SOCIAL REACH

Historically, trial recruitment has been a challenge and, despite technology, remains as such. A recent study published in PLOS ONE found that nearly 60% of researchers surveyed failed to meet recruitment targets – a problem that can impact the statistical significance and overall success of a trial – or required additional time to meet these targets, delaying development and increasing cost.[3]

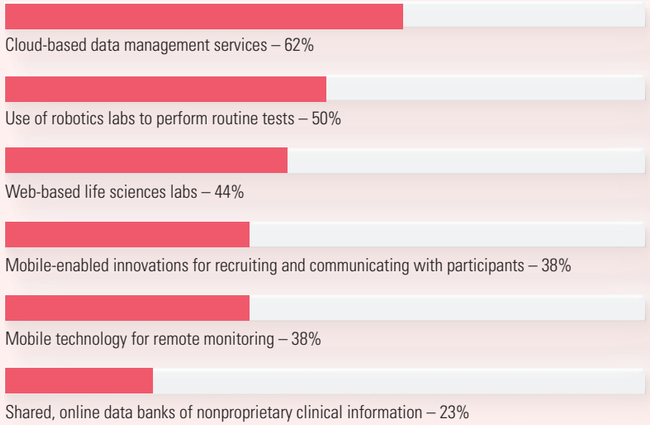
Another review, conducted over eight years, found that "only 31% of multi-center randomized controlled trials achieved their original recruitment targets in a timely manner."[5] Technological advancements can help to improve outreach and engagement in this area, and may help to explain why 38% of respondents felt that mobile-enabled innovations for recruiting and communicating with participants presented a great opportunity for cost and/or time savings in Nice Insight's Annual Pharmaceutical and Biotechnology Outsourcing Survey 2015. Just one year later, 48% of respondents reported outsourcing services related to clinical trial recruiting.[2,4]

The immediacy of communication and the massive reach made possible with social media and digital communication can prove beneficial here, with the PLOS ONE study also finding that supplementing traditional recruitment practices with social media led to a 12-fold increase in recruitment for phase II of the trial in question (as compared to phase I, which only recruited within traditional channels).[3] With that, all related social efforts were responsible for approximately 78% of recruitment during the second phase.[3]

→ **OFFERINGS THAT COMPANIES ACQUIRE OR PLAN TO ACQUIRE FROM CROS FOR CLINICAL TRIAL SERVICES NEEDS**

	TOTAL	BUYER CATEGORIES			
		BIG PHARMA/ BIOTECH	MID SIZE PHARMA/ BIOTECH	SMALL PHARMA/ BIOTECH	EMERGING PHARMA/BIOTECH
Clinical Trial Design	54%	54%	56%	43%	58%
Clinical Trial Phase I/IIa	51%	50%	57%	41%	42%
Clinical Trial Phase II/III	51%	50%	58%	41%	37%
Clinical Trial Data Management	50%	50%	53%	49%	32%
Clinical Trial Recruiting	48%	50%	48%	41%	47%
Clinical Trial Project Management	42%	41%	47%	35%	29%
Clinical Trial Phase IV	38%	36%	43%	31%	29%
Clinical Trial Monitoring	37%	39%	37%	31%	37%
Clinical Trial Material Temperature Controlled/Cold Chain Logistics	36%	36%	36%	41%	21%
PK/PD (Pharmacokinetics/ Pharmacodynamics)	34%	31%	38%	25%	40%
Bioequivalence	28%	28%	30%	21%	24%
Clinical Trial Supplies/Storage/ Logistics/Distribution	24%	25%	23%	21%	24%
Bioavailability	23%	23%	23%	24%	21%
None	1%	-	0%	1%	5%

→ **THE GREATEST OPPORTUNITIES FOR COST AND/OR TIME SAVINGS WHEN IT COMES TO CONTRACT RESEARCH**



In addition to extensive reach, recruitment via social media is more cost effective in terms of both paid advertising and direct interaction/outreach (i.e., tweeting to followers and/or posting to Facebook/YouTube). When compared to the cost of traditional advertising, which can range from $20 to $500, Facebook ads, for example, typically range from approximately $15 to $20.[5] However, if the CRO has an active, respected social media presence, paid advertising may not be necessary; natural engagement is potentially more effective. Despite significant cost and time savings, social forums can also lead to participant issues after a trial is underway.[5]

GOING SOCIAL — OPEN COMMUNICATIONS, OPEN COMPLAINTS ... AND CONCERNS

Though social media channels may make it easier to recruit and communicate with trial participants, embracing the social landscape can potentially lead to participant issues as well. The growth of the internet as a trusted health information channel has led to the rise of "eParticipants," or participants that are active on social media during trial participation.[6] In 2013, The Pew Internet Project found that 59% of adults in the U.S. use the internet to search for health-related topics. This does not necessarily mean that these interactions are beneficial, however. Social media misuse during clinical trials – including those via social platforms, forums and blogs – can potentially affect the scientific integrity of a study.[6] Participants may even disclose sensitive information such as investigational terminology through these interactions, or compare medications with each other.[6]

The Center for Information and Study on Clinical Research Participation – a nonprofit organization providing clinical trial research information, education and resources to participants and the general public – is attempting to combat these challenges with, in part, a website called "Smart Talking About Clinical Trials." This initiative aims to educate participants on the risks of openly discussing study specifics by focusing on the influential power of these networks.[7] Though organizations such as the Society for Participatory Medicine encourage the involvement and engagement of patients in health decision-making, CROs and sponsors alike must be aware of the risks that this empowerment introduces; additionally, researchers need to be aware of how attempting to monitor such social interactions can jeopardize their own blinding in the trial.[6]

Though research in the area of eParticipants is still relatively limited, and CROs are striving to keep pace with upcoming technology while ensuring that they do not invite unanticipated FDA scrutiny in an area marked by little guidance to date, the industry has much to learn and gain from embracing the social space for recruitment efforts. Engaging an outsourcing partner for everything from clinical trial design to clinical trial data management – outsourced by 54% and 50% of respondents, respectively – may allow sponsors to take advantage of existing expertise that could already include work in the digital space.[2]

As technology continues to evolve, social platforms grow and system integration becomes deeper across trial sites, sponsors and CROs – an area in which cloud technology will likely play a major role – the digitization of recruitment and other aspects of clinical trials is likely to become a main point of differentiation among CROs looking to innovate in the market. With the term "digital CRO" already appearing and innovation listed as the third-most-important consideration for sponsors considering outsourcing partners, it is likely the move toward social recruitment is already here.[2] P

54%

OF COMPANIES ACQUIRE OR PLAN TO ACQUIRE CLINICAL TRIAL DESIGN SERVICE FROM CROS

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INNOVATION FEATURE PART 3

Flexibility in Manufacturing Is Fundamental to Production Success

ith record-high drug approval rates, and next-generation therapies that operate via novel mechanisms of action showing great promise in the clinic, the likelihood of innovation seems guaranteed as long as numerous manufacturing challenges are addressed.

Flexibility in all aspects of plant operations, including outsourcing relationships, will be crucial for meeting changing market and regulatory expectations.

Traditional manufacturing strategies won't allow drug makers to respond quickly enough to increased competition from generics or the entry of new market players, nor reduce development times and costs. With the shift in demand; growth from mature to emerging markets; emerging expectations for local production; a renewed focus on targeted, highly potent therapies; and the ever-greater complexity of new drug substances, fixed, single-product batch manufacturing facilities are no longer relevant for most candidate drugs in the pipeline. Multi-product sites – designed to allow rapid switching between smaller-volume processes for the production of high-quality, high-purity, highly potent, cytotoxic or otherwise challenging and specialized APIs and biologic substances – will be the new norm.

NEW PRODUCT DEMAND OVER- OR UNDERESTIMATED BY DRUG COMPANIES

CONFIGURABLE, ADAPTABLE

State-of-the-art flexible facilities are designed to be configurable and adaptable with more open architecture (facility-wise and equipment-wise to avoid dependence on single suppliers) and extensive automation systems.[1] Continuous manufacturing strategies are typically incorporated at some level, and for biopharmaceutical plants, single-use technologies are widely used, although hybrid setups consisting of both disposable and stainless-steel equipment remain common to achieve optimum performance.

For biologics manufacturing, NNE Pharmaplan refers to this approach as the "bio-on-demand" standard.[1] Such flexible facilities allow production of different product volumes to meet the needs for both clinical and commercial manufacturing and to rapidly respond to changes in expected market demand (a recent survey of 50 pharmaceutical industry leaders conducted by ORC International, and sponsored by Patheon, revealed that many drug companies over- or underestimate new product demand by up to 25%).[2] They also are typically designed to enable rapid switching between different products and product packaging (i.e., vials, cartridges or syringes for parenterals).[3]

MANY ASPECTS TO FLEXIBILITY

Multi-product manufacturing and scalability are key features of flexible facilities, as are mobility and replication. Segregation of heating/ventilation/air-conditioning (HVAC) systems for each production area allows for the manufacture of multiple compounds in a single plant. Continuous manufacturing provides ready scalability from the development lab to the clinic, and on to commercial production. Modular systems provide both mobility and duplicability.

MODULAR AND FLEXIBLE

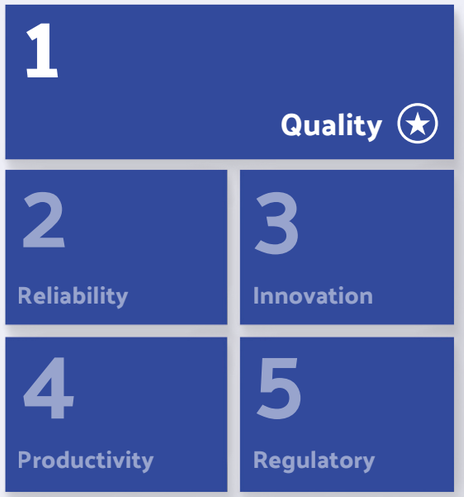
It is important not to confuse modularity with flexibility. Stick-built facilities constructed of modular panels are no more flexible than traditional sites, nor are modular units physically connected in a permanent arrangement that rely on a single HVAC system. Only modular units with individual HVAC systems (autonomous cleanroom POD solutions as referred to by G-CON Manufacturing) that can be readily decontaminated and sanitized for reuse are truly flexible and designed for multi-product processing.[4] They are also mobile and can be easily replicated. In addition, because modules are pre-engineered, they can be constructed, installed and commissioned much more rapidly than traditional facilities.

The full benefits of flexible facility designs are only realized with the implementation of appropriately flexible process designs. Modular processing systems and "plug-and-play" equipment provide easy scalability as well as customization for specialized manufacturing and rapid switching of production solutions.[5] In bioprocessing, the ability to reconfigure downstream process trains using flexible, portable, disposable units is preferred in multi-product manufacturing sites because often these operations vary significantly for different types of biologics.[6]

ADVANCES IN AUTOMATION

When effectively implemented, automation can increase efficiency, productivity and quality while reducing costs. The reason: effective automation requires high-level process understanding in order to identify key areas for both control and optimization.[7] Automation is being employed in a variety of applications ranging from batch and recipe management to individual processes to whole-facility automation, including integration of production scheduling and purchasing

→ **INDUSTRY DRIVERS**



Effective automation requires high-level process understanding in order to identify key areas for both control and optimization.

operations. Connectivity and integration of control systems with different aspects of plant operations allows remote access for monitoring of processes and, when combined with simulation/modeling tools and extensive data collection and analysis, manufacturers are afforded the ability to respond rapidly to process excursions. This also allows for proactive management and exploration of trends for both process optimization and early identification of potential issues.[7]

Automation is also fundamental to the integration of individual unit operations based on disposable technologies for flexible and continuous manufacturing. In lieu of this need, GE Healthcare's Life Sciences business and Emerson Process Management announced in late 2015 that Emerson's DeltaV distributed control system would be incorporated in GE's FlexFactory integrated biomanufacturing platform based on single-use technologies. Senior Vice President of Industry Solutions for Emerson Process Management, Jerry Brown, expects that "the collaboration will support more predictable processes that eliminate unnecessary work, which translates into a reduced time to market for our customers."[8]

PROGRESS WITH PAT

Truly flexible manufacturing requires continual access to real-time process data for greater understanding, ongoing optimization and the ability to rapidly respond when upsets or other unexpected events occur. Process analytical technology (PAT) is essential for achieving true consistency, given the variability always present in pharmaceutical raw materials, equipment and processing conditions.[9] Advances in portable, nondestructive analytical technologies (e.g., particle imaging, near-infrared, Raman, mass and Fourier transform infrared spectroscopies, focused-beam reflectance) with applications like PAT are making their way into pharmaceutical manufacturing. Effective PAT implementations can result in increased quality, faster product release, reduced cycle times and lower labor and energy costs.[10]

PAT, combined with automated control platforms, is also key to successfully implementing fully integrated continuous manufacturing operations.[9] Companies like Siemens and Rockwell Automation are focused on developing comprehensive solutions that incorporate both. Rockwell, for instance, has been working with

→ **TOP DRIVERS WHEN SELECTING A CRO PARTNER**

	TOTAL	BUYER CATEGORIES			
		BIG PHARMA/ BIOTECH	MID-SIZE PHARMA/BIOTECH	SMALL PHARMA/ BIOTECH	EMERGING PHARMA/BIOTECH
Quality – Highest-quality standards and deliverables	66%	71%	64%	58%	63%
Reliability – Meet all project milestones and timelines	10%	9%	10%	10%	24%
Innovation – Innovative approaches that will improve operations and add value to my in-house capabilities	9%	8%	10%	9%	5%
Productivity – Deliver on agreed-upon technical objectives	6%	5%	6%	8%	3%
Affordability – Adds a value component along with pricing that fits my budget and needs	6%	3%	7%	10%	3%
Regulatory Track Record – Reputable and consistent regulatory compliance history	4%	4%	3%	6%	3%

OF COMPANIES CONSIDER QUALITY AS THE TOP DRIVER WHEN SELECTING A CRO

G-Con under a grant from the Defense Advanced Research Projects Agency (DARPA) to build a modular facility for flu vaccine manufacturing that can be rapidly installed and up and running in third-world countries.[9]

CONTINUAL DEVELOPMENT OF CONTINUOUS SOLUTIONS

Continuous processes provide the scalability needed for flexible manufacturing. The amount of product produced can be increased or decreased simply by running the processes for longer or shorter periods of time. When microreactors are used, numbering up with parallel systems is another solution for increasing production volumes. There are also additional benefits, including a smaller operating footprint, reduced material and resource consumption, reduced quality control needs, more consistent product quality and reduced out-of-spec material.

In fact, in April 2016, the U.S. National Science and Technology Council (NSTC) listed continuous manufacturing of pharmaceuticals and biopharmaceuticals as manufacturing technology areas of emerging priority.[11] Several other U.S. government agencies are involved in projects related to continuous pharmaceutical processing.[12] In its December 2015 guidance document, *Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base*, FDA outlined the work its Emerging Technology Team (ETT) is doing with companies to increase the understanding of continuous manufacturing.[13]

FDA has also recently approved drugs manufactured via continuous processing, including Jannsen's Prezista, which previously was produced in a batch manner in April 2016.[14] The process was developed in collaboration with researchers at Rutgers University, the University of Puerto Rico and the Engineering Research Center for Structured Organic Particulate Systems (C-SOPS), an academic-industry partnership.[14] Janssen Supply Chain (JSC), a subsidiary of Johnson & Johnson, is currently investigating applications of other continuous manufacturing techniques for the production of other products that may provide reduced scale-up times and decreased time to market. In addition, Janssen and Johnson & Johnson aim to "manufacture 70% of highest-volume products using continuous manufacturing within eight years, increase yield by reducing waste by 33%, and reduce manufacturing and testing cycle time by 80%."[15]

New approaches to continuous process development are also being evaluated. Rather than focus on pharmacokinetics, researchers at C-SOPS look "at material characterization and how minor changes affect manufacturability as part of a system," according to Associate Director for Industrial Relations and Business Development Doug Hausner.[16] Biopharmaceutical manufacturers are also making significant investments in continuous manufacturing technologies and facilities. Eli Lilly, for instance, is investing €35 million to build a continuous API manufacturing facility at its existing manufacturing site in Kinsale, Cork Country, Ireland. The facility will be used for development and commercialization of Lilly's late-stage pipeline.[17] P

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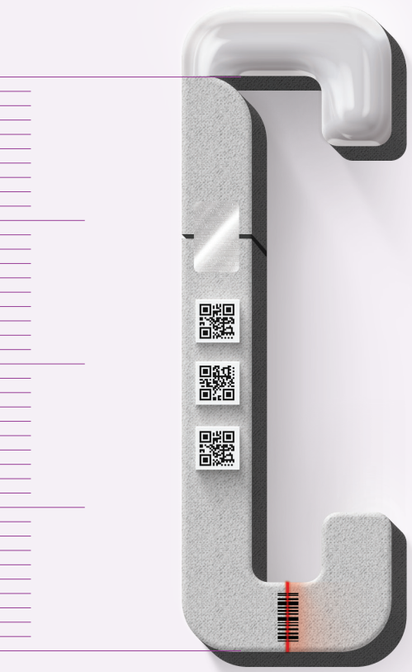
INNOVATION FEATURE PART 4

Distribution Channel Security in Ensuring Drug Supply and Safety



ongress passed the Drug Supply Chain Security Act in 2013. Three years into its phased implementation, industry compliance activity continues, as this benchmark ruling comes due in 2017.

Prior to the passing of the Drug Supply Chain Security Act (DSCSA), drug manufacturers were forced to comply with a patchwork quilt of drug "pedigree" laws that varied from state to state. In 2013, the Healthcare Distribution Alliance (HDA) noted that "18 states had adopted final rules regarding distributor licensing and pedigree requirements, three states had enacted legislation but rules were pending, eight states had enacted legislation, one state had proposed pedigree legislation, and 20 states had no legislation or regulations on the topic."[1] Regardless, the industry urged action because nobody wanted to entertain the possibility of having to comply with 50 different state laws.

Seeking relief, industry groups called for unified, federal-level regulation, which became law in 2013. According to FDA, the DSCSA "outlines critical steps to build an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the United States."[2] The FDA said the new system "will enable verification of the legitimacy of the drug product identifier down to the package level; enhance detection and notification of illegitimate products in the drug supply chain; and facilitate more efficient recalls of drug products."

For the most part, the world's pharmaceutical regulators have also joined the effort and are reconciling their regulations to improve the ability of the global pharmaceutical industry to create a robust, transparent supply chain that ensures the drug supply is reliable, safe and secure from counterfeiters, or any others looking to profit by exploiting gaps.

Initial FDA guidance promised "ten years after enactment, the system will facilitate the exchange of information at the individual package level about where a drug has been in the supply chain." For drug producers that means by 2023, every vial, bottle, blister pack, combination inhaler and topical tube must be marked and coded accordingly so it can be tracked through every exchange or transaction along the supply chain and its journey to the consumer.

SERIALIZATION IS COMING … SOON!

The FDA timeline shows the next major deadline facing drug manufacturers is the requirement to serialize all products by November 27, 2017. While the feasibility of this is debatable, there are few real technological barriers to implementing an adequate solution, whether locally or system-wide, across dispersed operations and facilties. In a June 2016 Contract Pharma article – "Is the Industry Rising to the Challenge of Serialization?" – Staffan Widengren of CDMO Recipharm noted that global pharmaceutical companies selling products at a high risk of being counterfeited have implemented a traceable, unique ID on each product pack for years.[3] "In all countries, the unique information required for a pack should be printed both in human-readable format and in some form of data matrix or barcode," said Widengren. "However, while most countries require a GS1 standard solution they can differ from country to country, such as is the case with the linear barcode required in China and the 2D matrix required in Turkey."

Pharmaceutical companies need to be well on their way towards implementing a standard solution that includes serialization features, such as thermal printing, 2D-matrix code verification, human-readable text, brand-neutral tamper-evident labeling and the ability to create a standard file format for reporting and storing serial numbers.

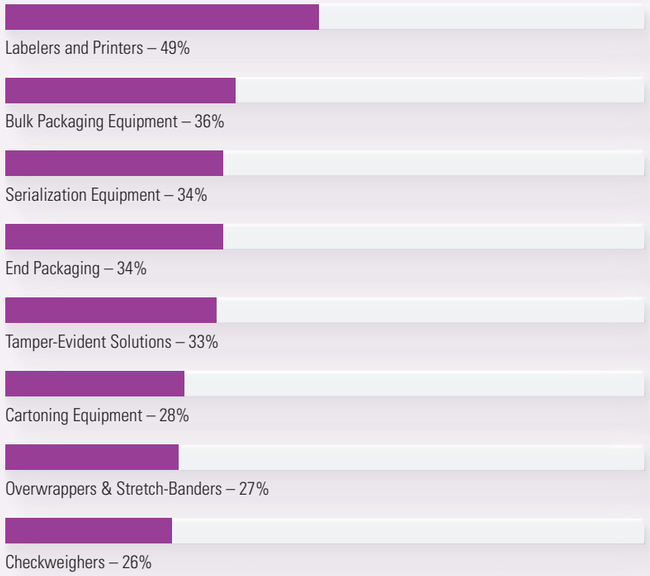
There is evidence this advice is being adopted. Nice Insight's 2016 Pharmaceutical Equipment Survey found that 49% of those interested in purchasing secondary packaging equipment were seeking to specify labels and printers. New serialization equipment and tamper-evident solutions were among leading technologies being considered for purchase as well, garnering 34% and 33%, respectively.[4]

Serialized products allow for a much faster and more effective response to quality/safety excursions and the ability to efficiently remove products from the market well past the point of sale.

According to the Rockwell Automation whitepaper, "Serialization: An Implementation Guide," a serialization solution should be holistic relative to operations, and enable pharmaceutical manufacturers to comply with current regulations into the future.[5] Rockwell's Global Serialization Lead, Joe Whyte, said the company's solution is built on industry standards (IEC 61131, ANSI/ISA-88, ANSI/ISA-95) and uses open network and communication protocols, as well as commercial off-the-shelf technologies. An effective solution must provide the required data links and web services to connect serialization data layers to the ERP layer and the supply chain cloud, said Whyte. Rockwell Automation identified five layers based on the enterprise and control system levels of the ISA-95 data model:

- Level 0: Printers & vision systems: serialization numbers printed & inspected
- Level 1: Unit-level controller & human-machine-interface stations: serialization & aggregation data management per station
- Level 2: Line controller: serialization & aggregation data management for the entire packaging line
- Level 3: Site server: serialization & aggregation data management for the entire facility
- Level 4: Business planning & logistics: serialization interface to enterprise resource planning & manufacturing execution system
- Level 5: Supply chain track & trace serialization data event repository

→ **PERCENTAGE OF RESPONDENTS THAT INDICATED INTEREST IN SECONDARY PACKAGING**



To be effective, a serialization solution requires data input from all layers. Whyte's paper explained standards such as GS1 for the supply chain and EtherNet/IP for manufacturing, combined with off-the-shelf programmable-logic controllers for data connectivity/data management with packaging machines, printers and marking devices and vision systems, will achieve the integration required to drive better business outcomes.

Providing a high-tech electronic pedigree to all drug products, even on a unit level, can be more than just another expensive regulatory cross to bear. Serialized products allow for a much faster and more effective response to quality/safety excursions and the ability to efficiently remove products from the market well past the point of sale. In fact, industry manufacturing-centric information and control technology suppliers like Rockwell and Emerson maintain that the data generated from tracking and tracing drugs will bring tremendous opportunities for "big" data analysis and allow for much more effective decision-making related to distribution and other metrics that improve strategic performance as well as business outcomes.

Track and trace is poised to completely change the way drugs are manufactured, distributed and sold. These systems will increase transparency and, therefore, accountability of all involved in the supply chain. Track and trace technologies will become an even more critical component as drug developers respond to society's right to a safe, reliable drug supply.

34%

OF COMPANIES LOOK FOR SERIALIZATION EQUIPMENT

INNOVATION AMBITION: TO BE CONTINUED

To secure an innovative future, drug developers and manufacturers are marshaling their resources and applying technology in ways that might have been unrecognizable 40 years ago. For example, drug discovery pathways are increasingly reliant on automated technology and equipment to screen millions of compounds. Investment here has proven to deliver substantial returns, as lab automation has the ability to accelerate large-scale sample analysis while maintaining the high degree of reproducibility and accuracy demanded by regulators.

Innovation in drug discovery will remain dependent on technological advances like Eve, which combines the drug screening pipeline's three elements into a systematic, integrated process. Eve and similar technologies will be in high demand to introduce new efficiencies into compound screening, speeding hit validation and enhancing data integrity. Similarly, CADD methods will play an important role in drug innovation supporting structural-based and ligand-based *de novo* drug design using construction algorithms.

As knowledge of therapeutic value and market potential of compounds or molecules occurs in clinical trials, innovation is paramount in this sector as well. Trial recruitment managers are quickly learning to leverage social media. General access to the internet by consumers allows eParticipants to be active online during trial participation, which allows for a controlled and monitored trial, ultimately producing the data required to prove value.

Future innovations will also be extremely reliant on an elastic supply chain, ready to contract during market adversity or stretch to meet growth in current demand. Here the integration of flexible manufacturing capacity with the latest automation – PAT – and increasingly continuous processing techniques will have an important and lasting impact on the industry's ability to respond to both consumers' and regulators' demands.

Society is demanding so much from the pharmaceutical industry in general, with the pressure to deliver being felt across all sectors of the life sciences and healthcare supply chain. P

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DRY-POWDER INHALATION FORMULATION: BALANCING PERFORMANCE AND MANUFACTURABILITY

→ BY **CONRAD WINTERS** AND **EUNICE COSTA**, HOVIONE

There is growing demand for dry-powder inhalation formulations of drugs to treat both respiratory and systemic diseases. Composite particle technology is allowing the development of more efficient formulations, even for challenging molecules. Spray drying is an enabling technology for composite particle preparation. Formulators must be aware, however, of the tradeoffs between properties that improve aerodynamic performance in the lung but negatively impact process yields or throughputs.

GROWING IMPORTANCE OF COMPOSITE PARTICLE TECHNOLOGY

Traditional DPI formulations are physical mixtures of a coarse carrier and micronized API with an aerodynamic particle size of 1 to 5 microns. It is important to note that understanding the properties of the API – as well as any excipients that are used and their possible interactions – is key to the successful formulation of drugs for use in dry-powder inhalers. Precise control of capsule filling once the carrier and API are blended together in the final formulation is also crucial. DPI drugs are typically formulated at very low doses; the filling process must be very precise in order to ensure accurate dosing.

While use of a carrier is an established formulation strategy and these formulations are relatively easy to develop, they can suffer from variability of the API and of the carrier, leading to lack of homogeneity in the filled capsules due to the very low doses. Composite particles are therefore receiving increased attention as an attractive alternative to carrier-based formulations. In these DPI formulations, the API is embedded in an excipient matrix, and all of the ingredients in the formulation are incorporated into engineered particles that can be inhaled. As a result, the API is more efficiently delivered to the lung for improved performance.

ADVANTAGES OF DPI FORMULATIONS FOR BIOMOLECULES

Composite particles are also appealing in the formulation of biomolecules, including peptides and proteins, as DPI therapies. These sensitive molecules cannot withstand the traditional technologies used for carrier-based formulations. Particle engineering can help stabilize such challenging molecules and enable their delivery to the lung, which provides a very large area for absorption and delivery to the bloodstream.

Delivery to the lung is an attractive alternative to parenteral delivery, which is the most common type of formulation for biomolecules. Following oral delivery, these biomolecules either do not survive the harsh conditions within the GI tract or are subject to first-pass metabolism. Parenterals also often require cold storage, and in some cases can only be administered via intravenous methods, which may require a visit to the hospital and can lead to reduced patient compliance.

The size of biomolecules will impact their suitability for DPI formulation, however. Peptides that are too small might be eliminated from the lung, while the complexity of drug formulation increases significantly for larger biologics. Consequently, the range of peptides and proteins that can be delivered through the lung is determined by their physiochemical and structural properties, as well as their behavior under physiological conditions.

LEVERAGING SPRAY-DRYING EXPERTISE FOR DPI DEVELOPMENT

Spray drying is an enabling technology for the preparation of composite particles for inhalation formulations. It is also ideal for generating engineered particles of biologic drug substances. During spray drying, a solution of the drug substance and suitable excipients is subjected to mild flash drying, which allows for careful control of particle properties (particle size, bulk density, degree of crystallinity, etc.).

The process is readily scalable, which ensures that composite particles generated at commercial scale have the same properties as those designed during the development phase. Spray drying is also applicable for challenging thermally sensitive and hygroscopic/sticky compounds, including biomolecules. The mild conditions and the careful choice of surfactant and glass-forming excipients help prevent denaturation, aggregation and undesired degradation or dehydration due to stress exposure. In composite particles, it also provides the advantage of improving the particle properties for efficient inhaled powder formulations.

We at Hovione have been providing spray-drying services to the pharmaceutical industry for over 12 years. The major challenge in scaling up spray-drying processes for inhalation is to ensure that the particle properties are maintained across scales, namely a small particle size and low residual water content, when increasing process throughput in larger spray-drying units. We use extensive proprietary modeling capabilities to closely correlate laboratory conditions to those at commercial scale, allowing a reduction of the number of manufacturing runs required to establish an effective commercial-scale spray-drying process based on laboratory data. Engineering solutions are implemented to expedite scale-up and ensure that fine inhalation powders are generated and efficiently collected in commercial units under high-process throughputs, such as multi-nozzle atomization heads and custom-made high-efficiency cyclones.

CONTROL OF CAPSULE FILLING IS CRITICAL

As mentioned above, most dry-powder inhalation formulations contain very low doses of the active pharmaceutical ingredient – as low as a few milligrams. In traditional capsule filling, the amount of product filled into each capsule is measured using the gross capsule weight after filling. For example, if a capsule weighs 50 mg for a fill weight of 5 mg, the significant variations in the filling weight might not be detected: a difference of only 1 mg in fill weight in a capsule with a 5 mg fill weight equates to a 20% deviation. Consequently, Hovione is moving to the use of low-compaction, dosator-based, precision capsule-filling units with 100% net-weight verification for both pilot and commercial manufacturing.

DESIGNING IN ACCURACY AND CONTAINMENT

At present there is no pilot-scale capsule-filling machine designed to operate on a net-weight measurement basis in completely contained conditions. This is why we at Hovione are collaborating with two partners to develop a filling machine that will close this important gap.

As described in the text, net-weight measurement is necessary to ensure precise and consistent filling of capsules with dry-powder inhalation formulations that contain very low API contents. Containment is essential for many DPI formulations because they are highly potent. Protection of operators and the environment from exposure to these compounds, as well as preventing cross-contamination, is essential and requires specially designed containment equipment.

Together with our partners, we are developing a filling machine that will operate on a 100% net-weight measurement basis and be fully contained. The machine will be capable of filling 140,000 capsules per hour with highly potent DPI formulations with fill weight as low as 5 mg.

BALANCING MANUFACTURABILITY AND PERFORMANCE

The fine particle fraction (FPF) of DPI formulations typically determines the performance of these types of drugs upon aerosolization. Using quality-by-design principles, we have found, however, that there is a negative correlation between these values and the manufacturability of DPI formulations, with respect to their rheological and capsule-filling rejection rates. Using advanced modeling tools, we are able to quantitatively define these relationships and show customers how the yield of a process is affected by changes in FPF values.

For carrier formulations, the particle size distribution of the API and the percentage of fine lactose in a formulation are the main parameters that influence aerodynamic performance. In addition, the formulation has a significant impact on blending and capsule-filling yields. Specifically, formulations that enable improved FPFs are detrimental to the process yield, leading to significant product loss in the blending and capsule-filling steps.

As a result, there is a need to balance the desired aerodynamic performance with the manufacturability properties of any given DPI formulation. Specifically for carrier formulations, whenever possible the fine lactose percentage should be minimized to < 10% and low fill weights of < 10 mg should be avoided in order to achieve the best balance between manufacturability and aerodynamic performance.

For composite particle formulations, similar relationships are observed. Namely, higher FPF are typically obtained for lower-process throughputs.

For new projects, we use information about the physicochemical properties of the API, the targeted disease and type, patient population and intended device design to determine which technology in our portfolio will be best suited for formulation of a DPI therapy. At the proof of concept stage we establish the *in vitro* aerodynamic performance and confirm that the targets are being met.

Early during the development of the formulation and capsule-filling process, manufacturability and performance are both investigated by assessing the effect of different key parameters on the FPF value, and the ideal balance is identified. As we have established scalable carrier-based formulation methods and spray-drying processes, the lessons obtained at the development stage are applicable to larger-scale processes as well. In fact, we specifically do not develop stopgap solutions for any stage of a project. All processes are designed to provide the desired performance at any scale, including commercial production. This approach makes it possible to identify optimum formulations early on in the project, which leads to reduced development times and costs. It also reduces the risks associated with process transfer and scale-up.

INTEGRATED OFFERING FOR DE-RISKED DEVELOPMENT AND COMMERCIALIZATION

The development of scalable processes is just one aspect of our strategy to offer fully integrated services to our pharmaceutical partners. At our site in Portugal, we offer comprehensive solutions for DPI formulation development, manufacturing for clinical supplies and small commercial-scale drug products. A single team supports the development of scalable processes, and methodologies are used to predict the right balance of manufacturability and formulation performance. The result is timeline compression and seamless project management. In addition, with our capabilities in low-dose/high-yield capsule filling – including MultiNett 100% net-weight verification and potent API handling – as well as our extensive experience in both carrier-based and composite-particle formulation development, we are able to develop highly efficient DPI formulations for even the most challenging drug substances. P

DELIVERY TO THE LUNG IS AN ATTRACTIVE ALTERNATIVE TO PARENTERAL DELIVERY, WHICH IS THE MOST COMMON ROUTE OF ADMINISTRATION FOR BIOMOLECULES.

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Conrad has a background in solid-state pharmaceutics with a Ph.D. in pharmaceutical technology and more than 20 years' experience in the pharmaceutical industry and has led the Drug Product Development Group in Hovione since 2012. He has worked on oral, parenteral, topical and inhalation formulations, always focusing on understanding material properties, interactions and the effects of processing. He was an invited speaker at conferences in Canada, the U.S., China and Europe and has presented to the FDA and MHRA.

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Eunice Costa joined the Drug Product Development group at Hovione in 2011 and has since worked on particle design and formulation development, particularly for inhalation drug products. At Hovione, she has also been the scientific advisor for Ph.D. programs in particle-design technologies for optimizing pulmonary drug delivery and in biopharmaceuticals. Eunice holds a Ph.D. in bioengineering systems from the MIT-Portugal Program.

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RX-360: AN INDUSTRY GROUP LIKE NO OTHER

→ BY **GUY VILLAX**, RX-360 AND HOVIONE

RX-360 IS AN INDUSTRY CONSORTIUM FOUNDED IN 2009. Our mission is to ensure patient safety by enhancing the authenticity and quality of medicines around the world. To do this, Rx-360 embraces everyone: large and small pharma; innovators and generic manufacturers; CDMOs, suppliers, drug manufacturers and device manufacturers; producers of APIs, excipients and packaging materials – whether regulated or non-regulated; providers of logistic services and analytical services; dosage form manufacturers and producers of chemicals and intermediates – any organization that is involved in the healthcare supply chain is welcome.

Rx-360 has no home country; it was designed from day one to be global, to welcome all organizations from all nations and all cultures. Our member companies have sales that add up to half a trillion dollars, supply close to half of the world's prescription drugs and come from all the major countries. Rx-360 is active not just in the developed world; we have specific working groups that focus on India, China and Africa.

THE RX-360 DIFFERENCE

Rx-360 members know that working together is the only way to successfully improve the security and authenticity of the global medicines supply chain. Rx-360 is open-minded, transparent and collaborative. Volunteers are motivated by an important goal: protecting the patient and working to stop criminals who take advantage of the trust in medicines that has taken us a hundred years to build. Regulators trust us because we do not defend the interests of our member companies; rather, we exist to protect the patient.

Rx-360 provides procurement professionals with an early-warning forum. Indeed, back in the summer of 2007, six months before anyone died of falsified heparin, the price per kilo of heparin exported from China had trebled in price – this was a big red flag that could have helped save those patients' lives, had it been tracked.

RX-360 BENEFITS

A central part of the vendor qualification process is the quality audit. While necessary, audits are repetitive and tedious. They are disruptive and costly. Rx-360 is able to assure increased compliance and to provide timely access to valuable data while reducing the frequency of audits and auditing costs.

SHARED AUDITS

Our members post onto our database the suppliers they want to have audited. When more than one pharma company wants to audit the same supplier, a shared audit is flagged. The cost of the audit may be divided between two, three or more sponsors. After closure, the audit report is put into our audit library, with a CAPA plan in place, and can be further licensed to any company the supplier authorizes. If the reader visits our website, the visitor can see the audit report library available for licensing. Depending on membership, the license fee for one audit report ranges from $2,500 to $5,000 (USD).

SUPPLY CHAIN SECURITY

Did you know that every week, just about every major pharmaceutical company has cargo stolen? This occurs frequently in Brazil and Mexico but also almost everywhere else too, including the USA. These thefts occur in patented as well as off-patent medicines. Did you also know that donated medicines are often diverted by recipients and then sold in other countries?

Rx-360 works on cargo thefts, access to medicines, and a host of other issues related to supply chain security. As possibly the only forum that embraces everyone, Rx360 is designed for the sharing of experiences and for the development of best-practice white papers.

For example, Rx-360 recently completed the fourth of its international GDP programs in Africa. These meetings of our Africa GDP working group have been oversubscribed. We look forward to the next one, which will be in November, in the Ivory Coast.

I INVITE YOU TO JOIN US IN HELPING PROTECT PATIENTS

We need **YOU** – as a member company and as a volunteer. Over 300 individuals from around the world contribute to making Rx-360 a vibrant pharmaceutical and medical device ecosystem, and we all do this in addition to our full-time jobs.

There is no better networking environment. With over 17 different working groups in Rx-360, one of them will surely align with your day job!

Rx-360 is open to all. Joining has a low annual price tag ($30,000 for pharma manufacturers, $12,000 for small pharma manufacturers and $6,000 for suppliers). Industry associations, regulators and other interested parties may join for free as observers. P

COME AND JOIN US. We are doing amazing things and making a real difference for patients worldwide. To join and for more information, please email **Mark Paxton**, Rx-360's CEO, at **mpaxton@rx-360.org** or visit **www.rx-360.org**.

Guy Villax
CEO, Hovione

VIRTUAL PANEL

SEEKING QUALITY DEALS: CONSOLIDATION AND ACQUISITION

→ BY **ANDREW FERRARO**, NICE INSIGHT

NICE INSIGHT'S VIRTUAL PANELISTS EXPLORE THE DEAL-STRUCTURING SHIFT IN THE PHARMACEUTICAL MARKET FROM AN INVESTOR PERSPECTIVE.

Consolidation has been a watchword for the pharmaceutical industry in recent years. Major pharmaceutical companies are looking to enhance their pipelines through the acquisition of competitors with complementary portfolios in terms of treatment classes, geographic markets or other synergies. They are also snapping up small or emerging firms with promising early-stage clinical trial results. At the same time, they are looking to become more virtual and unload mature products facing generic competition.

These activities have affected the contract services sector and other suppliers to the pharmaceutical industry. There are fewer potential customers for contract research organizations (CROs) and contract development and manufacturing organizations (CDMOs), and those that remain are looking to simplify their supply chains and develop deeper relationships with fewer suppliers. CROs and CDMOs are consequently seeking to expand their offerings through acquisition of companies with complementary or specialized capabilities in order to position themselves as integrated, full-service partners that can support pharmaceutical customers across the entire cycle, from discovery through commercialization and beyond the loss of patent protection.

Private equity and venture capital firms have played a role in many of the transactions that have taken place. Indeed, fundraising for both types of investments continues at a brisk pace despite the fact that a seller's market has persisted for a number of years. Quality deals have become harder to find, however, and targets are shifting.

STATE OF THE INVESTMENT MARKET

The tremendous activity in pharmaceutical investments in recent years has affected the ability of companies to find quality deals, according to Robert Auritt, President of Brant Point Partners, LLC. "The number of private equity (PE) transactions is declining while valuations have increased dramatically due to the fact that there is a much smaller number of quality companies coming to market," he notes. For PE firms there is, therefore, an ongoing shift to deploy capital for companies that have reached later stages of the drug development cycle.

At the same time, large biotech and pharmaceutical companies are struggling to fill their pipelines solely through internal R&D activities. "There is a drive to achieve growth through the acquisition of companies developing novel compounds, even if they are in early-phase clinical trials," says Auritt. As a result, venture capital firms find themselves investing sometimes at earlier stages of the drug development cycle.

The state of the market also depends significantly on the particular sector. For instance, pharmaceutical services (including CROs, CDMOs and CMOs) are in high demand, and it's not just large strategic

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> Robert Auritt – Brant Point Partners, LLC

→ ABOUT THE PANELISTS

Robert Auritt
President, Brant Point Partners, LLC

Banks Bourne
CEO and Senior Managing Director, Bourne Partners

buyers that are fueling this marketplace, according to Banks Bourne, CEO and Senior Managing Director with Bourne Partners. "We are increasingly seeing top-tier private equity firms capitalizing on the tremendous growth in the industry and acquiring major players as platform companies or bolt-on acquisitions for companies within their current portfolios," he observes. Contrast that with specialty pharmaceuticals, which he notes have been pummeled over the last twelve months and experienced a tremendous slowdown in what was a historically frothy M&A environment just two years ago.

Fund-raising for both venture capital and private equity deals continues to be quite successful, however. In addition, highly capitalized financial players with the ability to do top-tier deals are feeling some pressure to deploy capital to achieve their strategic goals, according to Auritt. "It has been a seller's market for an extended period of time, and there is fear that when it ceases to be a seller's market that attractive targets may take themselves off the market," he says.

MEET LOWER-MIDDLE-MARKET INVESTOR BRANT POINT PARTNERS

Based in Philadelphia, Brant Point Partners pursues three principal activities: private equity co-investing, mergers and acquisitions and investment advising. "We have a strong reputation for identifying valuable targets and getting deals done," notes President Robert Auritt. The company typically partners with other PE firms and family offices with complementary expertise. In particular, Brant Point Partners actively works with companies with revenues of up to $65 million-$70 million and typically at least $3 million-$5 million of EBITDA.

SHIFT IN VALUE CREATION OPPORTUNITIES DRIVING BIG CHANGES

On a macro level, the paradigm shift within big pharma to deemphasize early-stage R&D in favor of building pipelines through M&A has had a tremendous effect on both the services and specialty pharmaceutical sub-sectors, according to Bourne. "Ultimately, the value creation opportunities shifted, which led to smaller companies (some single-product) focusing on taking promising opportunities to an inflection point (phase I, phase II or further) with the goal of selling or licensing these more mature development programs to big pharma. Unfortunately, the smaller companies that did not have the same economies of scale for handling clinical trials, manufacturing, etc. were not economically viable. So they looked to outsourced solutions to meet these needs, which helped accelerate growth within the pharma services sector. In addition, it helped fuel M&A activity within the pharmaceutical sector," he explains.

The increased M&A activity in the space led to expanded multiples, and companies took on sizeable amounts of debt in order to complete some of these acquisitions. With pharma companies trading at such high multiples, most corporate acquisitions were immediately accretive and near-arbitrage opportunities, according to Bourne. Additionally, legacy portfolio rationalization was seen by big pharma as a tool for funding additional acquisitions. "This situation led to smaller companies buying legacy portfolios at a discount (product multiples are historically much lower than corporate multiples) in order to use the newly acquired cash flows to fuel R&D cost or additional acquisition. In a weird way, big pharma was selling products at a discount just to buy them back at a premium as a means to build out their R&D pipelines," Bourne comments.

The market got crowded with buyers, however, and as a result portfolio prices got higher and acquirers resorted to riskier strategies to recoup these higher costs. A common lever to increase these returns was raising price (most commonly to a normalized market price, but in some instances profiteering occurred). "Given the recent public criticism over ethical pricing practices within pharma, we've seen a tremendous devaluation across the industry," says Bourne.

He notes that this description merely scratches the surface of the market dynamics. "Ex-U.S. manufacturing quality concerns, generic drug approval backlogs, the Affordable Care Act, the steady rise in opioid abuse, drug pricing, managed care coverage and tax-inversion strategies have all played equally large roles in the current environment," Bourne asserts.

SELLER'S MARKET FOR SERVICES

While pharma is a buyer's market right now with plummeting values, the life sciences service segment is experiencing the exact opposite trend, according to Bourne. That can be a challenging situation for buyers. "As a buyer, we are more attracted to markets that are in turmoil because we believe our expertise will allow us to pick the quality companies that have been negatively affected through association only. We think this ability holds true in a similar sense for operating within a seller's market. You have to be able to identify the highest-quality companies with unique value propositions and operational excellence. It's a losing strategy to overpay for companies that are being positively affected through association only," he explains.

> YOU HAVE TO BE ABLE TO IDENTIFY THE HIGHEST QUALITY COMPANIES WITH UNIQUE VALUE PROPOSITIONS AND OPERATIONAL EXCELLENCE. IT'S A LOSING STRATEGY TO OVERPAY FOR COMPANIES THAT ARE BEING POSITIVELY AFFECTED THROUGH ASSOCIATION ONLY.
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> Banks Bourne – Bourne Partners

MEET BOURNE PARTNERS: FOCUSED ON HEALTHCARE AND LIFE SCIENCES

Bourne Partners is in equal parts a private equity firm and an investment bank that focuses exclusively on fulfilling the unique needs of established, middle-market healthcare and life sciences companies. The firm has assisted clients around the world with corporate sales transactions and divestitures, assets sales and licensing deals in the areas of specialty pharma, pharma services and consumer health and has been exclusively dedicated to this sector for nearly 20 years, investing in and advising some of the best healthcare corporations and financial sponsors in the business, according to CEO and Senior Managing Director Banks Bourne. "Across the board, our strength is getting the right talent on 'the bus' and keeping them for the long term."

Given how competitive some sectors of the life science market are, it is important for buyers to focus on companies with strong growth potential, according to Auritt. "Buyers are paying additional EBITDA turns in this market than they would at other times in the cycle. It is critical, therefore, to choose targets that not only have already demonstrated successful organic growth, but also have a number of promising initiatives planned and underway that will lead to further growth. Portfolio synergies and the company's position in the industry are also important," he says. Auritt adds that it is absolutely crucial to do a proper basic analysis in order to identify such targets.

Buyers in the middle market (up to $1 billion in sales) should also be prepared to find themselves in a broad bidding situation given the limited number of quality companies that are available today. Head-to-head battles are much less likely, according to Auritt.

Venture investments are typically targeting companies with strong track records of performance and established expertise in the life sciences. Good chemistry between the VC team and the principals of the target company is also a common requirement. These factors can, in fact, be more important than price. "We have, for instance, seen deals that have closed with investors with the best track records over those with the better deals," Auritt observes. Here again, homework is key and quality matters.

ATTRACTING INVESTORS

So what should a company that is looking for investors do to ensure a smooth and successful financial experience? How can they become an attractive target given the current market conditions?

First and foremost, according to Bourne, companies need to know what kind of capital they're looking for, and knowing the differences between private equity and venture capital isn't sufficient. "A savvy company will understand the various subcategories of each larger group and identify firms that can provide the best fit (both from a cap table perspective and from an operational perspective). Depending on the size of the company and its financial position, I would almost always recommend hiring a banker to help with the capital raising process, because I truly believe that having an experienced team vetting potential capital providers, negotiating terms and helping to pull the deal together on your behalf is worth the cost in the long run (and often leads to a better overall deal for the company net of fees)," he says.

Pharmaceutical companies looking to attract venture capital need to have products at a reasonable stage of development and a nearly complete management team, including a CEO preferably with extensive commercial experience and proficient technical knowledge, according to Auritt. While they typically haven't yet achieved any sales, they do have a highly developed understanding of the approval pathway; have identified a CRO partner and completed the clinical trial design, a comprehensive business plan and impressive scientific advisory and corporate boards; have succeeded in raising some initial financing; and have appointed a leading IP attorney and corporate securities firm and have a reputable accounting firm. "Credibility is key. All of these items point to a company that has more than a promising drug candidate; they have shown that they have the commitment, wherewithal and understanding needed to convert a business based on drug development into a value-generating enterprise," Auritt states.

Smaller, middle-market companies looking for private equity investors need to have an established market profile and generally have niche products with the potential to hold, or which are already holding, leading positions. They also have a demonstrated growth rate of 20+%, a complete management team in place, including sales, and an expanding product portfolio based on internal R&D efforts and in-licensing deals. Ideally they are also exploring, if not entering, international markets. On the softer side, Auritt notes that there should also be board and management consensus regarding the desire to sell and the willingness to give up controlling interest to the PE firm.

Bourne agrees that each firm will look for different things. Bourne Partners focuses on finding companies within its areas of expertise that have solid management teams, cultures that strive for operational excellence and unique differentiators that are underexploited or not exploited at all. "We prefer to invest in companies that are at or near an inflection point where our expertise and guidance as operators will be equally as valuable as the growth capital we can provide," he adds. P

→ ABOUT THE AUTHOR

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Andrew is a Wall Street veteran, with a track record and a focus on the drug discovery and biotechnology industry. He brings with him a considerable understanding and experience of the financial aspects of the life science business and markets, including 15 years working with biotech and drug discovery companies as well as small-molecule oncology therapies in phase II-III trials. He has a proven track record of developing and managing relationships in the financial and life sciences markets. He studied neurosciences at the University of Delaware.

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CULTIVATING A PROACTIVE QUALITY CULTURE

→ BY **PHILIPPE DARTIGUELONGUE**, SERVIER

Preventing patient risk is perhaps the most important goal for any pharmaceutical manufacturer. The quality of a drug substance or product is directly linked to where and how it's made. As a result of the gravity of production, management must ensure that process variation is eliminated, consistent quality is guaranteed and there are no threats of defects that may potentially harm patients or interrupt supply. To assure quality, Servier takes a holistic approach, bringing people, process and policy together to create an efficient, agile QA/QC culture.

The success of every company developing and producing finished drug product, active pharmaceutical ingredients, excipients or raw materials is dependent on an institutionalized quality effort. Quality assurance/quality control (QA/QC) is an essential element of operational excellence. Assuring product quality across a drug manufacturing organization requires an intensive effort, including the martialing of a broad range of company resources and personnel. In any commercial drug manufacturing environment, quality has many challengers along the production/processing continuum.

Chief among these challenges is to be capable of managing variability in process for any drug manufacturer's QA/QC effort. It is clearly understood that the organization must detect process drifts and prevent product defects to avoid facing risk from many quarters and exposure to a broad range of unacceptable liabilities. Strong process design and control strategies at the line level are certainly a part of it, but a robust quality regime and the institutional framework to support an effective quality management system (QMS), quality risk management (QRM) approaches and a continuous improvement program is critical to managing risk and sustaining product quality over the long run.

Variability can arise from many sources, like variation of active pharmaceutical ingredients and excipients, the improper characterization and control of incoming materials, technical issues regarding equipment or poorly written standard operating procedures (SOPs) that can generate human error. It is incumbent on the quality organization to understand process excursions and support an effective and documented corrective and preventive actions (CAPA) program to prevent them from occurring again.

Other sources may include risk management practices and data integrity issues. A sustainable, high-performing quality regime seeks transparency and collaboration from all facets of the organization, spanning operations, procurement and executive management.

SERVIER'S APPROACH TO QMS

In managing for quality, Servier's main goal is to prevent any risk to the patient; it does this from a foundation built on continuous improvement. A focus on quality also requires an interdisciplinary approach that promotes collaboration and institutional culture. Servier's QA/QC effort has a distinct operational/manufacturing operations bias and features interdisciplinary quality management system teams from each Servier facility. Local teams are managed through a core, corporate QMS team that ensures consistency of QA/QC activities across Servier's manufacturing operations.

QUALITY SYSTEMS REVIEW

Servier quality relies on a proactive quality system review (QSR) process based on audits, process data analysis, equipment condition, periodical review of internal and external sources of data or inputs for QRM. The goal in identifying and listing risks in this fashion is to assign priority and address it commensurate to its relative threat, the highest threat being anything that would potentially impact patient safety. An internal strategy is then defined, with the appropriate tools to manage CAPA response efficiently. Servier quality personnel, for example, are trained extensively to identify operational risk, and are provided the means to collect the best data before ultimately implementing the corrective process to fix the problem.

MORE THAN PASSING INSPECTION

Few regulatory environments are as intensive and pervasive as those brought by the world's prominent drug and consumer

SERVIER

Company Overview

Servier is an international pharmaceutical company governed by a nonprofit foundation and headquartered in France. With a strong international presence in 148 countries and a turnover of 3.9 billion euro in 2015, Servier employs over 21,200 people worldwide. Corporate growth is driven by Servier's constant search for innovation in five areas of excellence: cardiology, oncology, metabolism, neuropsychiatry and rheumatology, as well as by its activities in high-quality generic drugs. Being completely independent, the Group reinvests 25% of Servier's products turnover in research and development, and all its profits in its growth.

health agencies, FDA and the EMA chief among them. Proactive compliance at Servier manifests itself as a "*Right First Time*" ethic. Being proactively compliant means not waiting for an issue to decay, but to anticipate it, thinking ahead so that the organization can respond more efficiently with a high-performing response.

Compliance strategy based on remediation can be shortsighted and become a drag on operations. To combat this, Servier's corporate QMS monitors anticipated regulatory change in order to craft the best policies and cost-effective solutions. To emerge ahead of compliance, Servier's quality team assesses regulatory guidance – as it arises, to determine the impact on operating units – especially those in regions that the QMS team understands will be expecting new or revised guidelines in the near future.

Though it can be challenging, global compliance is an important prerequisite for any pharmaceutical manufacturer conducting operations internationally, and especially across a network of production facilities. In general, the rule is to comply with U.S. cGMP and EU GMP principles at a common level, and that applies to both fine chemical and pharmaceutical manufacturers, respectively. However, the global organization should never lose sight of how important it is to comprehensively involve the company's compliance champions at the local level and to comply with local specific regulations.

IT IS ESSENTIAL FOR ANY DRUG MANUFACTURER'S QA/QC EFFORT **TO BE CAPABLE OF MANAGING VARIATION** IN PROCESS.

Organizationally, Servier identifies experts from their quality and manufacturing operations that have experience dealing with their specific regulatory agencies. Combining local expertise and central quality authority helps Servier manage its global compliance efforts effectively and assure the performance of its chemical and drug substance quality systems worldwide.

Approximately 10 years ago, Servier instituted a comprehensive inter-site corporate audit program, which brings the company's quality managers to perform audits together annually. During this time, the team reviews the performance of each of their eleven sites, with the end goal being to increase the harmonization of the total organization. Servier conducts its own audits of select facilities and then invites quality managers from those facilities to present their findings to colleagues. This effort has proven to be very effective in aligning corporate and local QMS. Indeed, Servier's annual audit program is key in developing continuity.

Ultimately, the performance of Servier's quality systems are dependent on the connectivity and knowledge sharing that stems from the company's collective, cross-discipline collaborative approach, policies that promote continuous improvement and feedback to guide the organization. These efforts cascade across the enterprise via best practice sharing and the promotion of QMS efficiency. Creating a world-class QA/QC effort takes time, though it cannot exist in a siloed, hierarchal organization that segregates business units (and people) while creating barriers to the internal collaboration critical to a robust quality effort. P

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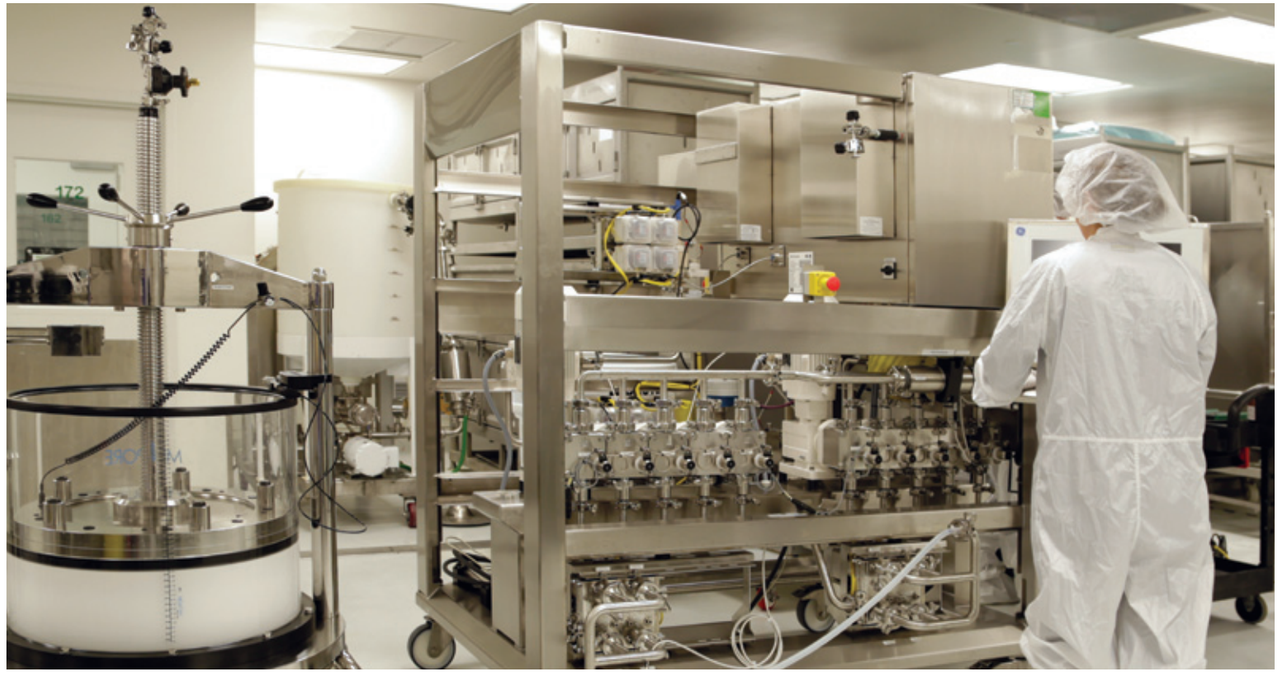
ACHIEVING CONTINUOUS DOWNSTREAM BIOPROCESSING

→ BY **MICHELLE NAJERA, Ph.D.**, CMC BIOLOGICS



In recent years, improving downstream manufacturing has become an emerging challenge to the biopharmaceutical industry. Initially, the bottleneck in biopharmaceutical manufacturing existed in the output of bioreactors. Due to advances in cell line development and upstream process (i.e., perfusion), the output of bioreactors has increased at a much faster pace than downstream processing capacity.

For monoclonal antibodies (mAbs), titers have increased almost 30-fold over a 15-year period.[1] In addition, mAbs and other therapeutic biologics represent the fastest growing sector of the entire pharmaceutical market with many pipeline candidates reaching late-stage development, including 53 mAbs in phase III trials as of late 2015.[2] By 2019, the biological market is expected to exceed 20% of the global pharmaceutical market share at a value of $386.7 billion.[3] The rapid growth of biopharmaceuticals and increasing upstream production yield has imposed substantial pressure to the existing downstream processing capacity.

Traditionally, downstream purification has been governed by batch chromatography, in which desired products are captured and purified via a single large chromatography column. An imbedded drawback of batch chromatography lies in its limited ability to expand processing capacity. Once installed, switching the existing capture column to a larger-size column is often physically and economically challenging. Another design flaw in batch chromatography is its inability to load chromatography resin to its full capacity since product breakthrough must be avoided, which can translate to an underutilization of the resin and hence considerable resource waste.

To cope with the increasing demand on downstream processing, capture columns generally have to be cycled multiple times, which creates additional holding time when the load material is not being processed.

The biopharma industry would benefit greatly from an improved process to more efficiently use the resin in the capture step. Multi-column chromatography achieves both better productivity and cost reduction, making it an attractive solution to meet this challenge. Most importantly, remarkable recent progress has been made in this area, enabling smooth implementation of MCC into downstream bioprocessing.

MCC OVERVIEW

MCC is based on the same fundamental principles as batch chromatography with slight differences in design, operation and application.[1]

HOW IT WORKS

In a multi-column paradigm, product is captured during the load phases using a series of small columns connected in series to create a load zone, instead of one large column in batch mode. Each column size can be 10 to 20 (or more) times smaller than a single conventional batch column.[5] Effluent material from the first column is passed over a second column, thereby collecting any breakthrough product not bound by the first column in the series. During operation, once the first column is fully loaded and washed, it is disconnected from the series and the second column becomes the lead-loading column in the load phase. The first column is then eluted, regenerated, equilibrated and cycled back to the end of the column series while the second column reaches saturation and is ready to be separated from the system. Product breakthrough is no longer a major concern in MCC since the unbound products are bound by the second column in the load series.

In a complete MCC cycle, a column is loaded before going through wash, elution, regeneration and equilibration steps sequentially without even interrupting the loading of the other columns, thus achieving continuous processing. By contrast, in batch chromatography, the loading is stopped well before the saturation of the resin with the product, and the whole column must be processed through the entire sequence of phases before additional load material can be processed.

Overall, MCC must still operate within the limitations of the inherent binding kinetics of a given target molecule and resin, but the configuration of sequential columns optimizes the process to allow higher operating binding capacity compared to batch mode chromatography. This major improvement in MCC allows the operational binding capacity to approach equilibrium binding capacity, or complete resin utilization. Conversely, in batch chromatography, the resin is typically loaded to less than 80% of the dynamic binding capacity (where product breakthrough is observed), which corresponds to ~60% of the complete utilization that MCC targets.[5]

BIO SMB TECHNOLOGY

MCC not only enhances resin capacity utilization but also significantly increases productivity (grams of product purified per liter of resin per hour, g/L/hr) and reduces the volume of resin needed as well as buffer consumption. In a comparison study of a typical clinical-scale (2,000-liter bioreactor; 3.5 g/L mAb) Protein A capture process, the MCC process using Cadence BioSMB technology (Pall Corporation) achieved a productivity of 50 g/L/hr using 8 columns with 20 centimeter (cm) internal diameter (ID) and 7 cm of bed height and 17 liters of resin. The corresponding batch process

reached a productivity of 8.17 g/L/hr using a single column with an ID of 80 cm and height of 20 cm and 100 liters of resin. Total buffer consumption was reduced by more than 30%.[1,7] Overall, BioSMB technology requires reduced resin volume to operate but offers a higher degree of flexibility to accommodate capacity demands. The system can readily meet the desired processing capacity by adjusting the number of columns, and possibly switch times.

STRAIGHTFORWARD TRANSITION FROM BATCH TO MCC

The MCC platform is quite comparable to batch chromatography as they both are developed based on the same principles and use the same chromatography media and buffer systems. The product and process knowledge accumulated by batch processing can be used to set up and optimize MCC process. In addition, MCC technology is designed to be compatible with existing manufacturing setups. Therefore, converting a batch process into an MCC-based continuous process is surprisingly simple and straightforward.

The configuration starts with a few small-scale single column breakthrough experiments to determine the breakthrough curves that are used to determine the ideal operating bind capacity (OBC) for MCC (i.e., the amount of product bound to the first column before product breakthrough occurs onto the second column).[7] Another important parameter in MCC is the residence time calculated by dividing column volume with flow rate (column volume/flow rate).[8] The design space can then be modeled through a series of single column experiments to determine the range of optimal loading residence times to achieve desired productivity.

To facilitate the process transition, many MCC systems offer complementary software that enables in silico modeling of the MCC system. This computational approach can be a valuable tool in predicting the impact of process variability on process performance as well as selecting process parameters, especially during process scale-up. In addition, the simulation data generated from the software is fairly accurate in predicting physical performance of the process as it is verified by the experimental results.[9]

Another appealing feature of MCC is automation. The BioSMB technology, for example, is a fully automated MCC system in which the only manual labor required is to set up the buffer and column connections prior to the continuous run. Moreover, the BioSMB control software provides on-line monitoring and control functions that include UV/vis absorbance, conductivity and pH monitoring of multiple outlets, as well as pressure measurements at all inlets.[1] In addition, the use of disposable technologies, such as pre-packed columns, with BioSMB can further simplify the process and reduce labor cost and human error. In MCC processes, pre-packed columns are much preferred to ensure column performance consistency.

CMC BIOLOGICS LEADS THE TRANSITION TOWARDS MCC-BASED DOWNSTREAM MANUFACTURING

The multi-column chromatography technology offers prominent productivity gains and economic advantages for downstream bioprocessing. Despite the upfront capital expenses required for adopting MCC technology, the significant cost savings achieved from resin reduction and productivity improvement make it a justifiable investment, which will benefit the drug developer in the long run. Furthermore, the MCC process is especially beneficial for clinical stage biologics production when the manufacturing budgets are constrained.

Recognizing the financial burden associated with generating clinical products, CMC Biologics has become the first contract development and manufacturing organization (CDMO) that offers multi-column chromatography using BioSMB technology to help clients reduce clinical manufacturing cost through improved resin utilization. CMC Biologics' technology vendor, Pall Life Sciences, is proactively interacting with the U.S. Food and Drug Administration (FDA) emerging-technology group on topics relating to BioSMB and continuous biomanufacturing. With enabling technology and expertise in place, CMC biologics is playing a pivotal role in helping the biopharma industry transform from batch processing to MCC-based manufacturing. P

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Currently at CMC Biologics as a Process Development Scientist, **Dr. Michelle Najera** oversees both early-phase and late-phase biotherapeutic processing. In her role, Dr. Najera develops protein purification processes to include chromatography processing and scale-up to cGMP manufacturing. Before joining CMC Biologics, Dr. Najera worked at Genentech in Manufacturing Sciences. She earned her undergraduate degree in chemical engineering at University of California Los Angeles and her Ph.D. at University of Pittsburgh.

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NEW STRATEGIES REQUIRED TO MEET CHANGING NEEDS IN THE ANALYTICAL SERVICES MARKET

BY **MAGDALENA MEJILLANO** AND **LIJUN DUAN**, BIODURO

The pharmaceutical analytical services market is growing, but the competition is heating up. (Bio)pharmaceutical companies rely on analytical service providers to provide high-quality support for core testing needs so they can best leverage their internal resources. To meet industry needs for high-quality, rapid, cost-effective testing services, BioDuro is now offering clients an enhanced strategy to access its extensive analytical expertise for the support of discovery, formulation, development and manufacturing activities through new standalone analytical services.

STRONG GROWTH WITH INCREASING COMPETITION

Bioanalytical services accounted for the largest share of the global healthcare analytical testing services market in 2015,[1] reflecting the rising percentage of large-molecule drugs in the pharma industry pipeline – a trend that is expected to continue for the foreseeable future. On the other hand, the batch-release testing segment is expected to grow more than any other segment during the next five years, according to Markets and Markets.[1]

North America currently dominates the pharmaceutical analytical testing services market due to the large number of well-established service providers and high-quality standards, as well as rapid growth in the biosimilars and biologics segments in the region.[1] The Asia-Pacific market is growing the fastest, however, due to the cost advantages offered by companies in India and China.[1] There are challenges with outsourcing analytical services to the region, particularly with respect to quality and intellectual property. In China, the former is actively being addressed by China's Food and Drug Administration, which has issued stricter regulations and begun cracking down on noncompliant companies. These aggressive actions are anticipated to drive additional outsourcing to the country in the future.

The strong growth of the pharmaceutical analytical testing services market has attracted many new entrants, leading to steadily increasing competition for well-established, standalone service providers. Today, many contract development and manufacturing organizations (CDMOs), both large and small, that have analytical capabilities to support their development and manufacturing activities, now offer analytical services and some expertise as well. Numerous smaller firms specializing in analytical services only have also entered the market and compete on pricing and possibly shorter turnaround times.

OUTSOURCING ALLOWS REDIRECTION OF RESOURCES

As the complexity, not only of new drug substances, but also of drug development, formulation and manufacturing processes, continues to increase, (bio)pharma companies are pressured to make maximum use of project resources. Outsourcing of an ever-wider variety of essential analytical functions that don't require extensive training, expertise or equipment has therefore become the norm.

Analytical method development, including optimization and transfer, analytical method validation, release testing, stability studies and associated testing (e.g., micro testing) and raw material testing, are all core services required by all pharmaceutical companies and most frequently outsourced. By doing so, they free up resources for redirection to address more challenging research and product development issues and/or complex/proprietary activities related to specific products. Release, stability and raw material testing are the most commoditized analytical functions and offer the greatest opportunities for cost savings.

There are a few exceptions where the need for specialized expertise and equipment is driving outsourcing. Demand for extractable and leachable (E&L) testing has grown in recent years as the adoption of single-use technologies has become much more widespread at the commercial scale. Demand for API and product characterization are also on the rise. Both E&L analyses and characterization studies require expensive instruments (mass spectrometers and nuclear magnetic resonance imaging systems) and most companies cannot justify the expense of purchasing and maintaining such equipment and the experts required to conduct the analyses and interpret the results. Outsourcing of this testing, which often is the last testing required prior to filing of a new drug application (NDA), is growing.

QUALITY, COST AND TURNAROUND TIMES MATTER

While cost savings was initially the main driver for outsourcing in the pharmaceutical industry, today (bio)pharma companies seek much more than just reduced project expenses. Indeed, according to the 2016 Nice Insight CDMO Outsourcing Survey (n=587), improving quality is the number one goal, followed by reducing time to market, increasing efficiency and reducing cost.[2]

Manufacturers seeking analytical testing service providers look for quality in terms of technical performance – i.e., the quality of the data and work performed – as well as with respect to regulatory compliance. In particular, the ability of an analytical testing outsourcing partner to recognize out-of-specification (OOS) materials very early on in a project and proactively deal with such issues is crucial; if caught at a late stage, OOS issues can lead to the derailment of projects.

Cost does remain a factor, of course, particularly for more commoditized services. However, most customers do not consider cost as an independent determiner of partner selection. Rather, the cost versus value equation is the decision driver. Most clients are willing to pay a premium if the service provider offers measurable added value.

For analytical services perhaps more so than other outsourcing activities, rapid turnaround times are crucial to client success. The results of analytical testing are required before many key decisions in the drug development process can be made. Consequently, analytical service providers can impact the progress of a program at all stages, including formulation-selection manufacturing process decisions and release of clinical trial materials, to name a few.

> FOR ANALYTICAL SERVICES PERHAPS **MORE SO THAN OTHER OUTSOURCING ACTIVITIES**, RAPID TURNAROUND TIMES ARE CRUCIAL TO CLIENT SUCCESS.

For smaller and emerging (bio)pharmaceutical companies, the ability to provide regulatory expertise can be a real differentiator when it comes to choosing an analytical testing partner. These firms often require assistance with everything from initial new drug applications and NDA filings to addressing questions raised by the relevant regulatory agencies. Analytical service providers that have a deep understanding of the drug development process and extensive knowledge of regulatory requirements, combined with the ability and willingness to provide customized support, are viewed as offering real added value. These companies also appreciate outsourcing partners – including analytical testing service providers – that offer innovative contract options, including creative risk-sharing, dedicated resources (FTE models) and other financial incentive solutions.

NEW STRATEGY TO LEVERAGE DISCOVERY AND DEVELOPMENT EXPERTISE

As a provider of end-to-end solutions for integrated drug discovery and development, chemistry, DMPK, API synthesis and optimization, formulation development and cGMP manufacture of drug products, BioDuro has extensive analytical testing expertise to support all phases of drug development

from discovery to clinical-trial material manufacture. The company is implementing a new strategy to leverage these capabilities to meet the growing demand in the pharmaceutical industry for high-quality, rapid analytical testing support with the introduction of standalone analytical services.

With both discovery- and development-related analytical expertise, BioDuro can support clients across the full development cycle, including studies to support discovery and candidate selection; preclinical to clinical activities, including API synthesis, screening and characterization; preformulation and formulation development; and engineering batch and clinical trial material manufacturing efforts. The analytical data drives several critical decisions as one navigates through several CMC drug development processes. Having an expert analytical team equipped with the right know-how and tool box to accelerate scientifically sound decision-making is essential to any program's success.

By offering standalone services, the company will be able to leverage its analytical expertise to help clients at early stages of their development projects through late-phase clinical trials. One advantage of the analytical arm of a CRO and CDMO like BioDuro is the ability to better understand the physical, chemical and biological properties of the API and drug product as well as the challenges of the formulation and manufacturing process. This inherent expertise will enable the development and optimization of the analytical methods more effectively and efficiently. With this new strategy, BioDuro is also removing most of the barriers generally in place with standalone analytical contract organizations that support different phases of drug development.

Often not well-equipped with knowledge of background information on and experience with the API and dosage form process development, a contract analytical testing laboratory can be handicapped when it comes to selecting the best analytical approach to develop methods, or troubleshooting atypical or out-of-specifications analytical data, among other things. The extensive collaboration approach at the company – along with centers of excellence in chemistry, DMPK, solubility and bioavailability enhancement – will facilitate problem resolution, allowing the identification of analytical problems early on in a project before they become significant issues. As a result, the negative impact that analytical challenges can have on the overall program's quality, timelines and costs can be minimized.

New clients can also use the standalone analytical services as an effective mechanism for evaluating BioDuro as an outsourcing partner for formulation development, manufacturing and other services. Consequently, the new standalone strategy is anticipated to help grow BioDuro's business by utilizing various entry points within its continuum of service offerings. Expanding the analytical strategy from being a purely support function to a critical driver of the rest of the business functions within BioDuro is particularly aimed at enhancing the value that the company can provide to its customers.

As a key differentiator, being a smaller CDMO with niche areas of expertise, BioDuro is highly nimble and responsive and capable of forming deep collaborations with smaller/emerging (bio)pharma companies that desire flexibility and responsiveness from their partners and require additional technical and program management support. With its deep knowledge of the drug discovery and CMC drug development process, including its challenges and barriers to success, BioDuro is able and willing to help these partners fill in the gaps in order to accelerate development times.

CONCLUSION

Demand for analytical testing support is growing within the pharmaceutical industry as biopharmaceutical companies seek to maximize the use of internal resources for highly complex and proprietary activities. BioDuro, with both discovery and development components, has analytical expertise not typically found at other CDMOs that enables the establishment of analytical strategies and the resolution of analytical method challenges earlier on in the development cycle for reduced client-program risk in a more cost-effective manner. P

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Magdalena Mejillano is a proven industry leader with over 22 years of experience managing analytical contract organizations. She led the significant and consistent growth of PPD's cGMP laboratory for 19 years, where it became well-renowned for its breadth and depth of analytical capabilities. Prior to joining BioDuro, she served as a management consultant at Bristol-Myers Squibb's commercial biologics division, leading business process improvement initiatives. At BioDuro, she heads up the global CMC business — including formulation, analytical and clinical trial material manufacturing — and is based in San Diego, CA.

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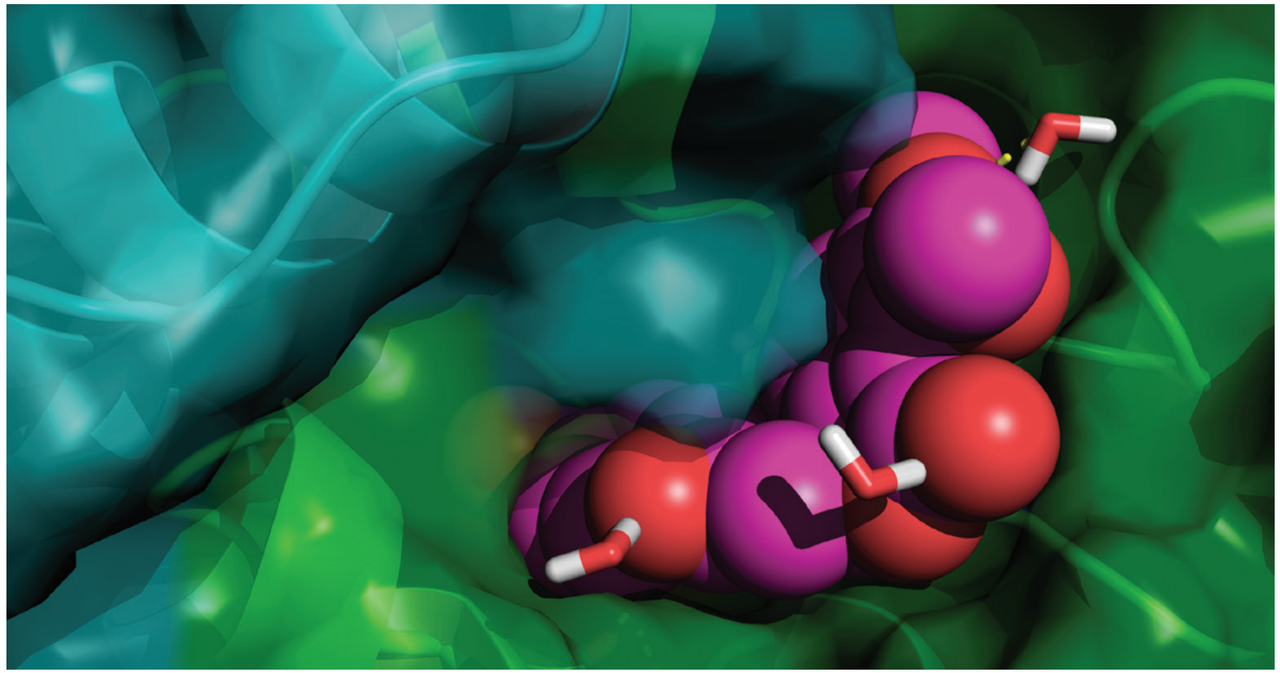
TRANSFORMING THE PHARMACEUTICAL INDUSTRY PIPELINE WITH IN SILICO APPROACHES

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

Fifteen years ago, the pharmaceutical industry was abuzz: Computational modeling was about to transform the drug-discovery paradigm. Compound modeling and screening in silico would save lives, years of research, millions of dollars in costs and largely put an end to animal testing.[1] Yet, when in silico success stories didn't start pouring in, a kind of general malaise toward this approach fell over the pharmaceutical industry.



"Most of the revolutions that happened in silico," says Douglas Krafte, Chief Scientific Officer of Icagen, Inc., "happened in the subfields such as biology and chemistry, not in the fully integrated design and generation of new drugs."[2] A 2009 article published on the topic of in silico models in *Drug Discovery Today* confirms this phenomenon: "Although the development of computational models to aid drug discovery has become an integral part of pharmaceutical research, the application of these models often fails to produce the expected impact on productivity."[3] The inability of these in silico methods to shorten the timetable from R&D to Investigative New Drug (IND) status – as the industry anticipated – made many of the larger pharmaceutical companies hold tight to more classical drug-discovery approaches, implementing computational models only as a type of follow-on when the traditional approaches failed.

Another major shortcoming of the early in silico approaches was the method's inability to detect off-target pitfalls. Compounds detected as having a high affinity for a specific target, which in silico models *had* predicted, produced detrimental downstream effects caused either by off-target binding or toxic metabolites.[1] The early computer simulations simply weren't robust enough to test many of the possible downstream outcomes, and so, evaluating the cost-benefit ratio of in silico approaches, many larger pharmaceutical companies decided to continue on the well-trodden path.

NIMBUS DISCOVERY

Then, also in 2009, the venture capital firm Atlas Venture teamed up with Schrödinger LLC, a New York–based company that primarily developed chemical simulation software and computational models focused on physics simulations, and with additional seed money from Bill Gates created the in silico–based pharmaceutical company Nimbus Discovery. With its expertise in multifaceted simulations for complex chemical structures, Schrödinger – along with top-in-the-field in silico scientists – hoped to customize and expand its software suite in order to make headway in what was then a sluggish in silico drug-discovery domain.

And it did. In April of this year, Gilead Sciences Inc. (best known for its effective hepatitis C treatments) purchased Nimbus Apollo, one of a half-dozen drug-discovery subsidiaries under the Nimbus Therapeutics umbrella, for a deal valued at $1.2b ($400M up front with up to $800M in development-related milestone payments).[4] The deal was based on Nimbus Apollo's successful phase I testing of an acetyl-CoA carboxylase inhibitor, "a master regulator of fatty acid synthesis and oxidation, [that] has been a sought-after yet intractable target over the past two decades."

EXPERIENCE OVER TERAFLOPS

The success of Nimbus did not go unnoticed by companies like Icagen Inc., a drug-discovery pharmaceutical company known for bringing many successful compounds to IND. In July of this year, Icagen made a transformative move that changed the face of the company by acquiring Sanofi's facility in Tucson. With the purchase of the Tucson facility, Icagen – known in the industry as the preeminent researcher and developer of compounds that target ion channels – acquired the second-best (only behind Schrödinger) high-performance computational suite for in silico drug discovery.

Although the computational power of the Tucson facility is praiseworthy, "in-house computational power doesn't mean much these days," says Anil Nair, director of In Silico Drug Discovery at Icagen. "Why build one house when you can rent houses all over the world? A pharmaceutical company could call up Amazon tomorrow and buy whatever cloud computing power they need for the day, a week, or a year: 200 teraflops, 400 teraflops – computing power greater than anything Icagen or even Schrödinger has in-house."

What Dr. Nair is alluding to is that advanced software suites and massive computing capabilities are available everywhere today – what makes a difference is experience. Companies like Icagen, with almost a quarter of a century's experience in drug discovery, are looking at the successes of Nimbus and realizing that by bringing in silico approaches to their existing platform, they can greatly reduce the time it takes to bring a candidate to IND. Some numbers being thrown around at Icagen these days are 24, or *even* 18 months to IND – a remarkable number considering the standard industry estimation is over five years.[6]

Besides being a transformative move, Icagen's acquisition of the Sanofi facility brought "incredible talent, experience and capabilities," says CEO Richie Cunningham, referring to the top scientists that will remain on-site at the Sanofi

facility as part of the agreement. This includes a group of scientists with a very high level of expertise with in silico drug discovery "that positions Icagen as a Target to Lead Generation company at a time when there is a significant gap and need in the industry for quality leads. We at Icagen believe that selecting the right targets of interest based on market needs, combined with targets that fit our areas of expertise, is the key to our success." What the move also brought about was the Sanofi Tucson facility's reach in terms of drug discovery. Although Icagen had predominantly focused on ion channels and transporters, the facility at Tucson has a much wider range of targets that Icagen now adds to its repertoire.

NARROWING THE PIPELINE: HOW IN SILICO WORKS

In many ways, scientists using in silico approaches for drug discovery have much in common with video game developers. When performing virtual screening, millions of compounds are docked into three-dimensional models of a specific target and scored based on the interactions. Molecular dynamics closely follow target conformation over time. Such simulations can be carried out for protein ligand complexes with solvent and membrane systems. The larger the system, the more the computing power needed and the longer the calculation (some can take weeks). Most steps require state-of-the art computer graphics hardware.

By supporting a drug discovery program in silico from the very beginning, a pharmaceutical company can weed out thousands of compounds that don't have a strong affinity for the target and compounds with potential liabilities. These include off-target activities, metabolism issues and suboptimal compound physico-chemical properties.

Fewer, stronger candidates means fewer compounds that chemists have to produce for any one specific target. Fewer compounds for any specific target means that a company can partner with a provider like Icagen and, without changing its size or makeup, run more drug-screening programs. A company that had its chemists producing 2,000 compounds for one drug screening program can now (by utilizing the advantages of in silico approaches) have its chemists produce only ~200 well-designed compounds for the same protein target and thus significantly accelerate the discovery program and use the spared resources to take on new programs

BRINGING IN SILICO APPROACHES TO ION CHANNELS AND TRANSPORTERS

The ion-channel drug market is expected to grow to $21.4b by the end of 2018, up from $12b in 2012.[7,8] Some of the most universally difficult targets for in silico approaches are ion channels and transporters, due to challenges in mapping their three-dimensional structures. Ion channels and transporters are integral to many cellular processes, and the too-many-to-list diseases and ailments that arise when they malfunction have caused Icagen to build a considerable suite of traditional drug-screening approaches targeting them. These include an extensive portfolio of cell lines expressing difficult targets such as all the major ion channels and transporters, a label-free X-ray fluorescence method for direct ion flux measurements and assays for drug candidate screening based on several different technologies combined with robotic ultra-high-throughput screening, available at the Tucson facility.

THE ION-CHANNEL DRUG MARKET IS EXPECTED TO GROW TO $21.4B BY THE END OF 2018, UP FROM $12B IN 2012.

Icagen's already-established ion channel discovery suite, paired with their now-considerable in silico capabilities, makes it an ideal partner for a pharmaceutical company looking to create compounds for an array of targets for which structural information is available. On the plate now are well-mapped-out structures for targets, whose mutations play a big role in human disease, such as inherited developmental and metabolic disorders and certain cancers. An ambitious client looking to target ion channels and transporters could find no better partner than Icagen. P

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Cynthia's role is in helping to translate science into content to facilitate the broader discussion between clients and their customers across the pharma-biotech market. Dr. Challener is an established industry editor and expert in the areas of chemistry and pharmaceuticals. Cynthia earned her BS in chemistry from Stanford University and holds a Ph.D. in organic chemistry from the University of Chicago.

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ACHIEVING SUCCESSFUL TREATMENT OUTCOMES THROUGH THE DELIVERY OF MANUFACTURING SERVICES

→ BY **JANICE GRAFF**, GLAXOSMITHKLINE AND
KASHAUNA ROHLEHR, GLAXOSMITHKLINE BIOPHARMACEUTICALS

In the rapidly growing but highly competitive biopharmaceutical market, drug innovators require the support of biologics contract manufacturers that offer more than just additional capacity. They must be financially stable, have an in-depth understanding of market needs and regulatory requirements, manufacturing expertise for right-first-time project implementation and a commitment to continuous improvement across all activities.

GROWING MARKET

In 2015, according to BioPlan Associates the market for biopharmaceuticals was valued at $200 billion and growing at ~14% annually.[1] Ten to 15 new biologic treatments are expected to receive approval each year, and the top products already on the market have annual sales of over $2 billion.[2] Notably, 66% of the (bio)pharma professionals responding to the 2016 Nice Insight CDMO Outsourcing Survey (n=587) indicated that their current and future product pipelines include large-molecule new biological entities (NBEs). In addition, 75% to 80% of survey respondents have biologic candidates under evaluation at each phase of development from discovery through Phase IV/post-launch.[3]

Given the healthy state of the biologic drug market, it is not surprising that the biopharmaceutical contract manufacturing market is also experiencing strong growth. The value of the market in 2015 was estimated by HighTech Business Decisions (HBD) to be $3 billion. HBD also predicted that biopharmaceutical contract manufacturers would increase mammalian cell culture production capacity by 14% and microbial fermentation production capacity by 16% by the end of 2016.[4]

As strong growth in the biopharmaceutical market continues, both innovator companies and contract development and manufacturing organizations (CDMOs) are being affected by three key trends: increasing concentrations for cell-culture and fermentation processes, which is creating the opportunity to adopt smaller-volume, single-use equipment and placing pressure on downstream processing systems; the need for increased capacity, which is driving significant investments in facilities and equipment; and a shift to parenteral formulations, which is creating demand for sterile fill/finish technologies and expertise.

CHALLENGING ENVIRONMENT

Despite the rapid growth of the market and the trends outlined above, changing market dynamics are creating challenges for sponsor companies and their contract service providers. With blockbusters being replaced by targeted/personalized medicines (e.g., antibody-drug conjugates and cell therapies), new approval pathways for biosimilars and growing expectations for treatments that provide improved outcomes over existing products at lower cost (i.e., value- or evidence-based medicine), there is more pressure than ever to be first to market. State-of-the-art manufacturing capabilities that are more efficient, more scalable and more cost-effective increasingly play a role in the ability of drug manufacturers to get life-changing treatments to patients.

NEED FOR RELIABLE OUTSOURCING PARTNERS

While reducing costs was initially the key driver for outsourcing of biopharmaceutical manufacturing, today there are many reasons why biologic drug makers seek support from CDMOs. Improving quality, in fact, is the top goal, according to participants in the 2016 Nice Insight CDMO Outsourcing Survey.[3] Reducing cost is of fourth importance after reducing time to market and increasing efficiency. Sponsor companies also hope to leverage contractor regulatory expertise, gain competitive advantage and access specialized technical and operational expertise.

Many of those goals can only be achieved through close collaboration with a reliable outsourcing partner – the type of collaboration that requires real commitment by both parties and results in long-term strategic partnerships. Operational, methodological and therapeutic expertise combined with a strong quality record and positive regulatory history will lead to a successful relationship or outcome. A demonstrated ability to meet project deadlines and clear commercialization successes that include delivery of product on or ahead of schedule and at or under budget are essential for CDMOs desiring to participate in such relationships.

Good communication skills, a thorough understanding of customer requirements, knowledgeable and professional experts, transparency and a willingness to go beyond contract specifications also facilitate strategic partnerships. Successful CDMOs collaborate closely with biopharmaceutical manufacturers and continually share information through open lines of communication, allowing for the identification and resolution of any problems before they become serious.

All of these characteristics enable CDMOs to help their biopharmaceutical customers reduce the risk of outsourcing and simultaneously achieve their other goals. Financial stability, which has become increasingly important as a risk mitigation factor due to the turbulent conditions in the pharmaceutical market, is also vital.

PROVIDING CAPACITY IS INSUFFICIENT

An integrated CDMO that is part of a world-leading pharmaceutical firm also has the ability to provide efficient and effective process and analytical method

“RIGHT FIRST TIME” TECHNOLOGY TRANSFER, WHETHER OF AN ESTABLISHED PROCESS **FROM A CUSTOMER FACILITY TO THE CDMO OR FROM THE PROCESS DEVELOPMENT LAB** TO THE PRODUCTION FACILITY WITHIN THE CDMO, **IS A CRUCIAL CAPABILITY** FOR COMPETITIVE BIOPHARMACEUTICAL CONTRACT SERVICE PROVIDERS.

development support, both of which are essential for achieving cost-effective, robust biopharmaceutical manufacturing operations. Processes designed with scale-up to commercial volumes in mind enable much smoother technology transfer, reduced manufacturing issues, higher product quality, lower processing costs and faster time to market.

“Right first time” technology transfer, whether of an established process from a customer facility to the CDMO or from the process development lab to the production facility within the CDMO, is a crucial capability for competitive biopharmaceutical contract service providers.

Process development begins with the expression system and continues through to biologic drug substance release, covering all of the upstream and downstream unit operations that lie in between, plus analytical and cleaning method development and validation. True biopharmaceutical CDMOs can support their clients across the entire gamut of process development activities, including cell line development and banking, scale-down, process characterization utilizing design space mapping via design of experiment (DoE) approaches, process optimization, and viral clearance studies and toxicology lot manufacture – in addition to scale-up, tech transfer, GMP manufacture and validation.

CONCLUSION

GSK's focus is to deliver more products of value, both as a CDMO supporting our biopharma partners and as a world-leading drug manufacturer. The ultimate goal is to provide novel medicines to patients in need. For instance, through our agreement with Verily Life Sciences (formerly Google Life Sciences) to form Galvani Bioelectronics, we will be developing and commercializing bioelectronic medicines. We have also recently introduced several new monoclonal antibody drugs, including Benlysta (belimumab) for the treatment of active systemic lupus erythematosus (SLE or lupus), the first lupus treatment approved by the FDA in over 50 years; Nucala (mepolizumab), an add-on maintenance treatment for severe asthma; and Sirukumab (INN, USAN) for the treatment of severely active rheumatoid arthritis (RA). In Europe, GSK will also be offering Strimvelis, a first outright gene-therapy-based cure for a rare disorder, specifically ADA-SCID, a sometimes-fatal inability in children to fight infections.

GSK continues to invest in high-quality manufacturing. At the Upper Merion facility outside of Philadelphia, GSK is expanding its cell-culture production capabilities at the 5000 L scale to support late-phase clinical and commercial production. These investments will enable GSK to continue to accommodate the strong organic growth that the biopharma sector is experiencing.

These examples highlight the depth of GSK's commitment and expertise in the development and commercialization of novel biotherapies. As a CDMO that operates as an independent group within a large pharmaceutical company, GlaxoSmithKline Biopharmaceuticals' goal is to utilize this extensive knowledge and our global manufacturing network in order to serve as a reliable partner that delivers more products of value through world-class manufacturing and thus contributing to exceptional treatment outcomes for patients. P

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FINDING THE IDEAL PARTNER FOR YOUR NEXT BIOTHERAPEUTIC

→ BY **HEATHER DELAGE**, BIOVECTRA

Specialty and biological drugs that require complex manufacturing, such as fermentation, are projected to account for half of the pharmaceutical industry by 2020,[1] with facilities that develop and manufacture many of these compounds looking to expand current operations by 25% in the same time frame.[2]

Biopharmaceutical companies with portfolios heavily staked in the development of therapeutics that require some form of fermentation – namely many active pharmaceutical ingredients (APIs), peptides, antibodies and other small molecules – face the challenge of creating medium- and long-term production plans. Building a new bioprocessing facility that is capable of handling the development and manufacturing of complex biotherapeutics can cost anywhere from $50M to $650M, and may require up to four years to complete.[3] Although the upfront cost of building a facility may seem substantial, it is often much less than the potential revenue lost by missing a drug launch date, which is estimated at anywhere from $1M/day to $14M/day – with "blockbuster" drug releases reaching even higher.[4] In order to mitigate the amount of time and effort necessary to build a new facility, many biopharmaceuticals form strategic partnerships with specialized CDMOs that already have the necessary bioprocessing facilities in place.

Established on Prince Edward Island in Atlantic Canada 45 years ago, BioVectra has 10-plus years of experience in producing small molecules, APIs (including high-potent APIs and cytotoxic compounds), peptides, and complex antibodies using filamentous fungal and bacterial strains, native and recombinant bacteria, and salt-water microbial organisms. In the past year the organization has had a 100% success rate in fermentation reactions, producing 33 distinct sets with an average titer well above the industry standard.[5] Recently the company has expanded their fermentation capabilities to include a third commercial fermentation suite in the geographically distinct location of Windsor, Nova Scotia.

By the end of 2016, the three fermentation suites – each capable of producing cGMP products – will have a total capacity of over 65,000 liters. Each of the three suites house bioreactors of different capacities to meet a client's specific needs, whether it be research and development (2 x 30 L; 1 x 100 L; 1 x 130 L), clinical (1 x 500 L; 1 x 1,000 L; 1 x 1,500 L; 1 x 3,000 L), commercial (1 x 10,000 L; 1 x 15,000 L; 2 x 17,000 L) or any combination of the three. Experience paired with the diversity and breadth of upstream equipment makes BioVectra an ideal partner for producing both commercial mainstream biotherapeutics and assisting in the development and production of biotherapeutics for a niche market. P

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Heather Delage, Vice President, Business Development for BioVectra, has 25 years of experience in marketing management, project management and business development in the pharmaceutical, biotechnology and clinical diagnostic industries. She holds a BBA with concentration in marketing from University of Prince Edward Island.

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SPEED-TO-MARKET: PROCESS AND CAPACITY ON DEMAND

→ BY **ROBERT E. CHEW**, COMMISSIONING AGENTS, INC.

New pharmaceutical development and business models alike rely on speed-to-market for success. Those able to implement their process first by securing commercial-scale GMP capacity faster than their competitors will have a distinct advantage.

The business of drug development and manufacturing has fundamentally changed. On the one hand, commercializing and manufacturing new, class-leading drugs has become increasingly cost-prohibitive. Globally, most mature markets will continue to increase their per capita drug spending. China's growth rate, for example, is expected to jump 70% by 2018,[1] according to IMS analysis.

SPEED-TO-MARKET AS THE KEY TO SUCCESS

The pharma industry has capitalized on advances in medicine and science with product and process innovation. Companies have reshaped their business models to overcome regulatory and market access hurdles, while at the same time remaining competitive. They have extended the life of their portfolios. They have established operations in emerging markets in order to meet post-patent protection business goals, satisfy shareholder expectations and serve untapped markets. Speed – specifically, speed-to-market – has been and remains the key to success. In order to achieve fastest time-to-market, one must have reliable access to cGMP process capacity, when and where it is needed.

According to PricewaterhouseCooper, drug developers rely on four strategies in order to increase profits: research and development productivity, patent and product extension, marketing and sales initiatives, and manufacturing and supply chain cost-efficiency measures.[2] Advances in knowledge and information management have allowed companies to create new products and develop new processes more quickly. However, there are still limitations within the R&D process, particularly with regard to clinical development. In value-based systems, clinical demonstration is clearly becoming more important, and potentially costlier, to drug companies and innovators. That being said, as both human genomics and pharmaceutical science continue to advance, we can anticipate a higher success rate from trials. This means more therapies in less time, which, as a result, will put more pressure on those responsible for delivering manufacturing capacity.

A product's success depends on a rapid transition to market, which is why achieving full-scale production in less time has many benefits, such as extended patent protection for approved drugs. Likewise, penetrating new markets before the competition can produce a profound and lasting advantage. Manufacturing capability, once perceived as a time-consuming obstacle to initial market penetration, now determines success more than ever before.

Historically, costs over the life of the product were relatively small when compared to the initial cost of R&D. And so, in tandem with restrictive regulatory expectations, this view prompted many organizations to focus on R&D investment and marketing in order to be more competitive.

SPEED – SPECIFICALLY, SPEED-TO-MARKET – **HAS BEEN AND REMAINS THE KEY TO SUCCESS.**

But the environment has changed. Now, the ability to field operationally excellent manufacturing capability determines whether or not one can respond effectively to both market opportunity and to the current GMP regulatory climate. Indeed, in a survey conducted at a recent ISPE meeting, pharmaceutical executives indicated that *flexibility* was the most important characteristic of future manufacturing operations

Consumers are disinclined to pay for poor-performing drugs. In order to improve dose adherence and therapeutic performance, drug makers need faster access to advanced manufacturing capability. Likewise, drug designs have become more complex. In order to manufacture them correctly and compliantly, these newer drugs require a range of current design and engineering techniques, including more sophisticated automation.

To put the situation bluntly, those fastest to market will win, regardless of the product or the market strategy. And getting products on the market quickly requires flexible manufacturing capabilities. However, for many industry players, the capability to engineer and build manufacturing capacity can be extremely challenging. With all the intricacies and complexity involved in building and commissioning full-scale manufacturing capacity, even the most adept organizations are seeking better methodologies in order to acquire what they need within the tighter and tighter time frames.

As the healthcare product manufacturing industry has evolved, organizations focus more and more on delivering their core services. As a result, they rely on outsourcing, managing risk by fostering deeper, closer relationships with their strategic partners. They do this for two reasons. First, outsourcing allows them to access development and manufacturing expertise.

COMMISSIONING AGENTS, INC.

BioVoke™

Commissioning Agents offers a GMP information management suite, BioVoke™, which facilitates the successful delivery of a quality-by-design manufacturing operation. The software platform is designed to help pharma and its supply chain partners meet cost-reduction and schedule-reduction goals while answering the mandate to deliver quality and compliant manufacturing facilities. BioVoke provides operations managers and facility leadership with efficient information management and electronic testing capabilities. This in turn helps plant operations execute their mission to deliver highly reliable, high-performance, qualified facilities and processes.

Commissioning Agents, Inc. designed its web-based software to be a unified, single-system solution that seamlessly integrates process control strategy, quality risk control, user requirements, test plans, critical design aspects, commissioning, FAT, SAT, verification, protocols, punch lists, discrepancies, TOPs, SOPs, project changes, deviations, meeting minutes, scope definition, key decisions, action items and more. BioVoke allows for real-time collaboration and provides an efficient process to deliver GMP manufacturing capacity. BioVoke supports traditional C&Q approaches or the ASTM E2500 approach to meet quality risk-management expectations based on product and process knowledge.

Second, outsourcing allows them to span any gaps in manufacturing capability and accelerate their go-to-market plans.

We have established that developing flexible, fast and sophisticated manufacturing capabilities is essential to compete and succeed in the current market. For many, the question still remains "how to get there from here?" Constructing, commissioning, achieving full-scale operation and maintaining a GMP manufacturing facility is a complex process. In particular, teams responsible for delivering this capability must successfully integrate [1] the molecule and its process chemistry; [2] the equipment, systems and automation; [3] process control strategy; and [4] human performance elements. Most teams focus on placing an asset in service, fully qualified. But that does not get us to successful GMP operational capability. Instead, teams must engage with many stakeholders, interacting across functional and managerial boundaries to create, share and develop information. Projects of this magnitude are a personnel- and information-management challenge.

A FIELD GUIDE TO FULL-SCALE OPERATIONS

The recipe for success requires equal parts innovation and experience. Over the past twenty years, Commissioning Agents, Inc. has led the industry in helping our clients to improve the performance and reliability of their processing and manufacturing facilities. We have distilled our two decades of collective wisdom into a standardized method – entitled *FIELD BOOK: The Chemistry of Full-Scale Operations* – for bringing GMP manufacturing capacity to fruition, from concept to operations. The Commissioning Agents, Inc. platform distills GMP production into five integrated elements (see figure), which outlines the necessary steps to develop successful, cost-effective, high-yield, reliable, efficient and compliant operations.

The FIELD BOOK's rubric is organized into five well-defined modules to take a product from development to full-scale operations:

[1] Project
[2] Process/Product
[3] Staff
[4] Facility
[5] Quality

The FIELD BOOK's approach listens to the "Voice of the Product" to determine what a product truly needs from its manufacturing quality system to be reliably produced in a high-yield, high-quality manner. The FIELD BOOK integrates information technologies, staff development and operation design to allow owners to effectively manage and operate full-scale product manufacturing operations in a GMP-regulated industry. Speed-to-market has never been more important to drug owners and developers. Getting to commercial-scale processing the fastest with safe, robust GMP manufacturing is the goal, and the Commissioning Agents, Inc. FIELD BOOK offers the map and the means to achieve it. P

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Mr. Chew is President and CEO of Commissioning Agents, Inc. Commissioning Agents is a leader in helping companies achieve faster project delivery and higher levels of performance and reliability from their GMP-regulated manufacturing operations. The company has operations in North America, Europe and Asia. Mr. Chew began his career as a U.S. Naval Officer, serving on a nuclear submarine. He has a BS in chemical engineering from Case Western Reserve University, and is a registered Professional Engineer.

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THIS JUST IN

Get The Latest Industry News

New Capabilities and Capacity From Alcami

In August, Alcami announced plans to expand capabilities and capacity for the production of highly potent active pharmaceutical ingredients (HPAPIs). With investment into 2017, the company plans to enhance new and existing facilities at its Germantown, Wisconsin facility.

This 5,000-sq.-ft. renovation will include two new, fully qualified state-of-the-art cGMP production facilities housing up to 150L reactor-scale and cryogenic capabilities, and will increase capacity by 50%. These enhancements – scheduled to be operational by Q1 2017 – will pair with Alcami's potent drug product expertise and its existing API facility in The Netherlands to further strengthen the company's offerings. Additionally, a recent FDA General Inspection at the facility found zero 483 observations, further illustrating the company's expertise in and commitment to new clinical candidates.

Alcami, as the product of a merger between AAIPharma Services Corp. and Cambridge Major Laboratories, Inc., is a world-class contract development and manufacturing organization (CDMO). The company offers a suite of services from its seven global locations and boasts an advanced presence in the potent Drug Product market. P

Piramal to Acquire Ash Stevens

Ash Stevens, Inc. announced that it has been acquired by Piramal Pharma Solutions, a world-class CDMO with locations in North America, Europe and Asia. As a leading provider of active pharmaceutical ingredients (APIs) and highly potent APIs (HPAPIs), Michigan-based Ash Stevens will add to Piramal's existing presence in North America.

Ash Stevens customers are poised to gain from Piramal's full-service, global pharmaceutical manufacturing facilities. Similarly, Piramal's customers will benefit from the new addition of expert HPAPI services in North America, allowing for the single-source supply of HPAPIs and drug substances.

Located in Riverview, Michigan, Ash Stevens has over 50 years' experience in the development and manufacture of APIs, including HPAPIs. The facility offers cGMP manufacturing, extensive analytical capabilities, regulatory support for all phases of development and manufacture.

"The acquisition of Ash Stevens fits well with our strategy to build an asset platform that offers value to our partners and collaborators," commented Vivek Sharma, CEO of Piramal Pharma Solutions. "North America is a key market that we can now service with our three local facilities – the injectable facility in Kentucky for fill-finish needs, the Toronto facility for complex high-value APIs, and now Ash Stevens in Detroit for HPAPIs. Having facilities with a differentiated platform and a geographical proximity to clients are keys towards building strategic partnerships," he added. P

Two New Business Development Executives Join PCI Pharma Services

Sue Ritchie

Fred Schulze

In addition to several recently announced manufacturing investments, PCI Pharma Services announced two new additions to its U.S. sales team: Sue Ritchie and Fred Schulze. Sue and Fred bring extensive experience with selling in the North American market and, together with the larger PCI sales team, will work with clients across all of PCI's drug development services.

Previously, Sue has held positions at Delavau (most recently), Johnson & Johnson and King Pharmaceuticals, while Fred brings 30 years' experience across the market, specifically as VP of Sales and Marketing at Coating Place Inc.

PCI Pharma Services offers extensive drug development services that pair seamlessly with their clinical trial packaging, labeling and logistics offerings, as well as the company's commercial packaging capabilities. From phase 1 clinical trials through commercial-scale production and supply, PCI has been serving the larger healthcare industry for more than 40 years. P

> "We are delighted to welcome Sue and Fred to the PCI team. They bring extensive experience in selling services within the USA market to our client base of pharmaceutical and biotech companies, which will greatly support our continued growth ambitions.
>
> **Rob Jones**, Executive Director of Business Development, PCI

Icagen and the Nanion SyncroPatch384 Platform

> "We feel that the SyncroPatch384 is the ideal mechanism to leverage Icagen's decades of ion-channel drug discovery experience and extensive inventory of cell lines for our customers and clients.

Icagen Inc. is proud to announce the purchase of a SyncroPatch384 high-throughput electrophysiology instrument from Nanion Technologies, Inc. The companies have entered into an agreement focused on the development of ion-channel assays using this platform. Since purchasing the technology, multiple assays have been developed by Icagen. Douglas Krafte, Ph.D., the company's Chief Scientific Officer, believes SyncroPatch 384 is perfect for managing extensive cell line inventory and sees high value in Nanion's expertise. "We evaluated the available options in this technology space and are excited to have acquired the Nanion platform and to be working with this company. We feel that the SyncroPatch384 is the ideal mechanism to leverage Icagen's decades of ion-channel drug discovery experience and extensive inventory of cell lines for our customers and clients. In addition, we value the relationship with Nanion and the very high quality of engagement and depth of expertise of their people," Krafte commented.

Similarly, Nanion's vice president, Rodolfo Haedo, agrees that the joining of Icagen's ion-channel discovery experience and Nanion's technology will help to advance the field. Overall, the purchase is intended to improve Icagen's customer response regarding the expedited development of some of their clients' more challenging discovery targets.

Nanion Technologies has a global presence (Europe, North America and Asia) and 14 years' experience developing instruments for high-quality ion-channel research. Icagen is an ion-channel leader, with a growing toolbox that includes the XRpro® platform. XRpro® technology, enables high-throughput assessment of ion channels and transporters using X-ray fluorescence. P

Douglas Krafte, Ph.D., Chief Scientific Officer of Icagen, Inc.

Coperion Co-Hosts Continuous Direct Compression Seminar

Coperion offered in-class sessions on topics such as granulation and tableting.

Coperion K-Tron, a buisness unit of Coperion, recently joined forces with Fette Compacting, Glatt Air Technologies, QdB Process Technologies and C-SOPS to present a one-of-a-kind, hands-on seminar. Held at Rutgers University's Pharmaceutical Research Center in Piscataway, New Jersey, this seminar educated participants on several technologies, including continuous operations, tablet press operations, process design and integration, and PAT.

Attendees were encouraged to actively participate, while also learning from technical presentations and an integrated direct-compression line. Those interested in taking additional advantage of the expertise offered by the team of companies were invited to participate in a second day of training with topics including continuous dry granulation.

Based in Salina, Kansas, Coperion designs, develops, manufactures and maintains systems and machines for various industries, including pharmaceuticals. Coperion K-Tron, one of the company's business units, is a leader in the supply of material handling and feeding systems. P

Avara Acquires New Manufacturing Facility

In August, Avara Pharmaceutical Services, Inc. announced its acquisition of Astellas's wholly owned manufacturing facility in Norman, Oklahoma. All employees will remain at the Norman site, which will continue to manufacture certain Astellas products on a contract basis. Under this agreement, Avara will oversee Astellas's continued sourcing of a stable supply of high-quality products from the facility.

Regarding the acquisition, Tim Tyson, Chairman and CEO of Avara, commented, "We are excited to have the APT organization join the Avara team and to add this significant capability to the Avara company. We are honored to have the strategic partnership with Astellas and to manufacture key products for them."

Avara Pharmaceutical Services, Inc., is a Norwalk, Connecticut–based company with facilities in North America and Europe. As a CDMO with broad industry experience, Avara aims to exceed customer expectations with in-full, on-time delivery. P

Icagen Acquires Sanofi Facility

Icagen has officially completed its acquisition of Sanofi's Oro Valley, Arizona research facility, approximately 15 miles north of Tucson, Arizona. The acquisition of Sanofi's ultra-high-throughput biology, screening and chemistry capabilities enhances Icagen's current expertise as a specialized pharmaceutical company with a heightened capability in ion channels and transporters. As part of this agreement, Icagen and Sanofi will collaborate in a multi-year services contract on long-term discovery services.

Icagen's management of a vast Sanofi compound library makes it more accessible to potential partners, thereby increasing the potential for drug discovery. This facility has been operating since 1990 – though not always under Sanofi ownership – and offers capabilities in discovery biology, cell models, human biomarkers and stem cell–based assays. P

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Emilie is responsible for strategic content development based on scientific areas of specialty for Nice Insight research articles and for assisting client content development across a range of industry channels. Prior to joining Nice Insight, Emilie worked at a strategy-based consulting firm focused on consumer ethnographic research. She also has experience as a contributing editor, and has worked as a freelance writer for a host of news and trends-related publications.

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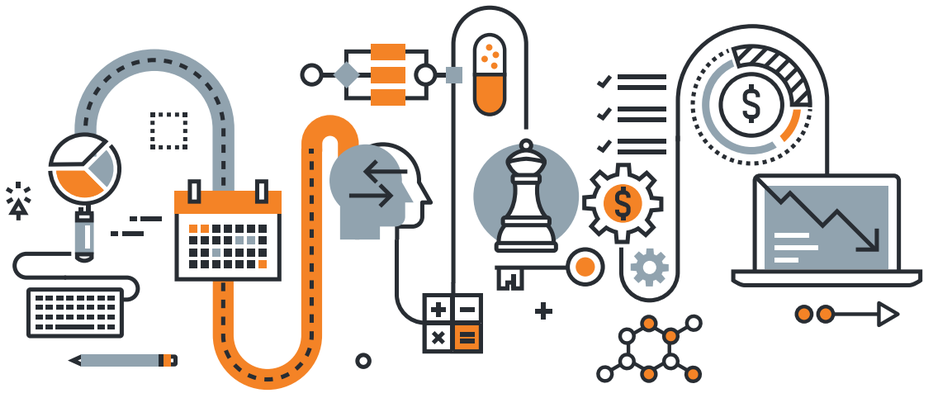
NICE CONSULTING REPORT

PERSPECTIVES ON PRODUCT PRICING STRATEGY AND PRACTICE



Drug pricing remains pharma's most contentious issue. Under tremendous pressure, the industry continues to evolve pricing strategy to satisfy intensive regulation, social/political scrutiny and competitive market forces – how other industries face the challenge of pricing may offer fresh insight to fuel an effective strategy. Getting pricing "right" is a tricky balancing act, but one that offers tremendous value for all.

→ BY **HAIG ARMAGHANIAN** AND **JOSH DUNN**, NICE CONSULTING

IN 2016, two drug-price-related "scandals" ignited near-universal criticism of the pharmaceutical industry, generating angry international headlines sustained by the intense scrutiny of social media. Regardless of the harsh rhetoric and political posturing, drug owners and developers are compelled to understand and consider an amazingly complex set of factors and influences to craft an effective, profitable pricing strategy in response – especially when attempting to introduce a new standard-of-care therapy that has no peer to help with its valuation.

To many consumers, advocacy groups and politicians, the pricing of drugs is seen as an arbitrary, exploitative process – the product of unbridled corporate greed and pursuit of profit above all else. Fortunately, for ethical companies the reality of pricing strategy is much, much different. The complexities associated with product pricing in the pharmaceutical sector continue to trouble the industry's leadership, who are increasingly being driven to justify and defend the valuation process to a broad range of special-interest stakeholders.

Effective pricing comes from discipline and process

It's nearly a given that the more sophisticated the product, the more sophisticated the organization behind it. This maxim applies to pricing strategy equally well, especially in the pharma sector. But no matter the industry, pricing strategy is a distinct discipline. Best practice for most sophisticated commercial and industrial players is to train professionals and staff internally and institutionalize a solid, viable pricing process that serves the commercial interests of the company best. Organizations like the Professional Pricing Society support the discipline, providing continuing education, information sharing and networking to help its members and member companies continuously improve their pricing models.

Pricing models vary, but there's no one-size-fits-all process. One fundamental tenet is that efficient pricing systems tend to be associated with low-margin industries. Retail gasoline pricing, for example, is highly efficient because it fluctuates constantly to balance micro and macro supply-and-demand signals. A prime advantage for gas stations is convenience – so a station located on the higher-traffic side of a street may often price higher; this sort of tactic does nothing to demystify gas pricing to the public. Regardless, if the price of gasoline is perceived to go above historic norms, the industry is subjected to public scrutiny and scorn similar to that experienced by the pharmaceutical industry.

Pricing at the intersection of supply and demand

Effective pricing policy strikes a balance between supply and demand; priced too high, demand falls and vice versa. The classic Disneyland example comes to mind: "When you have customers lining up to come in, your price is probably too low." Studies by the Institutes of Medicine show that if the point-of-purchase price is too high, people tend not to fill their prescriptions and never take the medicines they've been prescribed.

Pricing in the Natural Resource Industry

Oil and similar commodities have specific pricing challenges, and may offer insight into how to respond to fluctuating markets. Oil and gas retailers tend to operate in cyclic markets, commanding higher margins when demand outpaces supply and lower margins (often negative) when market conditions change and supply exceeds demand. As mentioned, gasoline retailers respond to the same inputs on oil-per-barrel price, but rely more on refinery-capacity surplus and shortages (supply) to set gasoline prices. The premise is simple: companies must maximize pricing (margins) during good times so they can cover the downturns in demand and sales during the bad times. In the petroleum industry, the cash and profit generated from high-margin sales and upcycle demand is often invested in exploration, acquisition and production expansion – which eventually leads to increased supply and lower prices/margins.

Cost-plus vs. Value-based pricing

It is generally accepted that value-based pricing is the more effective pricing method. According to Invento's Balaji Viswanathan (VP Products), "Cost-plus pricing calculations are often used by default by many organizations and it creates many problems."[1] Critics of the methodology point out that cost-plus pricing has the dubious ability to simultaneously leave money on the table and leave customers wholly unsatisfied.

One solution to control the industry's ability to set prices is to mandate a cost-plus pricing model. Under such regulation, the government only permits the company to charge just enough to cover production costs

THE TREND TO REGULATE DRUG PRICES VIA COST-PLUS POLICY IS WANING.

and make a "fair return" on the product's sale. This is possibly to allow the drug to be accessible to the general population and prevent the company from gaining too much profit.

However, the trend to regulate drug prices via cost-plus policy is waning. Both Germany and the U.K. have regulated toward value-based pricing regimes. The Affordable Care Act also introduced the value-based healthcare ethic to U.S. consumers as well. The reasons are legion, but setting price on a common understanding of cost and performance between buyer and seller has the potential to serve each party's interests.

Pharma Industry forward

It's clear that, contrary to the traditional approach of product pricing via a cost-plus margin rubric, these practices must now acknowledge the needs and perspectives of the customers as the starting point for any pricing/strategy development discussion. This applies as much to the pharmaceutical industry as it does to any other. The traditional pricing question of "What do I need to charge to cover my costs and make a decent return?" is quickly being supplanted by "Given the market's perception of my product portfolio's value, which of those products can we profitably produce?"

Pricing pharmaceuticals is a challenge. The complexities of establishing value can be both daunting and costly, starting with data from the earliest development phases, clinical trial results and eventually post-approval studies. The value-based pricing model is challenging to implement, especially when the product is first-in-class or aims to become a new standard of care. Ethical dilemmas must also be addressed; pricing to what the market will bear, for example, can result in disproportionately served populations.

Driving Efficiencies

The industry is seeking new ways to introduce efficiencies into all aspects of drug manufacture in order to help offset the external pressures that raise the cost of creating and manufacturing drugs, especially by developing longer-term product strategies that involve moving into the generic space. The rise of generics has also had a significant influence on drug pricing and product strategy, and is a great example of efficient drug pricing in close-competition environments. When margins drop, drug suppliers must refocus their business models on efficient pricing. This includes the need to manage production and supply chain cost more diligently. It's

PRICE OPTIMIZATION IS CRUCIAL FOR A BUSINESS SEEKING TO BOOST ITS BOTTOM LINE.

at this point that CDMO/CMOs can play a key role: As pricing pressure mounts, drug manufacturers can drive economies of scale via a flexible supply chain.

Value of Price Optimization

Price optimization is crucial for a business seeking to boost its bottom line. Experience across multiple industry sectors points to an opportunity on the order of 1% to 2% of gross revenue. In other words, optimizing prices can raise a company's annual revenue by as much as 2%. Overall, a business will gain value in terms of higher cash flow. For example, a $300M corporation can achieve as much as $6M a year in revenue as a result of minimal (<$1M) training and internal process development. Unlike many cost and productivity investments, price optimization can be done quickly (a matter of a few months) without the disruption of restructuring or the need for heavy CapEx investment. In almost all cases, pricing optimization has the better ROI.

Price optimization across the entire pharma value chain has the potential to yield benefits for all – pharmaceutical suppliers, pharma companies and consumers. Ultimately, pharma's drug-pricing policies must focus on discovering, demonstrating and communicating the value of their therapies and the performance of their products to all stakeholders. The world is demanding much more than symptomatic relief from high drug prices, and this has prompted an entirely new valuation calculus for the industry. P

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With over 25 years of experience, **Haig** has accumulated a wealth of knowledge and experience in global business leadership and strategic facilitation and planning. Over the last 15 years, Haig has built Haig Barrett into a leading consulting firm with clients from the chemical, automotive, energy, pharmaceutical and biotech sectors. Prior to founding Haig Barrett, Haig led divisions for leading global Fortune 50 corporations, including Rio Tinto. Haig graduated with a BSc (Hons) in chemical engineering from Surrey University, England.

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As a Senior Consultant, Strategy & Execution Lead for Haig Barrett, **Josh** brings more than 25 years of corporate Fortune 500 experience and over 5 years of consulting experience. Josh has spent most of his working career rising through two companies from the ground up: Avery Dennison and Rio Tinto. Josh has the experience to bring a strategic long-term view on how our clients can expand their market. Josh holds a BA in chemistry and an MBA.

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A NEW INDUSTRY THINK TANK FORUM FOR LEADERS OF OUTSOURCED SERVICES AND CUSTOMERS

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

That's Nice, The Science Agency, has developed "Nice Symposium," a unique industry think tank and interactive approach to enable supply chain partners and their customers to explore, demonstrate and push the envelope on real solutions to pharmaceutical industry needs. The first event, "Nice Symposium — OSD," will focus on challenges around oral solid dosage formulation and is planned for early 2017.

As the pharmaceutical industry undergoes unprecedented levels of change, there are significant opportunities for the development and formulation of breakthrough medicines that can dramatically improve patient lives. To convert those opportunities into successful new drug products, however, numerous obstacles have yet to be overcome.

There is a real need in the industry for innovative dialogue and content around these issues that can drive toward practical and effective solutions. Conventional trade shows and conferences do not create an environment and atmosphere that can truly foster deep communication. To meet this need, That's Nice has created Nice Symposium, an event designed to bring together pharmaceutical professionals from all stages of the drug commercialization cycle (discovery, development, formulation, manufacturing and packaging) so they can learn about and exchange technical knowledge with like-minded and innovative peers and supplier partners.

The first Nice Symposium event is tentatively scheduled for January 31 and February 1, 2017 in Durham, North Carolina and will focus on the challenges associated with oral solid dose formulation. The novel format, which includes a nontraditional open floor plan, is ideally suited for the refurbished American Tobacco Company complex, a unique venue that is itself a new resource in Durham, close to Research Triangle Park and easily accessible.

ORAL SOLID DOSE FORMULATION CHALLENGES

Oral delivery, when possible, is the preferred route of administration because it is the easiest method for patients and has the highest compliance rates. Oral formulations also tend to be the least costly, and there are many different dosage form options (tablets, capsules, gels, liquids, etc.).[1] As a result, oral solid dose forms are attractive not only for new drug candidates, but the reformulation of existing products to extend patent protection or introduce improved generic versions.

Advances in combinatorial chemistry and high-throughput screening (HTS) technologies, while allowing the rapid synthesis of vast numbers of new potential drug candidates, have also resulted in the identification of candidates with promising mechanisms of action but that suffer from poor solubility and bioavailability. These active ingredients present significant formulation challenges and are driving the development of new techniques related to particle manipulation, hot-melt extrusion (HME), spray drying, co-crystal formation and the use of lipidic vehicles.[1]

Many new chemical entities (NCEs) are also highly potent – approximately 25% of drugs on the market today are formulated with HPAPIs, and the overall HPAPI market is predicted to be growing at around 10%/year.[2] These compounds, many of which are solids, require special handling (facilities, equipment, procedures, training) to protect workers and the environment from unintended exposure. They also often are formulated at very low dosages that require specialized formulation technologies to ensure uniform incorporation into the solid drug product.[3]

GROWING INTEREST IN OUTSOURCING

In 2016, the contract manufacturing market size for solid dosage forms is anticipated to be $24.5B;[4]

THE **NEW NICE SYMPOSIUM** OFFERS PHARMACEUTICAL PROFESSIONALS A PLACE TO COME TOGETHER TO DISCUSS IMPORTANT ISSUES FACING THE INDUSTRY IN AN ENERGIZING FORMAT DESIGNED **TO FACILITATE COMMUNICATION AND IN-DEPTH KNOWLEDGE SHARING**.

the propensity to outsource oral solid dosage forms continues to grow modestly. Nice Insight's 2016 CDMO Outsourcing Survey results indicated that for small-molecule drug substance services, small-molecule API commercial scale manufacturing was more popular than large-molecule API commercial scale manufacturing, at 33% and 30%, respectively.[5] Similarly, for small-molecule drug product services, 76% of respondents indicated that they outsourced their drug product solid dose manufacturing (clinical scale) and 65% indicated they outsourced their drug product solid dose manufacturing (commercial scale).[5] Both were higher compared to outsourcing of drug product semi-solid and liquid dose manufacturing (62% for clinical and 60% at commercial scale).[5]

TACKLING TOUGH TOPICS

The first Nice Symposium event will tackle the tough issues associated with oral solid dosage formulation, including overcoming poor solubility and bioavailability, working with high-potency compounds, selecting appropriate excipients, coating design and application and meeting the needs of different patient populations.

Other topics that will be addressed include managing clinical trials, improving manufacturing efficiency and productivity, overcoming logistics challenges, and regulatory compliance. Tableting and encapsulation, release control, inhalation and other technologies will be covered. Effective brand/product control, patient efficacy, supply chain transparency, fraudulent/counterfeit medicines and lifecycle management will also be raised.

Six panels comprising supplier companies and their invited customers will focus on the following topics:

- The Composition and Functioning of the Oral Solid Dose Supply Chain
- Worldwide Demand at All Stages in the Oral Solid Dose Supply Chain
- Capsule Technology and Patient Adherence
- Outsourcing Challenges and Opportunities, Including Sponsor Needs, Partner Models and Project Management Approaches
- Counterfeiting and Meeting Serialization Requirements
- Collaboration Across the Entire Oral Dose Supply Chain – Best Practices

NONTRADITIONAL INDUSTRY EVENT

In addition to the panel discussion designed to incorporate perspectives of all sides of supplier-customer partnerships, the nontraditional open floor plan of the venue is designed to encourage increased interaction and engagement between all attendees involved in oral solid dosage delivery from clinical to commercial, including sourcing, manufacturing, quality and executive leaders of API and excipient suppliers, processing and packaging equipment manufacturers and large-to-emerging (bio)pharmaceutical companies.

Event sponsors each have their own "value stations," or unique configurations of kiosks, tables and chairs with lounge areas and flat screens. Sponsors also receive a 15-minute presentation slot and custom invitations to the event for their top customers and prospects, who are also invited to participate on the panels (invited attendees pay no entrance fee). They also have the opportunity for a one-on-one interview with an editor of *Pharma's Almanac* that will be featured on www.PharmasAlmanac.com for one month, published in a special section of the hard copy of Pharma's Almanac (on- and offline distribution of 97,000) and available as a PDF for the sponsor's own use.

Several networking and partnership opportunities will be provided over the two-day event, including breakfast and lunches on both days and a dinner and social mixer on the first night. All meals are included. Participants will also have the opportunity to provide direct feedback on their experience at the first Nice Symposium, including valuable learning, as well as areas for improvement.

After the show, sponsors will also be provided with a contact list of all customer and peer participants and a Workshop Report on oral solid dosage formulation, including an exclusive "first look" at the Nice Insight Annual Survey results for Top CDMOs in OSD.

ENERGIZING AND SUPPORTIVE

The new Nice Symposium offers pharmaceutical professionals a place to come together to discuss important issues facing the industry in an energizing format designed to facilitate communication and in-depth knowledge sharing. It is also designed to support the growing importance of preferred partnerships between suppliers and their customers, whether contract service providers and drug innovators or equipment suppliers and generics manufacturers. P

FOR MORE INFORMATION

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TRENDS TRADING

ORPHAN DRUGS

TWO PROMISING SMALL-MOLECULE ORPHAN DRUGS IN CLINICAL TRIALS

→ BY **BOOBALAN PACHAIYAPPAN, Ph.D.**, NICE INSIGHT

Ease of molecular synthesis and portfolio diversity enables small molecules to be consistently victorious compared to other drug modalities. A staunch focus on creativity in chemical space and enriched understanding of drug parameters are surefire ways to spur innovation and a concomitant cure.

SMALL MOLECULES RULE THE THERAPEUTIC LANDSCAPE

In the realm of chemical modalities, small molecules have consistently been a lucky charm. Over 90% of FDA-approved drugs are small molecules. A record number of 45 new molecular entities (NMEs) approved by FDA in 2015 – and about 16 NMEs until July 2016 – accentuate how the properties of a small molecule can be tailored to fit patient needs. In this article, I highlight two promising small molecules (see Figure 1 for structures) currently in clinical trials. The first part of the article investigates the role of CPP-115 (completed phase I) in epilepsy, whereas the second part focuses on the treatment of acute myeloid leukemia (AML) using quizartinib (in phase III).

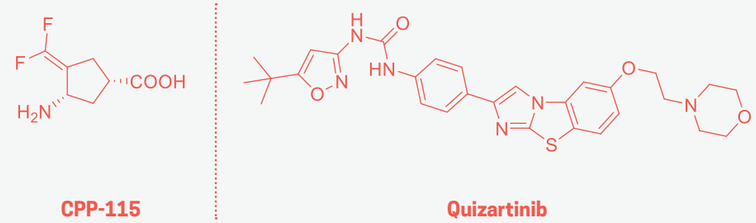
CPP-115: AN INVESTIGATIONAL DRUG FOR EPILEPSY

The fact that 1 in 12 people will have a seizure in their lifetime raises alarming signals to mitigate, prevent and cure epilepsy. The etiology is still unclear, but one of the pharmaceutical strategies to treat seizures is to replenish the local concentrations of GABA (gamma-aminobutyric acid, an inhibitory neurotransmitter in the human brain) that is degraded by an enzyme called GABA aminotransferase (GABA-AT). Mere consumption of GABA capsules is not effective, due to its inability to cross the blood-brain barrier (BBB). Therefore, an alternative strategy that involved stopping the function of GABA-AT was envisioned. Sabril is a first-in-class, FDA-approved antiepileptic drug; however, its daily dosage limit (1g – 3g) and adverse side effects, which include vision defects, call for further innovation.

Prof. Richard Silverman and his lab members at Northwestern University embarked on a scientific journey to identify BBB-penetrating antiepileptic compounds that would not cause visual defects. Through computational modeling and several cycles of optimization they discovered CPP-115 (chemical name: (1S,3S)-3-amino-4-difluoromethylene-1-cyclopentanoicacid; $k_{inact}/K_I = 52 mM.min^{-1}$.)[1] Mechanistically, CPP-115 binds to GABA-AT, undergoing product transformation that kills GABA-AT's function. In rat studies, CPP-115 suppressed spasms at a much lower dose (0.1 mg/kg) than Sabril (>200 mg/kg) and exhibited better tolerance without visual defects.

CPP-115 (licensed to Catalyst Pharmaceuticals) elicited no cross-inhibition. It is metabolically more stable, with favorable PK characteristics (including rapid absorption and clearance). In a randomized, double-blind, single ascending dose phase I(a) study, CPP-115 was very well tolerated in all six doses (n=55 patients; maximum dose 500 mg, therapeutic dose 80 mg/day).[2] Phase I(b) studies conducted in double-blind, placebo-controlled conditions demonstrated the safety and tolerability of CPP-115 in healthy volunteers. Intriguingly, an increase in brain GABA levels (150% to over 200%) was detected, accentuating CPP-115's antiepileptic potential.[2] Further clinical trials are currently in progress. CPP-115, with 12 years of unexpired patent life, has been granted orphan-drug designation in both the U.S. and EU for treating infantile spasms.

FIGURE 1 | TWO PROMISING SMALL MOLECULES IN CLINICAL TRIALS



CPP-115 | Quizartinib

QUIZARTINIB — AN INVESTIGATIONAL DRUG FOR ACUTE MYELOID LYMPHOMA

AML is a type of cancer characterized by uncontrolled production of myeloblasts (a type of white blood cell), red blood cells and platelets. This hematologic malignancy starts in the bone marrow, but quickly invades the blood and other parts of the body, including the liver, spleen and brain. A quarter of AML patients harbor FLT3-ITD mutation, an even more aggressive form of the AML. Current treatment options, including induction chemotherapy and transplantation, have met with mixed results because most patients display a high propensity for relapse after remission.

Bhagwat and his team at Ambit Biosciences (acquired by Daiichi Sankyo) attempted to stop this "backward sledding." The first-generation FLT3 inhibitors identified by them were potent; however, problems associated with solubility and PK precluded these inhibitors from further advancement. Bhagwat's team quickly transformed them into their flagship compound by appending water-soluble groups and clipping off an undesired carboxamide. Quizartinib (chemical name: 1-(5-(tert-Butyl) isoxazol-3-yl)-3-(4-(7-(2-morpholinoethoxy) benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl) urea; IC_{50} = 1 nM), a highly potent and selective FLT3 inhibitor, displayed excellent PK profile in rat and mice models, and killed tumors implanted on mice.[3]

In a dose escalation phase I study (12 to 450 mg/day) involving 76 patients, quizartinib exhibited safety, acceptable toxicity and clinical activity against both relapsed and refractory AML conditions.[4] In phase II (two cohorts), quizartinib sustained a high degree of activity in over 50% of FLT3-ITD(+) patients who showed composite complete response (CRc). About 50% of patients who were refractory (i.e., have not responded yet to prior AML therapy) achieved CRc as well.[5] Phase III results to assess the efficacy of quizartinib as a solo therapy, as well as in combination with other chemotherapeutic drugs, are in progress.

EPILOGUE

Out of 10^{60} theoretically possible small molecules, a majority are still unexplored. The small molecules presented in this article are highly innovative and are ambitiously expected to become drugs. Nature has a penchant for small molecules and so do pharmaceutical companies! P

NATURE HAS A PENCHANT FOR **SMALL MOLECULES** AND SO DO PHARMACEUTICAL COMPANIES!

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Boobalan is a trained medicinal chemist whose research interest broadly lies on the interface of computer-assisted drug design methods and organic synthesis. During the last 10 years, he diligently worked in several therapeutic areas, including Alzheimer's, oncology, infection (antibacterial and antimalarial) and epilepsy. Boobalan was awarded a Ph.D. degree in medicinal chemistry from the University of Illinois at Chicago.

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NICE DIGITAL

PHARMA'S ALMANAC CONTENT COMMUNITY

PHARMA'S ALMANAC: NICE INSIGHT'S CONTENT COMMUNITY GOES LIVE ONLINE

An Industry Portal for Data, Knowledge, Thought Leadership and Opinion

→ BY **ANDREW WARMINGTON, Ph.D.**, NICE INSIGHT

Nice Insight's PharmasAlmanac.com is live! The site is a resource for both industry analysis and thought leadership from some of the life science industry's most advanced companies and significant players.

Over the last 18 months, the Pharma's Almanac has attracted high-level commentary and strategic analysis content from some of the industry's most respected executives and operational experts. The online answer to the quarterly publication, PharmasAlmanac.com, is designed to be a platform that inspires opinion, ideas and collaboration. In addition to hosting articles found in print, the site will offer content exclusive to the web.

DISTRIBUTION

The reach of the Pharma's Almanac magazine, available as a supplement to the American Pharmaceutical Review (APR), is significant. APR's network includes 67,000 BPA Worldwide readers; That's Nice distributes to an additional 30,000 non-BPA readers and industry opinion leaders, for a total of 97,000 online readers. The online publication will no doubt increase this presence, likely more than doubling readership and unique visits.

INBOUND ONLINE MARKETING

Pharma's Almanac online, in conjunction with Nice Digital, offers the opportunity to create inbound, online marketing strategies with proven ways to selectively engage visitors with tailored, relevant content. Inbound techniques center on retaining organic visitors through automated suggestions. PharmasAlmanac.com includes News, Insights and Trends to guide readers in their experience of the site. Visitors can actively engage the site and choose increasingly selective points of access, prompted by their previous activity.

The site is intended to be a platform for companies seeking better visibility. By presenting the intrinsic value of operational and technical products and services to the market, business leads and opportunities are generated. Visitors to PharmasAlmanac.com, and readers from Pharma's Almanac print editions, represent companies seeking – or interested in – information about understanding or overcoming operational hurdles, poor-performing equipment and other institutional or competitive challenges.

In addition to the array of articles from the past several issues, 2017 will include insights from the Nice Insight Outsourcing Surveys, including those focused on contract manufacturing and development organizations, contract research organizations, excipient suppliers, pharmaceutical equipment providers and intermediates providers, with separate surveys on supply chain and logistics, as well as Private Equity/venture capitalists. This newly sourced data will be analyzed and revisited throughout the year, to indicate both market status and overarching trends in pharma.

GET IN THE CONVERSATION — BE A CONTRIBUTOR

If you have an area of specialty that you would like to share with our readers, you can submit article ideas directly to our editorial staff. Please refer to the Editorial Calendar, though we accept submissions on a broad range of topics throughout the year. P

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Andrew Warmington, Ph.D.
Executive Content Director

Based in the U.K., **Andrew** recently joined That's Nice as Executive Content Director, where he will mainly be involved in developing content for the online enterprise of Pharma's Almanac and leading critical custom projects. Andrew has been working as an analyst and journalist in the manufacturing industry, mainly chemicals-related, since 1993. For the last 14 years, he has been the editor of the highly respected monthly magazine, *Speciality Chemicals Magazine*.

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NICE INSIGHT

ANNUAL STUDIES

NICE INSIGHT LAUNCHES 2017 STUDY SEASON

→ BY **KSHITIJ (TJ) LADAGE** AND **GOVINDRA SINGH**, NICE INSIGHT

Nice Insight continues its research efforts, seeking fresh data, new perspective and technical, operational insight from the industry's key decision makers on Contract Research Organizations (CRO), Contract Development and Manufacturing Organizations (CDMO), Pharmaceutical Equipment Manufacturers, Excipient Suppliers, Clinical Supply Chain, Intermediates and Private Equity/Venture Capital players.

As another exciting year comes to a close, and corporate response to coming business cycles begins, collecting and analyzing data in order to understand the trends driving the industry continues to be an essential planning tool. Anyone who has ever presented a business proposal to an executive board will recognize just how necessary clearly presented market research data is when justifying a host of potential decisions, whether responding to competition, launching a new enterprise or serving expansion goals.

Nice Insight's research has emerged from the recognition that with clear, empirical market and trend data available, businesses more effectively focus their marketing efforts and make better projections to sustain their brands. Nice Insight's studies have surveyed the CRO, CDMO, excipient and equipment supplier landscape, starting for the first time in 2011, and continuing up until this year and into the next. In 2017, these surveys will be expanded to include Private Equity/Venture Capital, Clinical Supply Chain and Intermediates.

Every Nice Insight Study is designed to develop the sector's perceptions of market, sales and competitive trends measured via both a Customer Awareness (CA) and Customer Perception (CP) score. These scores, generated through the direct responses of survey participants, indicate the level at which polled companies are known in the market, and if they are known, how they are perceived. This can be used as a measure of market standing, specifically when comparing competitive brands against one another.

Through the launch of each survey, Nice Insight aims to create a panoramic view of the pharmaceutical market, considered from all sides, and using actionable customer insights to inform the most accurate analysis available. By taking each perspective into account, we are stringing together an informed gestalt, capable of tapping into trends as they are created. For a glimpse into the upcoming studies in 2017, please refer to our guide below, as we await next year's glittering insights!

NOW TRACKING 4 YEARS OF DATA

CRO — PRECLINICAL, CONTRACT AND CLINICAL RESEARCH ORGANIZATIONS

Respondents to the 2017 Nice Insight CRO Survey will generate perception data on 74 out of 125 leading contract research organizations. CROs are evaluated under three primary service categories, including research, preclinical and clinical offerings. Under research, respondents will be asked to indicate their interest in surgical, process chemistry, regulatory and *in vitro* assay services, for example. Similarly under the preclinical category, the study explores specifying habits for general toxicology, bioanalytical testing, particle characterization, chemistry stability testing and other analytical services across small- and large-molecule product development. Under the clinical category, the 2017 CRO Survey investigates the complex operational/logistical segments of clinical trial design, monitoring, data capture, recruiting, PK, PD and pharmacovigilance services.

www.niceinsightcro.com

CDMO — CONTRACT DEVELOPMENT & MANUFACTURING ORGANIZATIONS

Nice Insight's Contract Development & Manufacturing Survey will comprehensively profile 164 out of 316 of the industry's most prominent organizations. These organizations are selected by criteria that consider both the company's active status in the market and their minimum annual sales, which must equal at least $20 million in order to be included.

The 2017 CDMO Outsourcing Survey will be deployed to an international pool of more than 500 key, qualified industry influencers and decision makers, selected based on title, organizational role and department, as well as their influence on the selection and contracting of development and manufacturing service providers. These companies will be scored across a number of key categories, including primary drug substance and drug product operations; laboratory and specialized services, like lyophilization; and HPAPI handling. Subcategories of CDMOs' operational capabilities include small- and large-molecule drug substance API manufacture, blow-fill-finish, and aseptic fill and finish. The upcoming survey also prompts respondents to gauge their perceptions of a broad range of CDMO technical and operational capabilities, including biomanufacturing, clinical- and commercial-scale manufacturing across OSD, parenteral, combined and semi-solid products, plus primary and secondary packaging operations.

www.niceinsightcdmo.com

PHARMACEUTICAL EXCIPIENTS SUPPLIERS

Covering a list of 39 top excipient suppliers, participants in the 2017 Excipient Study will indicate their perceptions of the industry's prominent suppliers. Primary excipient product categories will include anti-adherents, solubilizers, thickeners, diluents/fillers, binders, disintegrants, glidants, lubricants, coatings and coloring agents.

www.niceinsightexcipients.com

ORIGINAL EQUIPMENT MANUFACTURERS (OEM)

For 2017, Nice Insight will survey a minimum of 500 respondents to evaluate equipment vendors based on process integrity, customer service, total cost of operations (TCO), overall equipment efficiency (OEE), post-sales support and reliability. Respondents will be asked about purchasing, specifying plans and projections

across two primary manufacturing processing categories: OSD tablets/capsules and sterile (primarily liquid) forms. The study will also examine processing equipment (machines and accessories), as well as packaging (primary and secondary) under both the OSD and sterile categories. Bioprocessing associated with sterile processing is also covered, as are the equipment and machines required to conduct operations (including primary and secondary packaging).

www.niceinsightpharmaequipment.com

NICE INSIGHT 2017

- **CRO** – 124 Profiles (73 Deep Dive)
- **CDMO** – 313 Profiles (163 Deep Dive)
- **Excipients** – 39 Profiles (31 Deep Dive)
- **OEM Equipment** – 128 Profiles (81 Deep Dive)
- **Supply Chain Logistics** – 21 Profiles (21 Deep Dive)
- **Pharmaceutical Intermediates** – 87 Profiles (48 Deep Dive)
- **Private Equity/Venture Capital** – 136 Profiles

CLINICAL SUPPLY CHAIN LOGISTICS

As we move toward 2017 and beyond, one tendency almost guaranteed to remain the same is pharma's growing reliance on its supply chain to deliver the therapeutic value of its products. With the increasing number of clinical studies occurring globally, there has been a growing amount of emphasis on better understanding the character and dynamics of clinical trial logistics. To address these questions, Nice Insight will survey industry respondents to understand the key aspects of the clinical supply chain, as well as trends associated with the different levels of partner engagement.

www.niceinsightlogistics.com (01/01/2017)

PHARMACEUTICAL INTERMEDIATES SUPPLIERS

Pharmaceutical Formulation Intermediates, or PFI, are the powdered materials excipients – and active ingredients (APIs) – compressed and mixed together to make pills and tablets. This sector of the pharma supply chain has a primary role in pharmaceutical production. The 2017 Nice Insight Intermediates Survey will explore the purchasing and specifying trends of this critical aspect of the supply chain.

NICE INSIGHT'S RESEARCH HAS EMERGED FROM THE RECOGNITION THAT WITH **CLEAR, EMPIRICAL MARKET AND TREND DATA AVAILABLE**, BUSINESSES MORE EFFECTIVELY FOCUS THEIR MARKETING EFFORTS AND MAKE BETTER PROJECTIONS TO SUSTAIN THEIR BRANDS.

Intermediates Survey participants will be asked to indicate their perceptions of the industry's prominent suppliers and primary intermediate product categories, including chemical and pharmaceutical intermediates.

www.niceinsightIntermediates.com (01/01/2017)

PRIVATE EQUITY/VENTURE CAPITAL COMPANIES

Respondents to Nice Insight's 2017 Private Equity and Venture Capital Survey will be generated from a pool of financial executives who are actively involved in the valuation and private equity/venture capital investment within the life sciences space. The PE/VC sector plays a pivotal role in innovation, providing early-, middle- and late-stage financing to drug development. For example, the biotechnology sector's ascendance can, to a large degree, be attributed to the vision and willingness of the PE/VC markets to fund the hundreds of biologics-related startups. The study will work to reveal recent trends in investments, exit strategy and company valuation.

www.niceinsightPEVC.com (01/01/2017)

BEST INFORMATION, BETTER DECISIONS

Nice Insight's study portfolio for 2017 is designed to shed new light onto the pharma industry and its partners, supply chain and otherwise. P

ABOUT THE AUTHORS

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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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Govindra was the first student to graduate with a dual degree from City College of New York, a BS in biochemistry and MS in organic chemistry. For his master's degree, Govindra conducted research on the synthesis of potential anti-cancer and anti-viral compounds. From this he was able to publish two research articles in high-impact journals. After, he worked as a scientist at industrial and pharmaceutical companies. In his role at Nice Insight, Govindra conducts market research studies, designs surveys and analyzes qualitative and quantitative data.

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COMPANY PROFILES

Nice Insight and the Pharma's Almanac editorial team would like to thank all the companies participating in this quarter's edition.

The following are the profiles of the industry-leading companies that have appeared in this issue. These companies make it their business to energize pharma's increasingly complex supply chain and pursue excellence every day in support of the industry's overall quality, health and safety goals.

alcami

AAIPharma Services Corp. and Cambridge Major Laboratories, Inc. have joined to form **Alcami**, a world-class supplier of comprehensive pharmaceutical development and manufacturing services. With seven sites across the globe, our combined capabilities include API development and manufacturing, solid state chemistry, formulation development, analytical development and testing services, clinical and commercial finished-dosage-form manufacturing (oral solid dose and parenteral), packaging and stability services.

- www.alcaminow.com
- +1 910 254 7000
- 2320 Scientific Park Drive
  Wilmington, NC 28405

Ash Stevens

Ash Stevens Inc. is a fully integrated CDMO, offering comprehensive drug substance development and API manufacturing services to clients developing innovative small-molecule drugs. To date, the company has received thirteen U.S. FDA approvals, including four with FDA Fast Track designations. Ash Stevens supports all aspects of drug development and cGMP manufacturing, from *de novo* process development to commercial API production. The company's state-of-the-art manufacturing facility, located in Riverview, Michigan, is FDA-registered and has the capacity to develop and manufacture APIs, from grams to batch sizes of up to 250 kilograms.

- www.ashstevens.com
- +1 734 282 3370
- 18655 Krause Street
  Riverview, MI 48193

Capsugel

Capsugel provides innovative dosage forms and comprehensive support from formulation to final production. The company offers a wide variety of high-quality, innovative capsule products and drug-delivery technologies, which translate to improved time to market for customers. The company also offers dosage form development, abuse-deterrent dosage form development, colonic dosage form development, formulation support, preclinical and clinical support, manufacturing and technical services in addition to quality management support, regulatory assistance and unique ways to help clients' brands differentiate and stay competitive.

- www.capsugel.com
- +1 862 242 1700
- 412 Mt. Kemble Ave., Suite 200C
  Morristown, NJ 07960

CMC biologics

CMC Biologics, a global full-service CDMO for biopharmaceuticals, is well versed and experienced in biopharmaceutical process development and manufacturing. During 14 years of operation, CMC Biologics has successfully developed more than 120 mammalian, bacterial and yeast-based products for preclinical studies through to commercial production. CMC Biologics has extensive experience in developing and validating analytical methods for a wide range of proteins. In 2015, CMC invested in state-of-the-art clinical and commercial manufacturing facilities to support the development and commercialization of its customers' products.

- www.cmcbio.com
- +1 425 485 1900
- 22021 20th Avenue SE
  Bothell, WA 98021

Federal Equipment Company

For more than 50 years, **Federal Equipment Company** has been a trusted equipment supplier to the pharmaceutical, chemical and plastics industries. With thousands of pieces of inventory in stock, Federal Equipment is dedicated to providing customers with immediate access to quality used equipment at competitive prices. Additionally, Federal Equipment offers a complete array of investment-recovery and asset-disposition services, including appraisals, auctions and liquidations, and equipment purchase and removal, as well as consignment sales to dispose of idle and surplus equipment.

- www.fedequip.com
- +1 800 652 2466
- 8200 Bessemer Avenue
  Cleveland, OH 44127

BIODURO

BioDuro provides end-to-end solutions for integrated drug discovery and development, API synthesis, optimization, formulation and cGMP manufacture of drug products. Using advanced, proprietary technologies, BioDuro offers services to enhance the bioavailability of poorly soluble compounds and provide seamless translation of high-value clinical candidates developed by BioDuro's preclinical group into more efficacious clinical trial material. BioDuro also provides scalable operations and phase I through phase III clinical development, as well as clinical and commercial cGMP manufacture of drug product in BioDuro's purpose-built San Diego processing facility.

- www.bioduro.com
- +1 858 529 6600
- 11011 Torreyana Road
  San Diego, CA 92121

BioVectra

BioVectra has been providing a unique combination of synthetic organic chemistry, fermentation of chemical and biologic molecules — including highly potent compounds — downstream processing, and MPEG production and conjugation chemistry services. BioVectra's more than four decades of experience and flexibility enable the company to work with small-to-large pharmaceutical, biotechnology, generic and early-stage companies. Committed to transparency and quality, BioVectra's specialized capabilities, quality history, long-term customer relationships and culture of versatility all contribute to achieving customers' unique and diverse requirements.

- www.biovectra.com
- +1 902 566 9116
- 11 Aviation Avenue
  Charlottetown PE C1E 0A1, Canada

CAI Commissioning Agents, Inc.

Since its founding in 1996, **CAI** has shepherded strategic projects for a number of high-profile companies in numerous regulated industries. The company offers a broad spectrum of services designed to enhance the performance and reliability of operations. They provide solutions and support in planning, project execution and production lifecycle for manufacturing industries. Their prime focus areas include capital project delivery and operational performance, and reliability improvement.

- www.commissioningagents.com
- +1 317 271 6082
- PO Box 34320
  Indianapolis, IN 46234

GRIFOLS

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

- www.grifols.com
- +1 34 93 5712200
- Avinguda de la Generalitat, 152
  Parc empresarial Can Sant Joan
  08174 Sant Cugat del Vallès
  Barcelona, Spain

gsk do more feel better live longer

GlaxoSmithKline (GSK) Biopharmaceuticals offers advantages to manufacturers looking for a strong, stable CDMO partner with extensive experience in biologics development and commercialization. In 2014, GSK Biopharmaceuticals opened a state-of-the-art process development laboratory in Rockville, Maryland. The lab's capabilities include process development, characterization, process scale-up and small-scale process validation. Overall, GlaxoSmithKline Biopharmaceuticals serves as a manufacturing knowledge center, enabling the launch, supply and management of GSK biopharmaceutical products around the world.

- www.gsk.com/biopharm
- +1 888 825 5249
- 2400 Research Boulevard
  Rockville, MD 20850

Hovione

Hovione is an international company with over 50 years' experience in the development and compliant manufacture of active pharmaceutical ingredients and drug-product intermediates. With four FDA-inspected sites in the U.S., China, Ireland and Portugal and development laboratories in Lisbon and New Jersey, the company focuses on the most demanding customers in the most regulated markets. The company also offers branded pharmaceutical customers services for the development and compliant manufacture of innovative new drugs and is able to support highly potent compounds.

- www.hovione.com
- +1 609 918 2600
- 40 Lake Drive
  East Windsor, NJ 08520

Icagen, founded in 1992, is a biopharmaceutical company that offers industry-leading scientific expertise for ion-channel and transporter-drug discovery and development. The company offers a range of services, from drug discovery to clinical development across multiple therapeutic areas and ion channels. The company's XRpro® technology, a novel method that enables high-throughput assessment of ion channels and transporters, demonstrates its expertise. Over the years, Icagen has built a portfolio of more than 1,000 cell lines.

www.icagen.com
+1 919 941 5206
4222 Emperor Blvd., Suite 350
Durham, NC 27703

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

www.servier-cdmo.com
+33 1 55 72 70 00
50 Rue Carnot
92150 Suresnes, France

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

www.unither-pharma.com
+1 585 475 9000
755 Jefferson Road
Rochester, NY 14623

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

www.upm-inc.com
+1 423 989 8000
501 5th St.
Bristol, TN 37620

SPECIAL THANKS TO:

Abzena
Aesica
Associates of Cape Cod
Bemis Healthcare Packaging
Bespak
Bosch Packaging Technology
Bourne Partners
Brant Point Partners, LLC
Constantia Flexibles International GmbH
CRB
CSP Technologies Inc.
Formulated Solutions
JSR Life Sciences
MilliporeSigma
M&W Group
Patheon
RX-360
SCHOTT Pharmaceutical Packaging
SGS Life Sciences Services
Siegfried
STEQ America

INNOVATION

Q: WHAT NEW TECHNOLOGY INTRODUCED WITHIN THE LAST YEAR HAVE YOU FOUND TO HAVE THE MOST IMPACT ON YOUR BUSINESS?

ROUNDTABLE

WITHIN THE PAST YEAR, there have been several new technologies introduced into SGS, some of which have had an immediate impact, and others expected to be more influential over a longer term. One example that may fall into both categories has been the introduction of a hydrogen-deuterium exchange (HDX) service that, when used with micro-LCMSMS technology, can be applied to probe the interaction of large molecules as well as provide details of the dynamics, mechanisms and precise location(s) of the resulting molecular changes. This methodology provides orthogonal data to many other techniques such as FT-IR and CD, and in some instances, may eventually replace these. It is highly likely that in the near future, the use of HDX will expand into more routine applications of drug production, facilitated by automation of the hardware and software systems. Evolution and development of the technology may also afford extremely rapid analysis.

Similarly, bio-layer interferometry (BLI) has the power to analyze molecular interactions in real time and can be used for protein quantitation, molecular binding affinity and kinetic analysis. Compared to existing technologies, BLI is faster, label-free and nondestructive and can be used on complex and unpurified samples. This means clients have access to a cost-effective and high-throughput analysis, allowing them to make decisions faster.

Mark Rogers
Vice President,
USA – Life Science, SGS

> Our serialization capability is having the most impact on the business and we believe it also makes us a frontrunner in the industry.

We are one of the first CDMOs to have serialization implemented and fully operational across all of our packaging sites. We have developed a "module" that is both flexible and scalable, enabling it to meet the serialization requirements of a wide range of countries. The module is capable of high-resolution printing at fast line speeds, with an advanced communication protocol for remote operation and high-speed serialization. We are seeing an increasing demand from customers for serialization and wanting products to be traceable online. Since legislation is already enforced in some of our customers' product markets, we adopted serialization early in order to continue to serve our customers. EU serialization legislation, however, is set to come into effect in February 2019 and the industry appears to be slow to respond. Many do not have a robust plan in place and may need to rely on outsourcing this capability, such as to CMOs. We are continuing to invest in serialization to ensure that we have the capability in place well ahead of February 2019.

Mark Hammond
Commercial Director, Aesica

> Within the last year, personalized medicine (or precision medicine) has surged to the front of the pharmaceutical industry.

In a recent Tufts Center drug development survey, 94% of companies said they were investing in personalized medicine research (up from 75% in 2010). Personalized medicine (which "converts DNA into data") is halting the development of blockbuster drugs. Instead, large pharmaceutical companies are shifting their attention to more targeted therapies, realizing that the limited number of strengths and dosage forms currently available don't support all patient profiles. As such, we've seen a substantial uptake of automated equipment that supports R&D for individual medicines. For example, the AR 403 (ERWEKA) is ideal for small batch sizes and features 22 interchangeable attachments. At a minimum, it's ideal for the production of powder tablets, ointments, creams and cosmetics.

The RoboDis II fully automated dissolution tester, now capable of half and full pH changes (to precisely imitate the pH changes that occur in the body) has also made a recent impact. This move towards genome sequencing is augmenting the use of science and technology to distinctly identify which patients will benefit from a drug or experience an adverse reaction. This emergence also ties into the development of new high-tech apps and devices being worn by consumers to supportively transmit data to pharmaceutical research institutes. All of this is shaping the industry's shift away from mass-production equipment to automated equipment that affirms the new generation of science, which sees no limitations on R&D and discovering tailored healthcare.

Natalie Landrito
Marketing Director,
STEQ America

The introduction of the Lynx® CDR connectors earlier this year really made a significant impact in the single-use space. This device changes the way pharmaceutical fluids are managed by allowing efficient fluid management through sterile connection, disconnection and reconnection — up to six times with one device. It does this by limiting the connection points into a single-use system, which simplifies fluid management, and reduces the opportunity to make incorrect connections. It also allows the user to connect in about 30 seconds, as opposed to the five minutes other systems can take. The Lynx® CDR connector is more efficient than tube welders, requires no capital and brings with it a heightened level of flexibility.

By design, the Lynx® CDR connector creates a barrier to the ingress of contaminants, providing the security found only in a clean room to ensure sterile drug processing. This device further enables the use of single-use technology by ensuring robust, simple, flexible, sterile connections in non-sterile, gray-space environments. The Lynx® CDR connector essentially provides the security of clean-room processing in the palm of your hand.

Andrew Bulpin
Head of Process Solutions Strategic Marketing and Innovation, MilliporeSigma

R

Recently, we have made significant investments in sterile manufacturing technology, including state-of-the-art prefilled syringe and vial-filling suites, increasing our freeze-drying capacity by approximately forty percent. We have also invested in a sterile development suite at our Greenville, N.C., facility. Later in 2016, we plan to introduce the company's first oral solid-dose continuous manufacturing suite as well. Lastly, we are in our second year of building a multi-year laboratory automation program, which will have every laboratory in the company on a paperless system.

Harry Gill
Global Vice President,
Operational Excellence,
Patheon

QUALITY CULTURE

Q: WHAT ARE YOU DOING TO BECOME A PREMIER OUTSOURCING PARTNER IN THE CONTEXT OF FDA'S RECENT SHIFT TO A FOCUS ON QUALITY CULTURE RATHER THAN JUST METRICS?

STEQ America has always acknowledged the importance of quality culture in the overall state of quality of both process and finished product. When a piece of equipment or spare part is purchased from us, we offer services and support in the areas of corrective action, proper training of personnel, and addressing the responsibilities and accountability of employees.

We believe in delivering a consistently higher-quality product to customers, from the vendor equipment we sell – which is of the highest industry standards and features regulation-compliant product traceability software – all the way through to the quality process improvements we advise upon. We are committed to supporting our clients not just in management goal metrics, but also in manufacturing-site quality performance.

In order for our clients to maintain a healthy quality culture, we recognize that their employees should have a sound understanding of their jobs and not be afraid to address their uncertainties in relation to the equipment they're using. That's why we'll also provide our full assistance in the areas of calibration, equipment commissioning, IQ/OQ qualification, technical support, process optimization and preventive and corrective maintenance.

Natalie Landrito
Marketing Director, STEQ America

At Aesica, we believe that good quality is simply good business practice.

Mark Hammond
Commercial Director, Aesica

Regulations and compliance are top-down: clearly the FDA is looking to have quality built in, and the pharmaceutical industry needs to address this. What people might not realize is that CMOs and CDMOs are audited on a more regular basis than our pharmaceutical customers, due to our wider offering. Not only do we have regulatory audits, but also customer audits. Our customers rely on our services to be of the highest standard, as well as being efficient and providing value for money.

At Aesica, we believe that good quality is simply good business practice. We have industry-standard methodologies, such as Six Sigma, Lean and Kaizen, and 5S and Britest tools in place. By having continuous improvement as part of our culture, it means that we are more likely to get things right the first time, thereby increasing productivity and reducing cost. In our manufacturing business, we have reduced manufacturing process cycle times to deliver an increased output of over 20%, increased production yields by over 15% and reduced the cost of manufacture.

We are fostering a quality culture – embedding quality in everything we do, from manufacturing to the final product.

Fostering quality has always been an essential part of our overall company culture, despite the robust and standardized processes and global quality-management tools we have in place. MilliporeSigma's quality mission statement declares that our overarching goal as a partner is to deliver quality – always. We have implemented a global quality initiative this year that includes "Quality Counts" workshops, in which employees focus on how we can understand and "live" quality – especially as a partner for our customers.

We also collaborate very closely, not only within our Quality and Regulatory Management team, but also across our Life Science functions and the company's business units. We established a Quality Operations Team/Group Quality Advisory Committee, and we share best practices by bringing the Quality Management Team together at a yearly Global Quality Conference. We also implement programs to fulfill the changing quality and regulatory requirements. We are committed to a quality culture and continuous improvement.

Robert Nass
Head of Quality and Regulatory Management, MilliporeSigma

SGS REGARDS QUALITY AS ONE OF ITS CORE VALUES AND APPLIES THIS NOT JUST TO LABORATORY TESTING, BUT TO ALL ASPECTS OF ITS BUSINESS.

This philosophy is implemented by a top-down approach in which the business leaders are accountable for execution in sales, operational activities and strategic considerations. The adage "SGS for Life" has recently been adopted to illustrate the importance that SGS puts on relationships with its clients, and the relationships that are founded on the quality of service that SGS provides.

Clearly, in the heavily regulated field of pharmaceutical and biopharmaceutical testing, the importance of a strong quality system is paramount. SGS recognizes the necessity for a comprehensive quality system, and therefore maintains quality structures at the local, regional and global levels. While such structures do rely on the regular compilation and tracking of certain metrics, SGS believes that these are secondary to the implementation and maintenance of a robust quality culture, and it seems that the regulators agree with this principle.

Mark Rogers
Vice President, USA – Life Science, SGS

PATHEON UTILIZES A QUALITY-ON-THE-FLOOR APPROACH TO INTEGRATE OUR QUALITY CULTURE AND FOCUS AT THE SHOP FLOOR LEVEL, which includes reviewing records in real time to providing a faster feedback loop for our shop floor operations clients. Thirty percent of our efforts in our OE program are specifically targeted at improving quality for clients, and we are actively participating in quality culture efforts pilot-sponsored by one of the leading pharmaceutical professional organizations.

Additionally, we leverage our operational excellence (OE) program, which has a strong emphasis on employee engagement, as more engaged employees significantly outperform those who are disengaged. We have a network-wide data integrity program that is purposed to actively engage managers, supervisors and the shop floor workers.

Harry Gill
Global Vice President, Operational Excellence, Patheon

ROUNDTABLE

SERIALIZATION

Q: WHAT IS YOUR PERCEPTION OF THE STATE OF SERIALIZATION IN YOUR SECTOR OF THE PHARMA INDUSTRY?

(CRO, CMO, BIG BIOTECH, BIG PHARMA, EMERGING, ETC.)

With serialization legislation already enforced in markets such as Brazil and China, and set to be fully enforced in the EU by February 2019, we've seen a very varied state of preparedness for serialization across the CMO sector. The ability to support drug companies to meet this complex regulatory packaging challenge appears to depend on the size of the CMO, the customers it serves and regions that those customers supply.

Serialization is complex and, with different country legislations having different requirements, serialization systems need to be configurable to be able to deliver what the customer needs. CMOs are at the service of the pharmaceutical customer, who determines the scope of support they wish the CMO to take on, whether it's external reporting requirements, artwork services or managing the whole process.

At Aesica, we have fully implemented a comprehensive serialization solution across all our packaging sites and are continuing to invest to ensure that our systems have the flexibility to support the various needs of our customers. Ultimately, it will be down to the specific business strategy of both drug companies and CMOs as to how they decide to meet the regulatory serialization demands. However, flexibility and a close relationship will underpin success.

Mark Hammond
Commercial Director, Aesica

STEQ AMERICA WORKS

Natalie Landrito
Marketing Director, STEQ America

with companies across all these sectors in addressing this from a general perspective — it's a serious problem. You can have counterfeiters in other industries and theft in various areas of a product supply chain, but in the pharmaceutical industry, you're ultimately risking the health and lives of patients.

It's essential to keep up with serialization because it's only going to continue to grow and become even more elaborate and precise (replicating products and labels), as there's a huge incentive for counterfeiters to duplicate original products for high margin profits. Currently the black market for counterfeited drugs amounts to over $75 billion annually. Not only do falsely labeled medicines with incorrect or poor-quality ingredients have a direct impact on reputable pharmaceutical companies, but even worse, they impact people's lives and health. Furthermore, there is the added complication that it's almost impossible to trace whether a patient's adverse side effect came from an approved drug on the market or one from illegitimate business.

More work needs to be done by pharmaceutical companies to prepare for the imminent change of legislation by national and international regulatory bodies. There needs to be a collective and uniform approach by everyone — scientists, manufacturers and packaging companies — in order to establish systems that comply with the upcoming regulations.

Patheon is a global contract drug development and manufacturing organization. As such, we work with a wide variety of brand-owner organizations from large pharma through small virtual companies. The state of brand-owner engagement and awareness varies across this range. On one end, some large companies have developed detailed specifications for their serialization CMOs and are driving engagement.

On the other end, smaller virtual companies are seeking support to achieve basic understanding.

As for contract organizations, Patheon feels it is well positioned to meet client needs for the various regulatory markets. At some sites, we're already serializing for early-market needs such as China and South Korea. There are certainly other CMOs who are also well prepared, but the general perception is that many CMOs are just beginning to engage in planning and execution. There appears to be some market concern that a number of CMOs will not be ready.

Chris Howell
Senior Director, Global Engineering and Technology, Patheon

GLITTERING INSIGHT FROM INSIDE THE INDUSTRY...