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Q4 2015 EDITION

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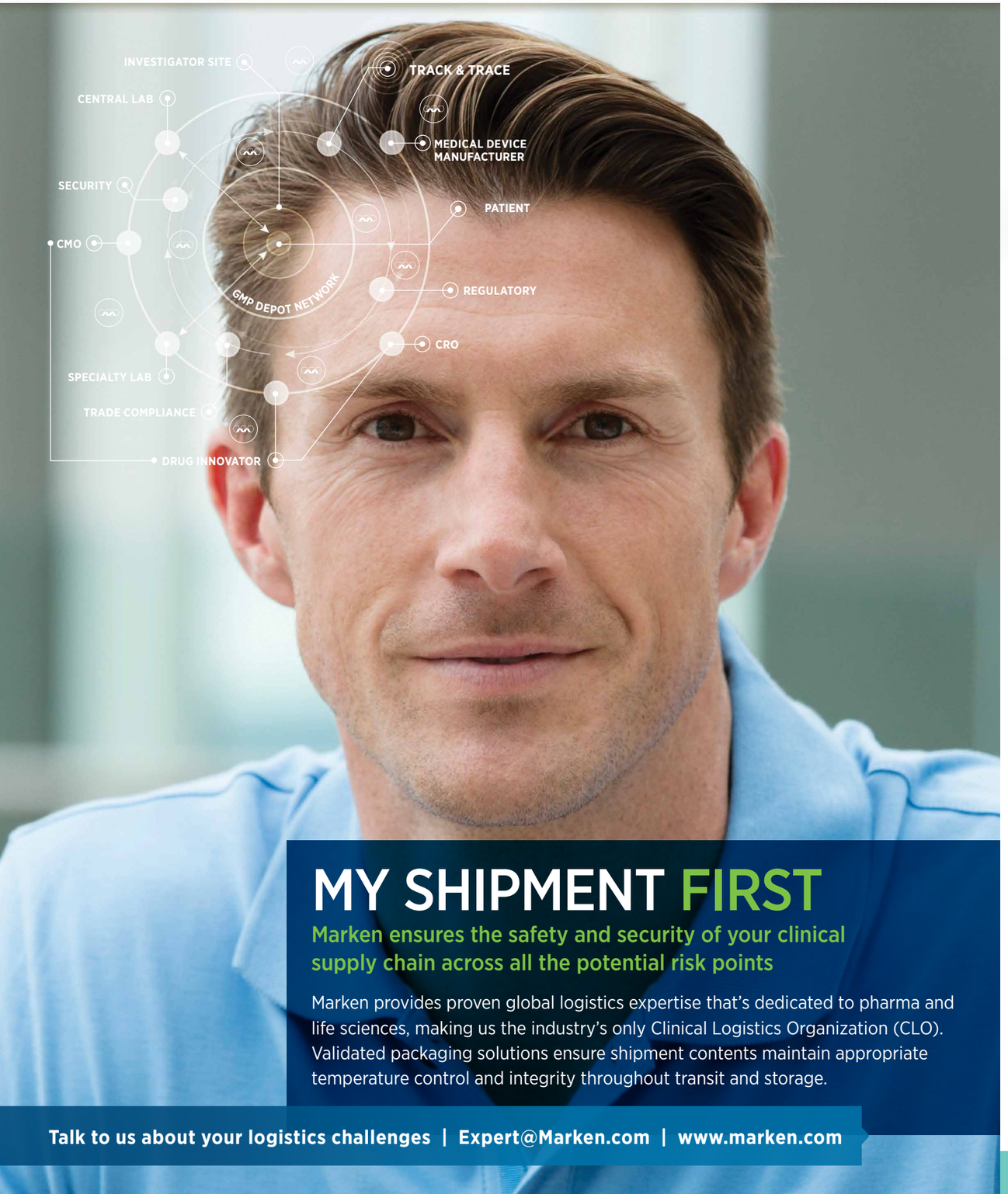

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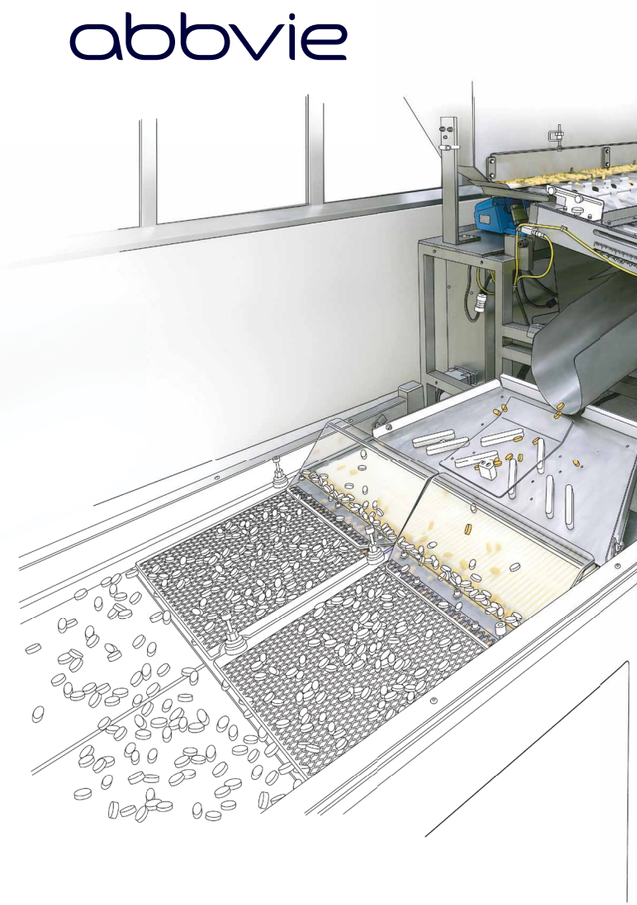

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GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS Q4 2015 EDITION

GROWING ROLE OF INNOVATIVE TECHNOLOGIES ACROSS THE PHARMA VALUE CHAIN

→ **BY CYNTHIA A. CHALLENER Ph.D.** Editor

Who would have thought 10 years ago that the pharmaceutical industry could get more complex? But it has. APIs are more complex — both small molecules (think fluorination and high potency) and biologics (virus-like particles), not to mention combinations like antibody-drug conjugates. Therefore manufacturing processes are more complex. More than half of drug candidates suffer from solubility and/or permeability issues, and thus their formulation is more challenging.

Because many new drugs target chronic diseases, clinical trials are longer; more patients are also often required in order to detect differences between new and existing treatments. The competition from generics is stiffer, so lifecycle management strategies have become paramount, and drug delivery and packaging systems are more crucial than ever before. Track-and trace, GMP requirements for excipients, and other new regulatory developments further complicate the picture.

Those companies that have proven to be successful in this climate focus on innovation to meet anticipated customer and market needs. They are also quick to adopt state-of-the-art technologies and partner with like-minded firms.

One key consequence of the growing complexity in the pharmaceutical industry has been a steady increase in outsourcing to providers that support the entire value chain from discovery to delivery with novel/advanced technologies.

Some examples include the following:

+ The increasing use of contract development and manufacturing organizations (CDMOs), rather than just contract manufacturers, to access innovative discovery and development technologies at the earliest phases of the drug development process, for both small molecule and biologic APIs

+ In conjunction with this trend is the growing preference for integrated providers with advanced capabilities that can support projects throughout all stages of development and commercialization

+ The growing emphasis on true collaborative relationships and strategic partnerships between sponsor companies and service providers, with advanced technologies and methodologies that are designed to speed development and reduce costs

+ The application of advanced data management technologies to increase the accuracy and reduce the time and costs associated with clinical trials

+ The rising importance of advanced formulation-development technologies to provide patient-centric solutions and achieve product differentiation

+ The increasing importance of advanced packaging technologies for improved product integrity

+ The growing recognition of poor patient adherence and the development of novel drug delivery/packaging technologies designed to address the problem

This supplement includes thought leadership articles from companies that are at the forefront and driving the industry trends outlined above. All facets of the pharmaceutical value chain are represented. For each organization, the development and implementation of innovative strategies and technologies to address key customer needs have helped them achieve top market positions.

The first article from Nigel Walker, founder of science agency That's Nice LLC and Nice Insight, the company's research arm, focuses on the importance of being innovative in today's pharmaceutical industry, given looming patent cliffs, shifts away from high-priced small molecule drugs to generics and biopharmaceuticals, and the growing importance of emerging markets.

In this special feature, Guy Tiene, Director of Strategic Content at That's Nice / Nice Insight, reviews 2015 Nice Insight survey findings for CROs and CMOs (and CDMOs) for Customer Awareness and Customer Perception. An interview follows with Amit Patel, President, and Trevor Wigle, PE, Director of Product Development at Capsugel Dosage Form Solutions, and Jim Nightingale, Ph.D., Managing Director, Bend Research, in which Capsugel highlights the key components of true customer-centric business strategies and how CDMOs that adopt this approach can help drug manufacturers overcome their pressing product development challenges and enable real product differentiation.

Fermion Oy's President, Arto Toivonen, gives us examples of how working with an outsourcing partner with a commitment to safety and sustainability can bring savings and security of supply to sponsors. He brings the perspective of specialists in synthesis, process engineering, scale-up, and commercial services, where the need for particle engineering and impurity control for HPAPIs is critical.

Because many new drugs target chronic diseases, clinical trials are longer; more patients are also often required in order to detect differences between new and existing treatments.

Ash Stevens' President & CEO Dr. Stephen A. Munk discusses the growing interest of sponsor firms in CDMOs with specialized expertise, integrated project management skills, and cost-effective services — or in other words, true full-service providers that can help get products to market both safely and more rapidly.

As a CDMO serving the biopharmaceutical industry, GSK Biopharmaceuticals recognizes that its clients are looking for strategic partners that can help minimize the risks associated with drug development and outsourcing. Greg Flyte, Director of CMO Alliance and Program Management, outlines the characteristics that can set a CDMO apart, including financial stability, an established track record for on-time delivery of quality products, and the ability to provide services across the spectrum from discovery to commercial production.

Kristine K. Senft, Vice President, Marketing, Hovione reveals the keys to successfully supporting pharmaceutical companies that focus on the development and commercialization of orphan drugs and breakthrough therapies. Leading CDMOs provide in-depth scientific expertise and achieve under rapidly accelerated timelines the development of cost-effective, robust, reliable processes that consistently yield high quality products.

AAIPharma Services' Chief Commercial Officer, Syed T. Husain, discusses industry trends and issues in the development and manufacturing of parenteral drugs and why more drug sponsors are relying on outsourcing partners to design and implement these increasingly complex programs. Whether small- and large-molecule parenteral products for liquids, lyophilized products, suspensions, emulsions, terminally sterilized vials, or prefilled syringes, meeting market demand is becoming increasingly competitive.

One key consequence of the growing complexity in the pharmaceutical industry has been a steady increase in outsourcing to providers that support the entire value chain from discovery to delivery with novel/advanced technologies.

SAFE, EFFICACIOUS, & AFFORDABLE TREATMENT

IMPROVE LIVES OF PATIENTS

The cost and complexity of clinical trials are both rising at rapid rates. Many different approaches are being evaluated to streamline clinical studies and provide increased efficiency and productivity, all of which require facile access to reliable, robust, and timely operational data. Zaher El-Assi, President of **Merge eClinical**, discusses how advanced, cloud-based electronic data capture, monitoring, and management platforms provide the real-time, integrated, accessible data necessary for addressing both the design and operational issues currently associated with many of today's clinical trials.

Jay McHarg, President of **American Aerogel**, covers the importance of maintaining temperature-sensitive pharmaceuticals, biologics, medical devices, and diagnostics within their acceptable temperature range along the cold chain. Choosing the optimum packaging technologies can prevent temperature excursions, mitigate risks, and avoid compromised product efficacy and patient safety, product losses, and delayed delivery to patients in need.

Kevin Haehl, General Manager, North America at **Unither Pharmaceuticals** discusses the subject of medication non-adherence, which carries significant risk for patients and substantially elevates the cost of care. Innovative drug delivery systems and packaging solutions are helping to ensure that patients take the right dose at the right time, including user-friendly, single-dose packaging with blow-fill-seal and stick-pack technologies.

Rounding out the supply chain, the rapid need for scalable manufacturing has seen the redeployment of surplus manufacturing equipment become part of the business model, with redundant or surplus equipment providing opportunities for resource recovery, as explained by Larry Kadis, CEO & President of **Federal Equipment Company**. He also describes how the buyer side of the equipment market fulfills a need for growing CDMOs and generics producers.

New on the industry scene is **Nice Consulting**, the combined offering of That's Nice LLC, a New York-based science agency, and Los Angeles-based Haig Barrett Inc. Management Consultants, which was formed to help customers grow value in the marketplace with access to a unique combination of industry knowledge, experience, and services. Dr. Rhea Kim, Chief Research and Development Officer, walks us through issues around cultural shifts, unique population healthcare needs, and the manufacturing and supply chain required to meet demand.

All of the companies represented in this supplement have extensive experience in their fields. They also recognize that the true goal, regardless of their position in the value chain, is the development of safe, efficacious, and affordable treatments that can improve the lives of patients around the world. Together they have real insight into the challenges faced by the industry and approaches to overcoming them. I hope you will find those insights to be of real value. P

SPECIAL THANKS

We would like to thank all of our contributors and supporters for Pharma's Almanac 2015. Many of these organizations will be present at the **American Association of Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition** being held in **Orlando, Florida, October 25th to 29th, 2015**, and we encourage readers to visit them there to learn more. Thank you.

AAI Pharma Services	#1017
Capsugel Dosage Form Solutions	#1415
EMD Millipore	#1636
GSK Biopharmaceuticals	#2145
Hovione	#1845
MPI Research	#1148
Nice Consulting / Nice Insight	#1548
Pfizer CentreSource	#1707
Unither Pharmaceuticals	#1451

BE INNOVATIVE!

MANEUVERING THE GLOBAL PHARMACEUTICAL MARKET

BY NIGEL WALKER Managing Director, That's Nice LLC / Nice Insight

Nigel Walker is the founder and managing director of That's Nice LLC, a research-driven marketing agency with 20 years dedicated to life sciences. With nearly thirty years experience himself as an entrepreneur in creative management, sales and marketing, and market research, Nigel harnesses the strategic capabilities of Nice Insight, the research arm of That's Nice, to help companies communicate science-based vision to grow their businesses. Prior to launching That's Nice, Nigel held the position of art director at multiple marketing and advertising agencies. Mr. Walker earned a bachelors degree in graphic design with honors from London College.

ABSTRACT

The recent spike of patent cliffs has made a huge dent in pharma sales revenue. To recoup the loss and sustain market position, pharma companies are in the race for new drugs. The hunt for the next blockbuster has shifted away from small molecules towards biologics. Biotech companies are leading the drug discovery efforts, especially the early stage. Faced with stagnating growth in the developed market, pharma companies have increasingly turned to emerging markets for new growth and profit opportunities. Mergers & acquisitions (M&A) and in-licensing partnerships are widely adopted by the pharma industry to enrich their product pipelines and strengthen their core competencies. Additionally, outsourcing is increasingly sought by pharma for their challenging projects to achieve quality results at low cost.

The global pharmaceutical market harvested a revenue of $989 billion in 2013 and was forecasted to reach $1.3 trillion in 2018 at a compound annual growth rate (CAGR) of 4%-7%.[1] Despite this healthy growth, the market incumbents face a wide variety of challenges from a more diverse and globalized economy, stringent government regulations, downward price pressure, and increased demand for better healthcare. The industry is increasingly dependent on new therapeutic entities (NTEs) and technological innovations to address unmet medical needs, accelerate drug discovery, improve production, and reduce cost.

DIFFERENT BUSINESS STRATEGIES ARE NEEDED FOR MATURE AND EMERGING MARKETS

In the field of drug discovery, large molecule biologics are in the limelight. The sales of several biologics have consistently made the top ten best-selling drugs: In 2014, eight of the ten best-selling drugs were biologics with a combined revenue of $70 billion, 84% of the combined revenue of the top ten drugs.[2] IMS predicted that the biological markets would grasp 20% of global pharmaceutical market share by 2017.[3] Current thinking among industry analysts is that branded biological products will not suffer huge revenue losses after patent expiration due to the difficulty in producing their generic versions (biosimilars). Additionally, tight complex regulations and high manufacturing costs present other hurdles for their generic rivals to clear. Consequently, pharma companies are in the chase for novel biological entities as their next blockbuster drug.

However, biologics are more complex and difficult to develop, characterize, and manufacture than traditional small molecules. Biological products are generally far less stable than small molecule drugs. Thus, they are more likely formulated as parenteral or injectable medications. There will be numerous challenges in every step of biological development; novel excipients, analytics, and technologies are needed to aid biological discovery, formulation, manufacture, quality control, and labeling and packaging. Under the constraints of time, cost, and quality, biopharmaceutical companies are increasingly seeking assistance from custom service providers who possess a full spectrum of technical expertise from discovery to commercial production, such as contract development and manufacturing organizations (CDMOs), contract research organizations (CROs), and related contract service organizations (CSOs).

TECHNOLOGICAL INNOVATION

62% CLOUD BASED DATA MANAGEMENT SERVICE

50% USE OF ROBOTIC LABS

44% WEB-BASED LIFE SCIENCES LABS

At the global scale, outsourcing provides a solution for pharma companies seeking to enter a new market. Partnering with local CROs and CMOs has been proven successful in assisting foreign companies to achieve regulatory, manufacturing and marketing goals in the emerging market. This market, led by the BRIC countries (Brazil, Russia, India and China), is growing at nearly double the rate of the developed market, with a CAGR of 8%-11% vs 4%-7% during the period of 2013-2018. By 2016, the emerging market will account for 30% of the global pharmaceutical market share and it will reach $358-$388 billion in sales by 2018.[1,4] Given its large population (70% of the world's population), growing middle class, and increasing healthcare demands, it provides a rosy picture for growth and profit.

Nevertheless, entering an emerging market can be a tough business decision to make, because this market not only demands a unique set of products but also offers a rather different business environment than the developed market. In general, the mature market demands high quality, patient-centric, and specialty medicines, whereas the emerging market focuses on affordable drugs, making generics a better fit. In addition, many factors can shake the economic stability in these regions. We recently witnessed China tactically devaluating currency to maintain their main relative export advantage – cheaper labor, which contributes to lower manufacturing costs. Devaluation also means that imported products would be relatively more expensive, which could make imported medicines less desirable in this region.

OUTSOURCING SERVES AS A BRIDGE TO NOVEL TECHNOLOGIES

To succeed in today's competitive market, pharma companies not only must be active in developing new drugs, but also swift in adopting new technologies. In Nice Insight's 2015 Annual Pharmaceutical and Biotechnology Outsourcing Survey, 62% of respondents (n=2,300) claimed that they have learned of new technological innovations for the biopharma industry in the past year that would benefit their company. The number clearly indicates the industry is constantly innovating and adapting.

Contract service providers are usually among early technology adopters. Using specialty CROs and CMOs can serve as a quicker way for pharma to access new technologies that benefit them when outsourcing. In Nice Insight's outsourcing survey, the respondents ranked five areas where they would benefit from the increased technological innovations, with Quality Control being the number one area followed by R&D, Manufacturing, Distribution, and Labeling and Packaging. When taking cost and/or time savings into consideration, 62% of the respondents believe that Cloud-Based Data Management Services offer the greatest opportunities for CROs. Other areas CROs can find the greatest opportunities include: Use of Robotics Labs to Perform Routine Tests (50%), Web-Based Life Science Labs (44%), Mobile-Enabled Innovations for Recruiting and Communicating with Participants (38%), Mobile Technology for Remote Monitoring (38%), and Shared, Online Data Banks of Non-Proprietary Clinical Information (23%).

The aforementioned areas are mainly within the realm of cloud, information, and mobile technologies. These technologies offer unprecedented opportunities for pharmaceutical companies to communicate and share information internally, as well as reaching out to their audience in a more direct and visible manner. The Cloud-Based Data Management Services; Mobile-Enabled Innovations for Recruiting and Communicating with Participants; and Mobile Technology for Remote Monitoring are used for clinical trial management. The result pointed out a great need for innovations in managing clinical trials. With clinical trials accounting for the most expensive part of drug development, it is not surprising that the industry demands more efficient and cost-effective measures to conduct and manage the trials. The growing expenditure on clinical trials is largely due to increased size, complexity, and length of the trial.

Regarding clinical information, there is a growing

COMPANY PROFILE

That's Nice — A Science Agency

That's Nice is a science agency, which reflects our evolution and focus in markets over 20 years. We began with opportunities in fine chemicals and move into specialty chemicals. Our significant growth into life sciences came with clients working in small molecule APIs — a significant long-term market for us, and one we still serve today. We also subsequently moved into large molecule biologics and then began to establish client relationships we have today with some of the world's leading drug innovators.

Nice Insight

Nice Insight offers custom primary and secondary research products and services focused on a variety of marketing intelligence needs, and conducts the largest annual industry survey on various purchasing parameters in pharmaceutical contract services outsourcing.

demand for increased clinical trial data transparency and sharing of information. In Europe, the European Medicines Agency (EMA) started to publish clinical reports contained in new marketing-authorization applications (MAA) submitted on or after January 1, 2015 once a request has been made.[5] The Agency also allows a third party to request the release of clinical documents held by the Agency. Internationally, the AllTrials initiative was launched in early 2013, aimed at making full clinical study reports from all clinical trials available to the public. So far, the initiative has been signed by 610 organizations, including big pharma company GlaxoSmithKline (GSK).[6] With these movements, it is foreseeable that more valuable clinical data will be available online in the near future. Therefore, opportunities will arise for CROs to help pharma-biotech companies navigate large, complex amounts of information facilitating their drug development.

BIOTECH LEADS THE DRUG DISCOVERY AND M&A FLOW

In the hunt for new drugs, biotech companies have become the vanguard in identifying promising new drug candidates, especially in preclinical and early-stage clinical development. According to Dr. William Haseltine, chairman and CEO of Human Genome Sciences, "(Today) about 40 percent to 45 percent of all drugs in human clinical trials originated in biotechnology," where "productivity is about tenfold greater in the discovery and development process than in the large pharma."[7] Biotech's success in leading drug discovery is largely attributed to the advancement in our understanding of biology and disease and the accessibility of novel technologies, such as high-throughput screening (HTS), automation, and molecular modeling and simulation. In addition, biotech companies are much quicker and more efficient in adopting new technologies, conducting research, and making business decisions with limited resources.

Recognizing biotech's efficiency in drug discovery, the large pharma companies increasingly seek to acquire or in-license late-stage drug candidates from the biotechs to minimize drug discovery risk, enrich product pipelines, and strengthen core competencies. In recent years, the industry has experienced a surging wave of mergers and acquisitions: 2015 probably will set a new record for M&A deals, as $221 billion worth of transactions have already been completed in the first half of the year.[8] The M&A deal or in-licensing/partnership is generally viewed as a complementary combination of biotech's technical expertise and big pharma's commercialization expertise.

In the hunt for new drugs, biotech companies have become the vanguard in identifying promising new drug candidates, especially in preclinical and early-stage clinical development.

GLOBAL PHARMACEUTICAL MARKET

$989B
REVENUE IN 2013

4-7%
COMPOUND ANNUAL
GROWTH RATE (CAGR)

Furthermore, the trend of consolidation is sweeping every corner of the pharmaceutical industry, including the generics market. Last July, Teva, the world's largest generic drug manufacturer, announced its purchase of Allergan's generic business for $40.5 billion. After completing the deal in 2016, Teva will control greater than a 20% share of the global generics market and rank among the top ten global pharmaceutical companies.[9,10] In addition to generating an expected annual savings of $1.4 billion, this acquisition will allow Teva to rapidly expand its Abbreviated New Drug Applications (ANDAs) from 130 to 320, including 110 first-to-file ANDAs.[10] Moreover, the inclusion of Allergan's generics R&D pipeline will facilitate Teva shifting its product portfolio to high-margin, complex generics.

Today, innovation is occurring in every aspect of the pharmaceutical value chain and constantly transforming drug discovery, development, and commercialization. The momentum of consolidation, outsourcing, and the growing emerging market will continue in the upcoming years. Lastly, a strategically selected outsourcing partner can successfully help pharma companies gain technical expertise, achieve quality at low cost, and enter a new market. P

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SPECIAL FOCUS– ACHIEVING STRONG CUSTOMER PERCEPTION THE CUSTOMER EXPERIENCE

The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives each year. Customer Perception (CP) of CRO/CMO/CDMOs is a major focus of the survey. Based on consistently high survey results, Capsugel Dosage Form Solutions is featured in this article to help readers learn more about creating an exceptional customer experience.

→ **BY GUY TIENE, M.A.** Director of Strategic Content, That's Nice LLC / Nice Insight

Guy Tiene is Strategic Content Director and Partner at That's Nice LLC. 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, PR, and thought leadership positioning. Prior to his return to the agency, Guy headed global marketing and communications for a large corporate business group in pharmaceutical manufacturing. A New Jersey resident with two grown sons, Guy holds a master's degree from Columbia University.

Survey respondents answer a range of questions based on their outsourcing needs and behaviors. The data provides ratings of company strengths for providers offering similar services based on various criteria, such as buyer group or service type.

The 2015 report includes responses from 2,303 participants who represent big pharma (16%), specialty pharma (20%), emerging, niche, or start-up pharma (9%), large biotech (19%), emerging biotech (14%), medical device (17%), and generics/biosimilars (5%) companies, and have positions in C-suite (17%), operations (17%), manufacturing (16%), quality assurance (16%), R&D/formulation (13%), and data/clinical trials management, purchasing, and regulatory affairs (5%-8% each).

The survey comprises 240+ questions, of which ~35 questions were randomly presented to each respondent in order to collect baseline information with respect to customer awareness and perceptions of the top CMO/CDMOs (~125) and CROs (~75) servicing the drug development cycle in North America, Europe, and Asia.

Respondents to Nice Insight's 2015 Pharmaceutical and Biotechnology Outsourcing survey consider technological innovation to be important for improving key operations within the pharmaceutical and biopharmaceutical sectors. In fact, survey participants indicated that quality control, research and development, manufacturing, distribution, and labeling and packaging would benefit the most in that order.

It should also be noted that most survey respondents (96%) have at least some interest in forming outsourcing partnerships with CMO/CDMOs that adopt state-of-the-art technologies to increase efficiency, safety, quality, and traceability. Specifically, 40% indicated they were interested in partnering with a CMO/CDMO that adopts state-of-the-art technologies, while 31% indicated moderate interest and 25% indicated some interest.

For purposes of the Nice Insight survey, Customer Awareness (CA) describes a potential or current buyer's knowledge of a particular company, product, or service offering. Customer Perception (CP) reflects how a current buyer or prospect rates a company based on information he/she has been exposed to, such as marketing materials and word-of-mouth influence, as well as personal experience. The ranges for the Customer Perception scores are 1-20 = Unsatisfactory, 21-40 = Poor, 41-60 = Average, 61-80 = Good, and 81-100 = Excellent.

The CP score is based on six drivers in outsourcing: Reliability, Quality, Innovation, Affordability, Productivity, and Regulatory Track Record. In addition to measuring customer awareness and perception information on specific companies, the survey collects data on general outsourcing practices and preferences, as well as barriers to strategic partnerships among buyers of outsourced services.

Gaining Market Leadership Through The Creation Of Exceptional Customer Experience

AN INTERVIEW WITH CAPSUGEL DOSAGE FORM SOLUTIONS

The 2015 results of the Nice Insight survey revealed a wide variety of predictable and more interesting findings. Considering the ongoing industry interest in collaboration, strategic partnerships, and overall "customer-centricity," we decided to take a look at some interesting aspects of the CP findings, including the role of innovation. Focusing on larger CDMOs in the study, we collected the CP figures for early phase services and the ratings given to purchasing/procurement/outsourcing departments.

In the area of Clinical Trial Management/Data Management, Catalent rated 84% (Excellent) for Innovation and Patheon 83% (Excellent) for Reliability. The CP results for R&D/Formulation for Aenova, Capsugel, Catalent, and Patheon were then compared. While Aenova scored highest with an 85% (Excellent) rating for Regulatory, Capsugel scored highest on all other drivers with a total average of 87% (Excellent), and notably with scores of 93% (Excellent) for Reliability, 90% (Excellent) for Productivity, and 88% (Excellent) for Innovation. The Purchasing, Procurement, and Outsourcing departments at Capsugel and Aenova received equal ratings of 85% (Excellent), while Catalent rated 83% (Excellent) for Affordability.

Considering all three of these organizational departments, it is clear that Capsugel rated highest overall with values of 81%, 83%, and 87%, respectively, for Clinical Trial Management/Data Management; Purchasing, Procurement, and Outsourcing; and R&D/Formulation. To gain insight into the reasons behind the excellent customer perception ratings received by Capsugel across numerous departments, Nice Insight spoke to company representatives about what aspects of their business garner them such recognition as a leading CDMO and what they believe drives customer collaboration.

NI: Capsugel has achieved clear success in Customer Perception. At the highest level, to what do you attribute the exceptional ratings given to Capsugel?

AMIT PATEL, President, Capsugel Dosage Form Solutions: It all starts with our vision: to be the leading provider of innovative dosage forms and solutions to healthcare customers around the world. Central to realizing this vision are a solutions-based approach grounded in science and engineering fundamentals, and an "alliance mindset" that positions Capsugel as a true partner rather than just a supplier. As a result, more and more customers are seeking to collaborate with us, starting at the design stage, to achieve their project goals.

Our breadth of technologies and depth of experience make it possible for Capsugel to tailor our support to each customer's specific needs and identify the optimal solutions that meet their target product profiles and commercial objectives. Customers can rely on us for integrated design, development, and manufacturing support, which serves to reduce costs and complexity when compared with having to access and manage multiple partners. In addition, we often work with customers across multiple technology platforms, projects, and project stages, which oftentimes involves a high level of transparency into their pipelines and strategies, and consequently a high degree of trust.

Capsugel Dosage Form Solutions has received very positive customer response to our new technologies resulting from internal R&D, infrastructure improvements and expansions, and acquisitions. The high perception scores reflected in the recent Nice Insight survey further confirms that we are on the right track. We also believe these scores reflect the benefits realized by our customers – accelerated development times, reduced costs, and most importantly, the fact that they are able to more quickly get innovative, safe, and effective medicines into the hands of the patients that need them.

NI: Please elaborate on what you mean by a "science-driven" approach to problem solving?

JIM NIGHTINGALE, Ph.D., Managing Director, Bend Research: We have always been passionate about high quality science and engineering in our drug delivery research. We focus on developing a fundamental understanding of the problem statement, and our definition of the problem statement is at times different than what our customer may have originally defined. Only through a deep understanding of the

CAPSUGEL REPRESENTATIVES

AMIT PATEL
President, Capsugel Dosage Form Solutions

JIM NIGHTINGALE, Ph.D.
Managing Director, Bend Research

TREVOR WIGLE, PE
Director of Product Development, Capsugel Dosage Form Solutions

→ What distinguishes Bend Research/Capsugel is its scientific engineering and problem solving expertise. They remain our number-one partner with regards to product development.
Capsugel Dosage Form Solutions client

physicochemistry of the API and biological properties of the site where the compound is administered – and taking into account the desired product profile, patient needs, potential scale-up issues, commercial objectives, and IP considerations – can an optimal approach and process for meeting a customer's goals be effectively designed and developed.

This type of unbiased approach is possible at Capsugel because we have breadth and depth of technologies as well as human expertise in the form of material scientists, mathematicians, physicists, biologists, chemical and mechanical engineers, and many others with invaluable backgrounds and experience in the fundamental sciences. Our product development teams therefore tend to complement the applied science expertise of our customers, and together we can best design and advance their compounds.

A key factor in Capsugel's continued innovation is having our own internal R&D group – we continually invest in new drug delivery technologies, formulation tools, and processing techniques that incorporate advanced modeling, process optimization techniques, and experimental protocols gleaned from the experience gained in advancing 1,000+ compounds. A good example is our technology selection methodologies, which include models developed from years of investigation, and enable our teams to select optimal enabling technologies and develop prototypes with minimal API requirements.

Our clients also rely on us for process development. The products we design have the end use in mind, and we account for ultimate "manufacturability" at the earliest stages of product development. The same fundamental science approach used in drug design has also been utilized to develop optimal processing techniques, and our emphasis on the science of scale has facilitated the development of phase-appropriate equipment. The application of fundamental science and engineering concepts, incorporating Quality-by-Design (QbD) principles, ensure smooth scale-up and technology transfer to larger equipment and commercial manufacturing.

Because Capsugel uses this science-driven approach across the product development cycle, and focuses on fundamentally understanding the client's problem statement, target product profile, and commercial objectives, we often identify optimum solutions previously not considered.

NI: It's been stated that Capsugel has an "alliance mindset" when dealing with clients in product development — what does this mean?

TREVOR WIGLE, PE, Director of Product Development, Capsugel Dosage Form Solutions: A deep level of trust is the hallmark of our ongoing customer relationships. We often state that "a customer's compound becomes our compound" as we work together to bring it to market. Certainly we strive to have an open, transparent, and collaborative relationship with all of our customers. We also focus on truly understanding them – not just their compounds, but their risk tolerance, how they define success, their specific project needs, the people we interact with on a daily basis, and the patient populations they are serving – so that we can support them in the most effective manner possible.

This type of collaborative relationship allows the back-and-forth discussion required to dig down to the real problem statement for each project, which is the first crucial step in identifying the optimum solution. We have also found that an initial project typically leads to multiple projects and a multifaceted relationship across customer functions and business units, and often incorporates our participation in broader customer pipeline discussions and project planning.

Capsugel's alliance managers ensure the high-level engagement needed to facilitate these types of relationships. Our teams are tailored to the customer teams' strengths and needs, so that we can together reach successful outcomes. Individual projects are supported by multidisciplinary teams whose compositions change in response to the varying needs of projects as they move from the design stage through development and on to commercialization.

SCIENCE-DRIVEN

+

SOLUTIONS-BASED APPROACH

+

ALLIANCE MINDSET

> What makes [them] better? It boils down to a few things, including technical competence, straightforward communication, a collaborative approach, and their ability to provide the flexibility we need.
>
> Capsugel Dosage Form Solutions client

NI: Has Capsugel made any recent investments to improve the customer experience further?

AMIT PATEL, President, Capsugel Dosage Form Solutions: Since Capsugel was acquired by KKR & Co (NYSE KKR) in 2011, we have been implementing a strategy focused on innovation and growth, and leveraging core science and engineering strengths. That strategy is reflected in our acquisitions of Encap Drug Delivery and Bend Research, our investment in internal R&D programs targeting novel drug delivery technologies, and our expansion of drug product design, development, and manufacturing infrastructure. All of our investments are aimed to address our customers' changing needs and their increased reliance on trusted partners to bring better medicines to market.

Our expanded toolkit of advanced technologies has improved our ability to find optimum solutions that meet our customers' target product profiles and commercial objectives. We are also leveraging the core capabilities of our legacy companies to develop innovative solutions to formulation challenges. Some examples include our new lipid multiparticulate technology, based on Capsugel's lipid formulation expertise and proprietary melt-spray-congeal processing developed by Bend Research. Intrinsically enteric capsule drug delivery technology has been developed based on combined polymer science expertise and capsule engineering capabilities. Advanced pediatric and pulmonary delivery solutions leverage our multiparticulate formulation range, particle engineering based on spray drying, and specially designed capsules.

Capsugel has also been investing to expand infrastructure at our colocated product development and manufacturing sites in the US, UK, and France. Over the last two years, Capsugel Dosage Form Solutions has invested approximately $50 million and added over 100 new colleagues at these sites, and that investment and growth still continues. Our investments reflect our custmomers' changing needs, e.g., high containment capability for handling highly potent APIs, and flexible manufacturing to accommodate lower-volume applications such as orphan drugs and pediatric dosage forms.

Our most recent investment is a great example – expanded commercial-scale spray dried dispersion (SDD) capacity, and capability for drug product intermediate production at Bend Research (Bend, OR). This expansion includes both development and cGMP capacity to accommodate rapid development and scale-up, QBD studies, and commercial manufacturing inclusive of high containment. As a result, we have combined premier SDD formulation expertise with the largest integrated SDD design, development, and manufacturing infrastructure in North America to support an ever-increasing number of client projects utilizing this technology.

We feel that Capsugel Dosage Form Solutions is an integrated and trusted partner for our clients and is well-positioned to optimally meet their evolving needs. The latest investment in innovation and infrastructure ensures that our clients can increasingly rely on Capsugel as their primary product development partner of choice, accessing an expanding range of solutions from product design through commercialization. We will continue to build on this strong foundation through organic growth, acquisitions, and the formation of additional alliances. P

CAPSUGEL CUSTOMER PERCEPTION (CP) SCORES

87% (EXCELLENT) **OVERALL SCORE**

93% (EXCELLENT) **RELIABILITY**

90% (EXCELLENT) **PRODUCTIVITY**

88% (EXCELLENT) **INNOVATION**

Source: Nice Insight's 2015 Pharmaceutical and Biotechnology Outsourcing survey

OUTSOURCING PROVIDES ADVANTAGES TO SPONSOR COMPANIES

REDUCING CAPITAL INVESTMENT WHILE GAINING ACCESS TO SPECIALIZED EXPERTISE

→ **BY ARTO TOIVONEN** President, Fermion Oy

Arto Toivonen was appointed President of Fermion Oy on January 1, 2015. Mr. Toivonen had worked at Orion since 2006 in the Alliance Management department as a Business Development Director. Before joining Orion, Arto worked for Juvantia Pharma Oy as Vice President of Business Development and as a member of Juvantia's management team from 2000 to 2006. From 1996 to 2000, he worked at Genencor International BV in Leiden, the Netherlands, and was responsible for sales of biotechnological products to global customers in several industries. Mr. Toivonen has a master of science (technology) degree in chemical engineering from the University of Technology, Espoo.

ABSTRACT

The pharmaceutical contract manufacturing industry is undergoing some important changes that reflect the current evolution of the pharmaceutical industry. An emphasis on cost control, a shift in growth from mature to emerging markets, the rising importance of generics and other low-cost drugs, the switch from large-volume blockbusters to small-volume targeted therapies, and the increasing potency of many new candidates are all driving the use of contract development and manufacturing services. At the same time, and not surprisingly, pharmaceutical and biotech companies are increasingly more selective when choosing service partners, and this is even more pronounced with new chemical entities (NCEs). Thus, while the pharmaceutical contract manufacturing market is growing, competition is fierce, and only contract manufacturing and development organizations (CDMOs) with a strong financial position and an established track record of performance, state-of-the-art production capabilities, specialized areas of expertise – particularly the manufacturing of highly potent compounds – and a demonstrated commitment to safety and sustainability will benefit. Fermion Oy, a wholly owned subsidiary of Finnish pharmaceutical developer and manufacturer Orion Corporation, is ready to meet this challenge.

ESTABLISHED TRACK RECORD

Outsourcing provides numerous advantages to sponsor companies, primarily reduced need for capital investments and increased access to specialized technical expertise. The potential also exists for increasing efficiency and lowering operating costs. However, outsourcing also carries substantial risks. As pharmaceutical companies face increasing cost pressures and as the complexity of drug candidates rises, they are therefore turning to outsourcing partners, but only to those with the necessary expertise and a demonstrated history of performance in terms of product quality, on-time delivery, regulatory compliance, safety, and value.

Fermion Oy has been producing cGMP-compliant pharmaceutical intermediates and active pharmaceutical ingredients since 1970, when it was established as a 50-50 joint venture between Rikkihappo Oy (now Kemira Oy) and Orion. Today, generic active pharmaceutical ingredients (APIs), approximately 25, and NCE APIs for both Orion and external customers are developed and produced by a staff of 330 people at its facilities in Finland, which have been FDA inspected and approved since 1979. To date, a total of 10 innovative APIs, including oncology products, have been commercialized worldwide or are currently awaiting regulatory approval (regulatory filings in the US, Canada, EU, Japan, Taiwan, China, Brazil, and Australia). As a strategic partner to innovative pharmaceutical companies, our focus is on providing cost-efficient, well-engineered synthesis, process development, and lifecycle management solutions.

EXCELLENT **PERFORMANCE** RECORD

+

FINANCIAL **STABILITY**

FINANCIAL STABILITY AND MORE

To attract new business, CDMOs must, in addition to having an excellent performance record, be financially stable. Pharmaceutical companies struggling to reduce costs are only interested in dependable third-party service providers that are committed to the industry and have the financial wherewithal to offer long-term supply security and partake in risk-sharing. As a wholly owned subsidiary of a public pharmaceutical company founded in 1917, the financial strength of Fermion is assured. In addition, we are committed to contract manufacturing and continually invest in state-of-the art technologies. Furthermore, as a manufacturer of generics we have gained extensive experience in the development and continual improvement of highly efficient processes, which allows us to provide our customers with very high quality products and services at very competitive prices. Working in close partnership with Orion, Fermion can also offer end-to-end drug development and manufacturing services.

→ Both of Fermion's API production facilities with a total reactor volume of 320 m^3 at Oulu and Hanko are highly automated.

USE OF ADVANCED TECHNOLOGIES

Although the pharmaceutical industry has historically been slow to adopt newer technologies, the advantages of innovative technical solutions, particularly those that increase efficiency and productivity and reduce costs, have become more appealing. Single-use solutions for biopharmaceutical manufacturing and continuous manufacturing of both small- and large-molecule drugs are two examples. Automation, which has the potential to improve all aspects of pharmaceutical development, manufacturing, and analysis activities, is another. Automation not only allows for time and cost savings by replacing inefficient manual processes, but consistency and reliability are often improved by the reduction (or in some cases elimination) of human interactions and thus opportunities for human error.

Both of Fermion's API production facilities with a total reactor volume of 320 m^3, at Oulu and Hanko, are highly automated. These production units have process management systems that are controlled by automation, and Fermion continues to make investments increasing the level of automation. The newest production unit in Hanko requires 50% less manual intervention compared to an older unit with less automation. In general, automation has decreased the need of manual intervention by 15% to 20%.

Automation enables the exact reproduction, for example, of a certain particle form and size from batch to batch. Automation also provides access to electronic reports on the flow of each production batch from which certain parameters can be chosen to be graphically displayed and printed as an attachment to a batch report. These graphs can then be used

for reference in test runs as well as in process and quality optimization.

These process management systems at Fermion are connected to the resource management system and enable the optimization of the supply chain with real-time raw material demands and consumption levels. These automation systems have been validated according to FDA standards. In conjunction with process development initiatives, investing in automation has enabled significant increases in the production volumes of products. Cost-of-Goods (COGS) have decreased and production times have shortened.

SPECIALIZED EXPERTISE

The complexity of drug compounds is increasing as pharmaceutical companies seek new classes of drug substances. Two particular aspects are challenging the production capabilities of many manufacturers: poor solubility and very high potency. Many new drug candidates are highly efficacious when properly delivered in the body, but suffer from low water solubility and thus limited distribution in the human body. A wide variety of solutions are being developed for these solid dose drugs, many of which require a thorough understanding of particle morphology and the ability to engineer appropriate particle designs. Separately, the manufacture of highly potent APIs (HPAPIs) requires specialized faculties and equipment in order to ensure the protection of operators, the surrounding community, and the environment.

Fermion has advanced capabilities in both of these areas. Leading experts apply their knowledge to the development of appropriate crystallization, drying, and milling processes that yield particles with the most desirable properties (stability, processability, etc.) and greatest impurity control. The development and manufacturing of OEL class IV (1 - 10 µg/m^3) and V (0.1 - 1 µg/m^3) HPAPIs (cytotoxic and noncytotoxic) in quantities from grams to tens of metric tons proceeds in dedicated, state-of-the-art facilities. In fact, a new pilot-scale unit at the Oulu site was inaugurated in March 2015. This dedicated module is equipped with one 250 L and two 400 L reactors with split valves, glove boxes, and isolators, plus a filter dryer equipped with a mill inside and an inverting filter centrifuge.

SAFETY AND SUSTAINABILITY PERFORMANCE

The safety of Fermion employees and our ultimate customers – the patients that depend on medicines made with active ingredients produced in our facilities – is of paramount importance. Fermion operates multipurpose facilities, and therefore the potential for contamination (mechanical, microbiological, or cross-contamination) is minimized through the use of strict, established standard protocols built into the procedures for all production and final handling operations. In addition, the facilities have been designed to allow for the use of dedicated areas and closed systems wherever possible, and contamination risk analyses are performed for any new equipment.

Sustainability is a primary concern at Fermion, and we have made significant progress in reducing our environmental impact. Wastewater at the Hanko plant is treated in its own activated-sludge wastewater treatment plant. Fermion's solvent recycling units serve the entire chemical production process with an annual solvent recovery capacity of approximately 8,000 tons. Although production increased in 2014, solvent consumption decreased by approximately one-third due to recycling. Fermion's energy and water consumption also decreased by approximately 8% and 20%, respectively, in 2014 due to conservation efforts. All hazardous waste is sent to an independent incineration plant designed specifically for this purpose, where it is used as fuel for energy generation. Significant efforts have also been made to minimize the carbon footprint of Fermion operations. Fermion and parent Orion are committed to Responsible Care®, and also the EK Energy Efficiency Program launched by the Confederation of Finnish Industries. Fermion has already met its energy savings target for 2016, but continues to invest in additional improvements. All together, a total of M€5 has been invested in sustainability-related programs at Fermion over the past five years, and further investments in new technology for wastewater treatment are planned.

CONCLUSION

Major trends in the pharmaceutical industry are leading drug companies to outsource a wider range of activities to third-party service providers. Those same trends, however, are also driving sponsor companies to partner with financially stable, reliable CDMOs that offer measurable added value in the form of comprehensive capabilities combined with specialized expertise. P

Advanced Capabilities

Fermion provides synthesis development and process engineering, analytical development and testing, scale-up, validation, and lab-to-commercial-scale production services providing customers with fully automated, best-in-class facilities combined with advanced particle engineering, impurity control and HPAPI production capabilities. Dedicated lifecycle management engineers provide a further value-added service for continuous improvements in cost efficiency and product quality. Fermion is a strategic partner for innovative pharmaceutical companies looking to leverage advanced technologies and expertise to achieve both high quality and cost-competitiveness.

AUTOMATION ADVANTAGE

15-20%
MANUAL INTERVENTION DECREASE

SUSTAINABILITY ADVANTAGE

8%
ENERGY CONSUMPTION DECREASE

20%
WATER CONSUMPTION DECREASE

WHAT DOES IT MEAN TO BE A FULL-SERVICE CDMO?

→ **BY DR. STEPHEN A. MUNK** CEO, Ash Stevens

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, Ash Stevens has received ten regulatory approvals for the manufacture of novel drug substances to treat serious life-threatening conditions. These approvals include bortezomib, clofarabine, 5-azacitidine, amotosalen, and ponatinib.

Dr. Munk is also an Adjunct Professor of Chemistry at Wayne State University and has served on the Board of Directors of MichBio.

ABSTRACT

Numerous trends in the pharmaceutical industry are driving drug manufacturers to outsourcing more activities, from discovery through commercial production and even life cycle management. In many cases they are looking for a combination of specialized expertise and integrated project management combined with cost-effective services. As a result, they are turning to true full-service contract development and manufacturing organizations that can help them get their products to market both safely and more rapidly.

Drug manufacturers are facing mounting cost pressures, and the industry is shifting from the traditional blockbuster model to one focused on niche products and targeted delivery. Simultaneously, drug molecules are becoming more complex and increasingly require both advanced synthesis and formulation expertise to realize cost-effective, efficacious medicines. Pharmaceutical manufacturers are consequently relying more frequently on contract development and manufacturing organizations (CDMOs) to control costs, gain access to specialized expertise, and significantly accelerate the successful development and commercialization of today's candidate therapies.

One key trend in pharmaceutical outsourcing is the preference of sponsor companies for full-service partners that can provide support through all stages of drug development and formulation for all types of drug substances and project timelines. For instance, as the market for cancer drugs continues to grow at a healthy rate, pharmaceutical companies are increasingly seeking assistance from CDMOs with established track records for the safe production of highly potent active pharmaceutical ingredients (HPAPIs). Given the need to get drugs into clinical trials more quickly than ever before, pharmaceutical companies also choose to outsource to CDMOs that have both a thorough understanding of the investigational new drug (IND) application process, and experience determining the necessary level of information that will minimize both risk and project timelines. Drug manufacturers looking to leverage US FDA Fast Track status also require CDMO partners that are aware of the significantly shortened development times, have established lines of communication with FDA regulators, and are prepared for the additional meetings and information exchanges necessary for reducing approval times.

HPAPIs REQUIRE REAL EXPERTISE

HPAPIs comprise the fastest growing segment of the worldwide API market, which will be valued at $15.3 billion by 2017, according to market research firm RNCOS. Also, business research and consulting company Roots Analysis reports that over 25 percent of all drugs worldwide are classified as highly potent.

$15.3B
HPAPIs
MARKET VALUE BY 2017

<25%
OF DRUGS WORLDWIDE ARE
CLASSIFIED AS HIGH POTENT

Given the high toxicity of these compounds, their manufacture presents many challenges. Protection of process operators must be assured, and the risk of cross-contamination must be minimized. The safety of healthcare workers and patients when using the final drug products must also be considered. Special protective equipment, manufacturing suites, production processes, management systems, transfer and packaging capabilities, and often entire facilities are required for the development and commercial manufacture of HPAPIs and formulated cytotoxic therapies.

For these reasons, many pharmaceutical companies elect to outsource these projects to CDMOs with expertise in working with highly potent substances. In particular, CDMOs with a proven track record for safely and effectively managing projects involving highly potent compounds during development and commercial production, and an excellent audit history and comprehensive regulatory records, are preferred. CDMOs can only achieve strong track records by understanding the potential risks associated with the production and handling of highly potent compounds – both at the initial stages when little direct information about the compound may be available, and later on during scale-up and commercialization – and the systems that are required to minimize those risks.

Proper facility design, approaches to barrier isolation, the incorporation of gowning/degowning areas, containment safeguards, comprehensive quality management systems, and continual operator education and training are all crucial for successful HPAPI manufacturing. The ability to perform state-of-the-art synthetic organic chemistry techniques, process development and optimization, product purification, and advances analyses, all under contained conditions, is also a must.

Overall, safety must be a priority when working with HPAPIs, and the protection of operators, contractors, healthcare workers, patients, and the general public should always be the first concern. Because it is not possible to achieve zero risk when working with highly potent compounds, CDMOs must minimize the risk as much as possible through the ongoing pursuit of new technologies, equipment, and procedures.

AWARENESS OF IND PITFALLS MAKES A DIFFERENCE

Collection of appropriate Chemistry, Manufacturing, and Control (CMC) data for IND applications and the use of appropriate manufacturing controls are just as imperative as having an effective clinical trial design. Decisions relating to data collection and manufacturing procedures can impact the overall project with respect to its budget, timeline, and quality, and consequently directly influence the outcome of the clinical trial and potentially patient safety.

Experienced CDMOs recognize the importance of such decisions and consider these factors when implementing IND projects. For example, while typically less data is needed for Phase 1 studies, more information will eventually be required if the drug candidate moves on to Phase II trials. Obtaining more extensive data prior to submission of the initial IND application for a Phase I study can in many cases help reduce project timelines. In addition, although the adoption of commercial current good manufacturing practice (cGMP) protocols for the production of Phase I clinical trial material may take additional time and effort, the added controls provide for reduced risk and FDA recognition and allow the use of any excess material in the subsequent Phase II study.

→ **COMPANY PROFILE**

Ash Stevens: Full-Service for Comprehensive Support

Ash Stevens is a true full-service CMDO, receiving a total of 12 US Food and Drug Administration (FDA) manufacturing approvals in the past nine years alone, including four with FDA Fast Track status and many HPAPIs.

With a business model predicated on providing the safest and highest-quality work product possible while meeting delivery obligations on time and on budget, 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 highly potent and other complex APIs under traditional and highly accelerated timelines.

+ Full-service CMO offering comprehensive support for small molecule drug substances
+ 30+-year collaboration for the development and commercialization of anticancer drugs with the National Cancer Institute and the National Institutes of Health (NIH)
+ Impeccable safety record
+ Award-winning EHS&S program certified by SOCMA's ChemStewards® program
+ Multimillion-dollar, multiyear, ongoing investment in infrastructure
+ Financial stability reflected in the highest possible D&B financial rating (4A1)

→ **COMPANY HIGHLIGHTS**

Ash Stevens Inc.

+ Twelve (12) FDA approvals for innovator small molecule APIs
+ Four FDA fast-track API manufacturing approvals
+ Manufacturing inspection approvals from the US, Korea, Japan, Australia, European Union, and Mexico
+ Engineering and containment controls for the safe handling and cGMP manufacture of small- and large-scale highly potent APIs with OELs ≤ 0.1µg/m^3

  Extensive experience in medicinal chemistry, advanced synthetic chemistry, and process scale-up
+ Recent addition of state-of-the-art production facilities at its API manufacturing facility in Riverview, Michigan, including advanced engineering and containment controls for the safe handling and cGMP manufacture of small- and large-scale HPAPIs, including APIs with occupational exposure limits (OELs) of less than 0.1 µg/m^2
+ Established lines of communication with FDA regulators
+ Work closely with drug sponsors and FDA to identify and mitigate any potential issues before they arise
+ Expert regulatory and analytical capabilities for all phases of drug development
+ Rapid process scale-up and optimization services for improved efficiencies (cycle times, waste minimization, yield)
+ Simultaneous development and validation of cost-effective large-scale processes
+ Use of a quality-by-design (QbD) approach, and early determination of critical quality attributes to ensure appropriate analytical methods

CDMOs supporting IND projects must also be effective project managers. Planning is crucial so that adequate time is provided for the development of a sufficient CMC package, including evidence for the structure of the active pharmaceutical ingredient (API), stability study results indicating that the drug product will be stable during the period of the clinical trial, and descriptions of both process and testing methodologies and quality control systems. Extensive experience in carefully balancing the financial, project timeline, and quality issues of an IND project is also crucial. The ability of a CMO to make rapid decisions based on all three considerations will have a direct impact on the success of an IND project.

A good relationship with the FDA and the ability to discuss the CMC package and any necessary amendments with the agency is also very important. Positive interactions with the agency can lead not only to a better clinical trial design, but a more efficient review of the IND. In essence, the CDMO plays a major role in ensuring that the agency's CMC requirements are met on a continual basis and that FDA regulators remain satisfied that the drug product is safe for use in the clinical study.

Finally, there are several basic requirements for CDMOs that support IND projects: state-of-the-art technologies, extensive expertise in API synthesis and/or drug product formulation, an effective quality program, effective communication strategies for interacting with the sponsor company and the group performing the clinical study, a strong track record of on-time or accelerated delivery, and available capacity.

WORKING ON FAST TRACK PROJECTS

AWARE OF **SHORTENED** DEVELOPMENT TIMES

+

GOOD COMMUNICATION WITH **THE FDA**

RAPID RESPONSES NEEDED FOR FAST TRACK PROJECTS

The US FDA Fast Track designation is intended to bring new drugs that treat serious conditions and that fill unmet medical needs to patients more rapidly. To leverage Fast Track status, however, pharma companies and their service providers must have excellent communication systems in place and be prepared to develop manufacturing routes and generate safety and efficacy data in much less time than they are used to.

Companies that receive Fast Track designation for a drug candidate have more frequent meetings and written exchanges with the FDA to ensure that the drug development program and data collection are proceeding appropriately. In many cases, the CMC section is submitted first, followed later by the Clinical section. Therefore, CDMOs working on Fast Track projects must be aware of not only the shortened development times (by as much as a factor of three), but also have established lines of communication with FDA regulators.

As importantly, CDMOs must have rapid process optimization and scale-up capabilities in order to develop effective routes for the production of preclinical/toxicity testing quantities in terms of cycle times, waste minimization, and yield. CDMOs that can develop and validate an efficient and cost-effective large-scale process and the associated analytical techniques while simultaneously producing clinical trial material can achieve significant reductions in project timelines while ensuring the quality and safety of the API.

In addition, because the timelines are reduced, there is generally less information about how the process can potentially impact product API quality, which can present challenges to qualification of process performance while also allowing for a slimmer margin of error. CDMOs involved in Fast Track projects must be aware of this issue and work closely with the drug sponsor and FDA to identify and mitigate any potential issues before they arise. A quality-by-design (QbD) approach and early determination of critical quality attributes can help ensure the development of effective and appropriate analytical methods, even under accelerated conditions.

Finally, CDMOs with integrated capabilities across development and commercial manufacturing and an established network of other providers to supplement specialized capabilities can reduce the complexity of project management needs and contribute to more compact development timelines. P

RISK MINIMIZATION THROUGH CAREFUL CDMO SELECTION

→ **BY GREG FLYTE** Director, CMO Alliance and Program Management, GlaxoSmithKline Biopharmaceuticals

Greg Flyte is the Director of Contract Manufacturing Organization (CMO) Alliance & Program Management at GlaxoSmithKline (GSK). He brings over 18 years of technical and business experience in engineering, validation, process development, alliance/program/project management, manufacturing operations, and business development. In his current role, he is responsible for the contract development and manufacturing organization (CDMO) business, including several collaborations with both small and large biopharmaceutical companies who are current clients of GSK. During his 16 years at the Rockville, Maryland, USA site (14 with Human Genome Sciences, which was acquired by GSK in August 2012), Greg has also been involved with managing the design through validation phases during the construction of all of GSK's manufacturing facilities, in addition to managing the large-scale manufacturing (LSM) facility validation team from inception through commercial production.

Prior to joining HGS, Greg spent two years as a validation engineer consultant. He holds a BS in chemical engineering from Drexel University.

ABSTRACT

The pharmaceutical industry is experiencing a period of significant change. Cost-cutting, downsizing, thinning pipelines, a lack of blockbusters, and the move to more biopharmaceutical – and in particular biosimilar – development, are leading many manufacturers to increase their reliance on contract development and manufacturing organizations (CDMOs). At the same time, because uncertainty creates risk, manufacturers are very careful about selecting CDMOs that are financially stable, have an established track record for on-time delivery of quality products, can offer services across the spectrum from discovery to commercial production, and are willing to form strategic partnerships.

INTRODUCTION

Due to the rapidly changing pharmaceutical industry landscape, both the branded biologics and biosimilars markets are predicted to continue on a rapid growth trajectory. Outsourcing of traditional manufacturing activities – as well as many other aspects of the drug development process, from discovery through to commercial production – is also on the rise. As pricing pressures increase, many biopharmaceutical companies are turning to custom service providers to avoid the very high capital expenditures and long lead times needed to construct, equip, and validate manufacturing facilities.

Branded and biosimilar drug manufacturers are also partnering with CDMOs that have the specialized expertise needed to manufacture the increasingly complex biologic drug candidates in their pipelines. With governments, payers, physicians, and patients all expecting real value in terms of significant, positive health outcomes, the most successful biopharmaceutical companies are developing novel products based on innovative new technologies and forming partnerships with reliable contract manufacturers that have advanced technical capabilities and an established track record of excellent performance across numerous metrics.

NEED FOR TRUST

Uncertainty, which is prevalent in the pharmaceutical industry today, creates risk. Outsourcing, while offering the opportunity to reduce costs and gain access to unique technologies, also introduces risk into biologics development. Companies that outsource traditional core and lower-value activities generally have fewer physical assets and a lower level of in-house expertise, and thus must adopt a long-term strategic approach. Biopharmaceutical manufacturers therefore seek to establish partnerships with CDMOs that will mitigate any risk attributable to outsourcing and potentially allow for distribution of the general risks associated with new drug development. To do so requires willingness on the part of both parties to enter into a true partnership based on trust and commitment.

Such trust and commitment can only be realized with CDMOs that have repeatedly demonstrated performance attributes that consistently meet the expectations of the biopharmaceutical company. Beyond the obvious need for operational, methodological and therapeutic experience and expertise; the capacity and equipment; and the ability to rapidly meet changing requirements, CDMOs seeking to be true partners for biopharmaceutical manufacturers must also have a strong quality record, a positive regulatory compliance/audit history, the demonstrated ability to meet project deadlines, and clear commercialization successes. Underlying all of these issues is the need for financial stability, which has become increasingly important as a risk mitigation factor due to the turbulent conditions in the pharmaceutical market.

Trust between CDMOs and sponsor companies is also built when there are clear pathways for communication and a high level of transparency. No project is without setbacks and unexpected issues. 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, thus avoiding disruptions and project delays. Effective CDMOs also blend their technical expertise with a facility-centric, flexible, and agile approach to relationships that focuses on the fundamentals that are important to each customer.

INTEGRATED OFFERINGS

Supply chain security is another important issue in the pharmaceutical industry today. Manufacturers of both small- and large-molecule drugs, including sponsor companies and CDMOs, must have a thorough understanding of their supply chains for all ingredients that end up in formulated products. Outsourcing does not alleviate the responsibility of biopharmaceutical manufacturers. Therefore, many sponsor companies are reducing the number of outsourcing partners and developing more strategic relationships with a few CDMOs that can provide truly integrated services and have clear supply chain management systems in place.

These CDMOs are typically integrated in multiple ways. First and foremost, they support all aspects of the drug development process, from discovery through to commercial production, and including lifecycle management activities for off-patent products. They also have the necessary expertise to support biologics production using both advanced mammalian and microbial fermentation technologies with multiple host organisms (different yeasts and CHO, mouse myeloma, and insect cell cultures),

The potential of biosimilars is significant, and therefore many branded biologics manufacturers are also developing products to serve this growing segment of the market. This trend will likely have a very positive impact on CDMOs, given that sponsor companies where possible prefer to manufacture the highest-value products in house...

and multiple process platforms (batch, fed-batch, multiple harvest, and perfusion).

In addition, truly integrated CDMOs have experience with numerous types of harvesting technologies and flexible downstream operations, and offer customers the ability to implement processes using disposable and/or stainless steel equipment. The most integrated CDMOs have facilities and protocols designed to minimize any risk of cross-contamination, and invest in automation and process analytical technology. They also have the capability to provide downstream process development services, and ideally have experience using design of experiment (DOE) and quality by design (QbD) approaches. The implementation of such an array of advanced upstream and downstream technologies provides more consistent product quality, and often increases manufacturing efficiencies.

BIOSIMILARS PRESENT OPPORTUNITIES

The potential of biosimilars is significant, and therefore many branded biologics manufacturers are also developing products to serve this growing segment of the market. This trend will likely have a very positive impact on CDMOs, given that sponsor companies where possible prefer to manufacture the highest-value products in house and thus will be more likely to outsource the production of their biosimilar portfolio.

However, given that growth of the biosimilar market will be largely driven in the near future by monoclonal antibodies, CDMOs that hope to win these projects must still have very advanced capabilities. In addition to modern manufacturing facilities and technologies, CDMOs that want to compete

GlaxoSmithKline Biopharmaceuticals
Manufacturing Your Products Like Our Own

As a CDMO that operates as an independent business within a large pharmaceutical company, GlaxoSmithKline Biopharmaceuticals offers many advantages to manufacturers looking for a strong, stable partner with extensive experience in biologics development and commercialization and access to expansive resources, including a wide range of analytical capabilities and in-depth regulatory expertise.

GlaxoSmithKline Biopharmaceuticals serves as a manufacturing knowledge center, enabling the launch, supply, and management of GSK biopharmaceutical products around the world. We leverage these capabilities to provide contract manufacturing services with market-leading quality, cost, and timeliness.

We have the proven history, technologies, facilities, systems, people, and corporate support you need to get your biologics products into development and out to patients efficiently and with maximum quality and safety.

+ Independent business of GlaxoSmithKline
+ Support GSK and external customers with drug substance (DS) and drug product (DP) manufacturing
+ Two facilities in the US for biologics DS production (fermentation and cell culture)
+ Two facilities in Europe for formulated DP manufacturing
+ Fully integrated supply chain support

CDMO PARTNERSHIP SELECTION TRAITS

in the biosimilar space must have access to state-of-the-art analytical techniques for biologic structure determination, the ability to use advanced simulation tools and complex algorithms, and achieve process development and scale-up at an accelerated pace in order to get products to the market in advance of the (significant) competition.

BENEFITS OF BIG BIOPHARMA BACKING

As mentioned above, financial stability is crucial for the success of CDMOs today. Biopharmaceutical companies looking to outsource for cost control or to gain access to needed expertise are only interested in partnering with reliable third-party service providers that are committed to the industry and have the financial wherewithal to offer long-term supply security and partake in risk-sharing. Achieving that level of security can be a challenge in today's industry.

CDMOs that have a direct connection to an established world leader in the development and scale-up of biologics do have the financial strength and stability demanded by sponsor companies. They are also committed to contract development and manufacturing and continually invest in state-of-the-art technologies. Of course, in order to allay any concerns regarding potential competitive issues, this type of CDMO must operate sufficiently independently of the parent biopharmaceutical company, with appropriate controls in place to ensure that the work it does for its customers remains confidential and separate.

Even so, a CDMO connected with a large biologic drug producer can offer its customers many advantages over independent service providers. In essence, such a partner can offer the flexibility of a small, nimble company combined with the financial stability, depth of technical (upstream, downstream, analytical regulatory) expertise, and development and production capabilities generally expected only from a large global manufacturer.

These CDMOs also tend to offer the most comprehensive integrated services – from early-stage development to commercial production using world-class, state-of-the-art equipment and facilities – and thus are in the best position to minimize the risks associated with outsourcing of biologics development and manufacturing in general, and challenging and complex products and processes in particular.

CONCLUSION

Numerous trends in the biopharmaceutical industry are driving sponsor companies to increase their outsourcing activities. They are, however, very selective when choosing CDMOs as outsourcing partners in order to mitigate the risks they face. CDMOs that are financially stable, offer truly integrated services, and have a demonstrated track record of high performance when rated against several different metrics (quality, on-time delivery, audit history, technical expertise, investment in innovation, etc.) are attracting the most attention. CDMOs like GlaxoSmithKline Biopharmaceuticals that operate as an independent business within a large pharmaceutical company can serve as strong, stable partners, with the breadth and depth of expertise and capabilities to provide contract development and manufacturing services with market-leading quality, cost, and timeliness. P

IN-DEPTH PROCESS AND PRODUCT EXPERTISE

THIS IS KEY TO CDMO SUPPORT OF ORPHAN DRUG AND BREAKTHROUGH THERAPY DEVELOPMENT & COMMERCIALIZATION

→ **BY KRISTINE K. SENFT** Vice President, Marketing, Hovione

Kristine Senft is a professional, inspirational sales and business leader with a proven track record of success in the pharmaceutical and fine chemical industries. She has achieved a distinguished 25+ year career introducing strategies to drive global growth within intensively competitive markets. Before joining Hovione, Kristine served in various roles as a Business Unit Director, DSM Biomedical, and SVP, Marketing and Sales, DSM Pharmaceutical Chemicals, where she led both regional and global marketing and sales organizations. She also worked for Albemarle Corporation for many years in mainly sales and business management roles in their Fine Chemicals and Pharmaceutical API businesses. Kristine is an active supporter of the Drug, Chemical and Associated Technologies Association (DCAT), DCAT Week, and has recently served on the DCAT Board of Directors. While residing in Europe she was also associated with the European Fine Chemicals Group (EFCG). Ms. Senft graduated from Eastern Illinois University with a BS in chemistry. In 2014, she completed the DSM Executive Leadership Program at Wharton, University of Pennsylvania.

ABSTRACT

As older blockbuster drugs lose patent protection and generic competition increases, many pharmaceutical companies are focusing discovery efforts on therapies with the potential to treat multiple niche populations. Increasingly, innovative small and emerging pharma firms are developing new drug candidates with orphan or breakthrough therapy status that are ultimately licensed or sold to large brand manufacturers. These companies rely heavily on contract manufacturing and development organizations (CDMOs) that can provide in-depth scientific expertise and achieve under rapidly accelerated timelines the development of cost-effective, robust, reliable processes that consistently yield high-quality products.

Until recently, most pharmaceutical firms were not interested in the development of small-volume drugs due to fears of limited returns. With the age of the blockbuster drug now history, many drug companies are finding that niche therapies, particularly those that may treat numerous indications, not only provide patients with life-saving medications, but also realize attractive financials if developed in a streamlined and cost-efficient manner. There are over 7,000 different types of rare diseases and disorders, yet only a couple of hundred approved therapies designated as orphan drugs. According to EvaluatePharma, although the average Phase III development time for orphan drugs is not shorter than that for non-orphan drugs, the Phase III drug development costs for the former are half those of the latter, and the anticipated return on investment for a Phase III/filed orphan drug is nearly twice that for a non-orphan drug.

As a result, EvaluatePharma estimates that the orphan drug market is growing at an annual rate of 11%, more than double that of the overall prescription drug market (5%), and by 2020 will reach $176 billion in annual sales and account for 19% of the total non-generic prescription market. In 2013 alone, 260 orphan drug designations were granted. In 2014, the FDA approved 15 NDAs and seven BLAs with the orphan drug designation, along with 24 supplemental approvals.

Many companies are also pursuing the new breakthrough designation established in 2012 by FDASIA, the Food and Drug Administration Safety and Innovation Act. A candidate qualifies for breakthrough therapy designation if preliminary clinical evidence suggests that the drug may have substantial improvement over available therapies on at least one clinically significant endpoint. The development and approval times for breakthrough therapies are typically half that of the seven years for conventional drugs, and both the sponsor and CDMO benefit from greater FDA guidance and communication with the agency. FDA's CDER approved 14 breakthrough therapies in 2014 and nine in 2015 as of August 21.

ORPHAN DRUG MARKET GROWTH

11%
CURRENT **ANNUAL RATE**

$176B
ANNUAL SALES PREDICTION
BY 2020

260
ORPHAN DRUG DESIGNATIONS
GRANTED IN 2013

Of the firms pursuing the development of orphan drugs and breakthrough therapies, many are small or emerging pharmaceutical or biopharmaceutical companies focused on niche, small molecule therapies. These companies often have limited resources in terms of laboratory, analytical, and manufacturing equipment (indeed, some are virtual companies in that respect) and depend heavily on service providers to perform crucial process and formulation development, validation, regulatory compliance, and manufacturing activities. The choice of CDMO can therefore have a direct impact on the success or failure of the new drug.

DEEPER SCIENCE

Whilst technical capabilities and synthetic expertise in a wide range of chemistries is necessary for any CDMO, the ability to accomplish practically any chemical transformation is no longer sufficient when supporting small and emerging pharma companies that are focused on the development of small-volume, niche drugs for targeted patient populations. Clearly, an awareness and understanding of their needs related to the development of orphan and fast track drugs and breakthrough therapies is a must.

Innovative smaller pharmaceutical organizations, particularly those in North America, also expect to have deeper discussions about technology and science. They no longer see CMOs/CDMOs as simple suppliers of manufacturing services; they select providers that can offer a unique depth of expertise, knowledge, and know-how that can help them address the challenges they face throughout the development and commercialization process, and increasingly at earlier stages. The same trend is also occurring with larger pharmaceutical companies that outsource discovery and early phase development.

All of these firms rely very heavily on CDMOs that have a deep understanding of both the processes and molecules they are trying to develop. Service providers with the right combination of technical capabilities and experience can help sponsor firms to reduce development times and costs, and provide assurance to regulators that the ultimately chosen cost-effective process will be robust and reproducible, and provide product with consistent quality, regardless of any need for technology transfer or scale-up.

→ In 2014, FDA approved 15 NDAs and seven BLAs with the orphan drug designation, along with 24 supplemental approvals.

It should also be noted that the rapid pace of advancement in chemical and biological technologies ensures that no one company can have expertise in all of the latest techniques and methodologies. Therefore, in addition to having specialized expertise in several scientific areas with applicability to pharmaceutical development, such as particle engineering and chromatographic purification on the lab to commercial scale, CDMOs viewed as preferred partners also have capabilities designed to aid in process understanding, and belong to a network of providers with other specialized expertise that they can tap if needed.

One technical area of particular importance is particle engineering. Because 40-60% of all NCEs are poorly soluble, CDMOs with the ability to identify solutions to solubility challenges have a real competitive advantage. Experience in particle engineering and the ability to create a wide range of physical forms with enhanced solubility is becoming a necessity today. State-of-the-art technologies such as spray drying and hot melt extrusion, combined with advanced modeling tools, enable significant reductions in development times and costs while providing high quality APIs with desirable pharmacokinetic properties.

RELATIONSHIPS MATTER

Indeed, relationships also play a crucial role in the success of accelerated drug development projects. According to a recent report by the Tufts Center for the Study of Drug Development (CSDD), to better serve public and patient communities by reducing rising development costs, shortening cycle times, and delivering better innovations, many pharmaceutical firms are also implementing highly collaborative approaches to validating drug targets; integrating real world data into the R&D process; employing flexible and adaptive clinical trials; and using green manufacturing techniques that include the sharing of pre-competitive information among government agencies, academia, patient groups, payers, and providers.

Because there is much less time to develop and validate the manufacturing process and analytical methods and generate safety and efficacy data, it is important that the CDMO and sponsor company have established a more strategic relationship, with the CDMO acting as an extension of its customer rather than only as a vendor. Strong sponsor-CDMO communication is particularly vital, so that potential problems can be caught and addressed before they become major setbacks.

Good relationships with FDA representatives are equally important. Orphan drug, breakthrough therapy, and fast track designations require increased interactions with the agency to ensure that the shorter development times can be met. CDMOs that have experience working with the agency and recognize the value of additional meetings and guidance from

Focused Expertise for Accelerated Drug Development and Manufacturing

Hovione has been providing support to small and emerging pharma and biopharma companies since the start-up of our New Jersey plant in 2002, which will double its size to support increased demand from our sponsor partners. Today we provide support for all stages of the drug development and commercialization cycle to customers large and small.

With our in-depth process and product knowledge, we are able to rapidly develop robust, reliable, and predictable processes with attractive long-term economics that provide products of very high quality. As a result, Hovione is ideally positioned to support the development and commercialization of orphan drugs and drug candidates with breakthrough and fast track designation.

+ Small-volume API manufacturing
+ Development by design (application of quality by design and process modeling technologies) for streamlined development
+ Advanced particle engineering capabilities (spray drying, hot melt extrusion capabilities, and jet milling)
+ Expertise in overcoming poor solubility and permeability
+ Facilities for the production and handling of highly potent compounds
+ Advanced cryogenic and hydrogenation capabilities
+ VPP Star Award facility as designated by the Occupational Safety and Health Administration (OSHA)

the FDA will be able to not only provide enhanced service and support to their small and large pharma customers, but also help reduce risk and facilitate earlier approvals.

To address the development challenges presented by the increasingly complex drug candidates of today, pharmaceutical companies are also seeking CDMOs that emphasize collaboration within their own firms. For accelerated development projects in particular, effective cross-functional teams are needed to ensure that CMC data development and stability studies are completed in a timely fashion, a suitable plan for scale-up and production is in place, the needs of other international authorities are considered for global products, and lifecycle management issues have been addressed. In fact, CDMOs with integrated capabilities across all stages of development and commercial manufacturing are increasingly preferred over traditional CMOs.

DEVELOPMENT BY DESIGN

There is very fundamental science behind all of the phenomena that occur during chemical/biochemical processes. The use of modeling technologies based on first principles provides the ability to design robust processes that behave the same regardless of scale. The application of quality-by-design (QbD) and process analytical technology (PAT) methodologies during both the development and commercialization stages, combined with the use of advanced modeling, allows simulation of the full design space well beyond what is possible using a design-of-experiment approach alone. At Hovione, this approach is a very powerful one that leads to the development of highly robust and reproducible processes, and in turn ensures smooth and rapid technology transfer and scale-up of the same high quality products regardless of volume or location. The enhanced process understanding and reproducibility obtained are also well-regarded as strengths by the FDA and other authorities. This approach ensures that only value-adding activities are performed, and are performed at the right time and in the most efficient manner.

IN CONCLUSION

Despite the turbulent times currently facing the pharmaceutical industry, there are many opportunities for both smaller emerging and larger established pharmaceutical and biopharmaceutical companies to develop novel medical treatments that will improve the lives of patients suffering from a myriad of as-yet-untreated diseases. CDMOs with a deep understanding of the process development and commercialization needs of both small and large sponsor firms faced with accelerated timelines can help speed new safe and efficacious drugs to market while ensuring that they are produced using cost-effective, robust processes.

Hovione, with years of experience developing and producing small-volume APIs at its US site, is ideally positioned to support accelerated orphan drug and breakthrough therapy projects. This is of particular benefit to emerging pharma clients, which enables the transition to commercial production regardless of the ultimate owner of the IP. We recognize that each customer has unique needs, and are therefore focused on meeting those needs through the tailoring of our comprehensive set of chemistry, particle engineering, process and formulation development, manufacturing, analytical, and regulatory capabilities. P

BOLSTERING CAPABILITIES FOR PARENTERAL DRUG DEVELOPMENT AND MANUFACTURING

→ **BY SYED T. HUSAIN** Chief Commercial Officer
AAIPharma Services–Cambridge Major Laboratories

Syed Husain serves as the commercial leader for AAIPharma Services–Cambridge Major Laboratories, leveraging in-depth experience in sales, business development, marketing, and operations for the custom development and manufacturing of small molecules, antibody drug conjugates (ADCs), peptides, biologics (mammalian- & microbial- based drug substances), and drug products. Previously Mr. Husain served as Head of Business Team at Lonza responsible for the API manufacturing business. From 2005 to 2013, he served in increasing Sales & Business Development roles of responsibility for APIs (chemical and biologic) and as Head of Sales & Business Development for the API manufacturing Business Unit. Syed earned a BS in chemical engineering from New Jersey Institute of Technology in 2003 and an MBA from Cornell University in 2009.

ABSTRACT

As the pharmaceutical and biotechnology markets undergo significant changes, companies are relying more heavily on CROs and CMOs to provide the needed services, expertise, and technologies to help them favorably compete in a challenging marketplace. Contract service providers, in turn, are strengthening their capabilities to satisfy current demands, in some cases by coming together. An example is the recent combining of AAIPharma and Cambridge Major Laboratories, forming a full-service global CDMO supplying drug substance and drug product development, manufacturing, testing, and packaging services. This coupling also supports drug sponsors facing the escalating challenges of developing and manufacturing parenteral drug products.

Contract development and manufacturing organizations (CDMOs) have been vigorously bolstering their capabilities to support the changing needs of pharmaceutical and biotechnology companies as the industry continues its transformation over the last few years. Pressures to reduce time and costs, expand product pipelines faster, and meet more stringent regulatory requirements are key drivers of the change. They are also triggering the continued growth of outsourcing, which is increasingly considered a strategic imperative. The greater demand for outsourced services is attributed in large part to the increase in outsourcing biopharmaceutical drugs, by both pharmaceutical and biopharmaceutical companies.

This article discusses industry trends and issues in the development and manufacturing of parenteral drugs and why more drug sponsors are relying on outsourcing partners to design and implement these increasingly complex programs.

TRENDS AND ISSUES IMPACTING PARENTERAL DEVELOPMENT AND MANUFACTURING

According to a 2015 Nice Insight survey of 2,300 pharmaceutical and biotechnology executives, the percentage of survey participants whose companies spend more than $50 million annually on outsourcing has remained fairly stable over the last three years. However, the percentage of companies that spend $10 million to $50 million on outsourcing has increased dramatically, from 38 percent to 62 percent, and the percentage of companies spending less than $10 million has decreased by slightly more than half.[1]

According to Frost & Sullivan, sterile parenteral contract services make up about 82.8% of the total sterile CMO market. This includes small-volume parenterals (vials, ampoules, and syringes), which make up the majority of sterile CDMO services with 88.9% of market share, and large-volume parenterals (bags and bottles). The sterile parenteral manufacturing subsegment is expected to reach a market size of $6.5 billion by the end of 2016.[2]

As the industry continues to outsource more of its development and manufacturing to contract research organizations (CROs) and CMO/CDMOs, pharma and biopharma companies are undergoing a wave of mergers and collaborations to build their internal strength. Just like their pharma and biotech partners, industry contractors, too, are forming alliances to strengthen their resources in response to new industry demands.

As an example of the trend of contract companies coming together, in 2014 Cambridge Major Laboratories, a full-service global CDMO providing active pharmaceutical ingredient (API) development and manufacturing, combined with AAIPharma, a global provider of pharmaceutical analytical testing, drug product development, and drug product manufacturing and packaging services, to become a major global supplier of integrated chemistry, manufacturing, and controls (CMC) services with centers of excellence in solid-state chemistry and formulation development services. The combination of these two highly respected, market-leading firms with proven expertise in API development, analytical chemistry, and finished dosage forms significantly boosted their ability to support market demand with expanded expertise and infrastructure. Recently, Atossa Genetics, the breast health company, signed manufacturing and quality agreements with the new organization, AAIPharma Services–Cambridge Major Laboratories, for the clinical supply manufacturing of an API in Atossa's leading drug candidate for breast hyperplasia.

One area where this alliance has brought considerable combined scientific and technical expertise is the development of clinical and commercial finished dose manufacture of parenteral drug products. Over the last four years, AAIPharma and Cambridge Major Laboratories have produced a significant amount of parenteral fills in its sterile manufacturing facility for small- and large-molecule parenteral products for liquids, lyophilized products, suspensions, emulsions, and terminally sterilized vials. The operational setup via the combined company allows for the seamless integration of services covering development, testing, and manufacturing from API to finished packaging through a single, dependable, flexible, and high quality vendor.

PARENTERAL DRUG DELIVERY: MEETING ESCALATING CHALLENGES

Parenteral drug delivery is the second largest segment of the pharmaceutical market following solid oral dose delivery, and accounts for nearly 30 percent of the market share. Valued at $27 billion, the parenteral delivery market is expected to reach $51 billion by 2015.[2] Outsourcing parenterals is anticipated to increase and continue to benefit established companies in this market.[3]

Considerable challenges are prevalent in the market, including quality concerns, stringent regulations, and lack of funding. Aseptic processing of parenterals involves challenges such as protecting the sterility of a product as it moves through each phase of formulation, filtering, filling, and packaging. Companies specializing in the aseptic processing of parenterals must use advanced controls and optimal processes and packaging materials to ensure patient safety.

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Many pharmaceutical companies do not have the resources necessary to manage the increasing complexity of producing and filling parenteral substances. To achieve optimal results, the development and manufacturing processes for parenterals require the high level of expertise and experience, as well as the specially designed infrastructure and sophisticated instruments and technologies, of a contractor that specializes in this area.[2]

Stringent regulatory requirements must be followed, including maintaining compliance with US and international regulatory requirements, including current good manufacturing practices (cGMP) to protect product safety, identification, strength, purity, and quality (SISPQ).

The parenteral drug pipeline has continued to shift from small molecules to complex biologics such as monoclonal antibodies (mAbs) and antibody drug conjugates (ADCs). A significant percentage of new items in the product pipeline are biologics. The expansion of biological therapies provides additional challenges for parenteral drug delivery specialists seeking to develop ways of improving standard injections and patient safety of these products. Biologics and biotech drugs are typically not stable in solutions, which can require cold chain and storage hurdles. Lyophilization can be an important process in maximizing the stability of a product. CMOs capable of developing and testing lyophilization cycles on a lab scale can prove to be cost-effective. Development and manufacturing processes around aseptic compounding equipment utilization have also become increasingly complex and resource-intensive with specific environmental monitoring and controls.

PARENTERAL MARKET

$27B
CURRENT VALUE

$51B
2015 EXPECTED VALUE

OUTSOURCING EXPERTISE NEEDED

The rapid expansion of biopharmaceutical products has resulted in a growing trend toward contract manufacturing of parenteral drug products. Outsourcing manufacturing affords biopharmaceutical drug sponsors a cost-effective, efficient way to gain the needed technical expertise, operational efficiency, and regulatory support needed to produce these products.

Sponsor expectations from a CDMO include broader analytical test methods for release, and stability of the increasingly complex drug products. The demand for analytic single-use systems has increased due to the need for multiple test methods to assess drug purity and stability.

The fill-finish process of aseptically prepared drug products requires sophisticated equipment in a highly controlled cGMP environment. These elements are vital to ensure product quality and patient safety. Single-use fill-finish assemblies must meet stringent requirements to ensure flow-path sterility and integrity as well as operational safety, and provide fill-volume accuracy. These solutions can also improve operational flexibility, and reduce capital investment in facilities and equipment.

Accuracy on the filling line is a significant technical challenge. Parenteral drug sponsors expect advanced filling lines that improve quality and save costs, such as fully automatic equipment to optimize yield. They are also interested in the ability to rapidly identify and characterize particles. In addition, there is a high demand for flexible equipment and processes, such as stainless steel and disposable systems, options in pumping and filtration systems, and the ability to handle new materials and injectable systems. These capabilities need to be paired with processes and equipment to contain drugs where limited toxicity data exists or potency/toxicity is high.

Continuous investment in advanced technology and staff training, as well as constant monitoring of the market and industry environment and keeping up with new regulations pertaining to parenterals, helps meet these challenges.

LOOKING FORWARD

Looking ahead, pharmaceutical and biotech companies will likely continue the trend toward outsourcing parenteral development and manufacturing. At the same time, complexity of active ingredients and production processes will grow. These industry changes will require strategic partnerships with highly competent, experienced CDMOs that have expertise and experience in this field and can respond to current and future challenges through flexible and creative supply chain solutions for their customers. P

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DIGITAL AUTOMATION IN CLINICAL TRIALS: THE PROMISE AND POTENTIAL

→ **BY ZAHER EL-ASSI** President, Merge eClinical

Zaher El-Assi currently serves as the President of Merge eClinical, a division of Merge Healthcare (NASDAQ: MRGE). Merge eClinical specializes in enterprise technology services and solutions for the clinical research industry through its unified, cloud-based study management and data capture platform, Merge eClinicalOS®. Under his leadership, Merge eClinical has become one of the leading solutions providers in the clinical research industry, with clients using its software to conduct trials in more than 80 countries around the world.

Mr. El-Assi earned a bachelor of science degree in computer sciences from Northeastern University and studied at the Vienna International School.

ABSTRACT

The use of mobile technologies and basic clinical electronic data capture (EDC) systems, both of which are encouraged by the Food and Drug Administration (FDA), is helping to streamline the clinical trial process and reduce costs. More advanced, integrated cloud-based platforms are achieving further gains with Web-based tools that track drug supply, manage images, coordinate reporting, and provide assistance with translation, endpoint adjudication, and more. The growing interest of major technology companies in advancing automation in the healthcare industry signals even greater changes to come. The result will be increasingly effective medications and more personalized healthcare.

COSTS AND TIMELINES CONTINUE TO RISE

Using traditional methodologies, clinical trial timelines have lengthened and costs have risen dramatically in recent years. Phase I, II, and III trials were estimated to cost on average more than $170 million ($24 million, $86 million, and $61 million, respectively) in 2010.[1] More data are being generated and must be collected, monitored, managed and shared. Those involved in managing trials – from sponsor companies to contract research organizations (CRO) and academic institutions – must continuously strive to reduce complexity, streamline business processes and workflows, and increase efficiencies at all scales.

REGULATORY SUPPORT ENCOURAGES EDC ADOPTION

Clinical EDC systems have proven to streamline workflows and increase data management efficiencies. The FDA has recognized EDC as an important enabling technology,[2] and the agency is strengthening requirements for its use.[3]

The FDA is encouraging the use of EDC systems because they support more accurate collection, analysis, and sharing of data. Moreover, EDC platforms help increase compliance with regulatory requirements and lower overall costs. Such tools also help spur adoption of the adaptive clinical trial model,[4] which can save sponsor companies between $100 and $200 million annually through early termination of unsuccessful studies.[5]

The FDA also is shifting its focus from one that stresses compliance above all to one that places quality first.[6] More and more, the FDA is emphasizing the use of quality metrics that can be readily obtained through advanced EDC software. The FDA has mandated that, beginning in 2017, all marketing application submissions for drugs and biologics be made using the electronic Common Technical Document (eCTD). Commercial INDs (clinical trial applications) will need to be submitted electronically by May 5, 2018.[7]

Cloud-based platforms are helping to meet these new requirements with central data files that are automatically updated and accessible for even greater collaboration. As companies like Google, Apple, and IBM explore solutions that speed decision-making at all levels, the implementation of efficient data management systems is crucial.

REPLACING THE BURDEN OF PAPER

EDC software helps improve clinical studies by optimizing communication and workflows and increasing accuracy of data entry, organization, and monitoring. By eliminating the need to manually create, track, search, and analyze thousands of paper case-report forms (CRFs), EDC can be used to more rapidly design and launch trials (sometimes in as little as 10 days).

Cost savings result from the diminished need for on-site monitoring as well as the decreased time required to rectify data errors.[8] But the elimination of paper CRFs has perhaps the greatest impact on increasing trial efficiencies.[9] One study found that study periods were reduced on average by more than 300 days[10] and trial costs by as much as 24 percent[11] when an EDC system was implemented. It's little surprise that nearly half of all new trials now use EDC.[12]

FUNCTIONALITY DRIVES INCREASED EFFICIENCY

Beyond EDC, many cloud-based solutions comprise Interactive Web Response (IWR) tools for tracking inventory, images, reporting, and endpoint adjudication. For example, the endpoint adjudication module from Merge eClinical gives sites, coordinators, and adjudicators online access to all files and automatically compiles electronic dossiers of required endpoint details and source documents. The timeliness and quality of endpoint data capture are enhanced, making faster adjudication possible. In addition, the levels of standardization and consistency are increased, helping to minimize process-driven variability that can influence end-point outcomes.[13]

WITH EDC/IWR SYSTEMS

QUALITY METRICS

INCREASED EFFICIENCY

SPEEDIER TRIALS

→ Clinical EDC systems have proven to streamline workflows and increase data management efficiencies. The FDA has recognized EDC as an important enabling technology, and the agency is strengthening requirements for its use.

For many early clinical EDC systems, management of randomization was not included, and EDC and IWR systems were often disparate and difficult to link. This problem has largely been solved as the majority of today's systems address all randomization and data-capture needs through a single platform. Many cloud-based systems go even further, letting users conduct randomization and inventory-management tasks across the entire supply chain from any Web-enabled device.

EMPOWERING USERS TO DO MORE

The growing use of software-as-a-service (SaaS) data management systems by small- to mid-size sponsors, CROs, and academic institutions also suggests that such solutions help distribute the benefits of IT more equitably across the clinical research landscape. When organizations of all sizes use advanced data management tools, researchers can bring safer, more efficacious therapies to the market more quickly and at lower costs.[14]

At the same time, many CROs wish to expand their ability to build studies independently and develop

→ COMPANY PROFILE

Merge eClinicalOS (eCOS) Highlights

Merge eClinical is a division of Merge Healthcare, Inc. (NASDAQ: MRGE), a leading provider of enterprise imaging, interoperability, and clinical systems that seek to transform healthcare. eClinicalOS (eCOS), the company's flagship product, is a single, scalable, cloud-based platform researchers can configure to suit a study's precise needs. From monitoring inventory and managing randomization to endpoint adjudication and archiving results, users pay only for the options they use.

Studies built within eCOS can launch in as few as 10 days, and the average deployment time from project start is 40 days. Through active sites in 80-plus countries, more than 50,000 clinical research professionals in small and large organizations have entrusted their study management needs to eCOS. The division also provides CTMS for Investigators, which was the first clinical trial management system on the market. More information is available at **www.eclinicalos.com**, and you can follow us at **@goecos**.

the capability to provide this service to clients. Some systems are therefore designed to facilitate internal study building and help customers automate their workflows. Through consistent and intuitive user interfaces, such systems simplify the study design process and make it possible for researchers without programming skills to build and deploy a trial within weeks.

PERSONALIZING HEALTHCARE

The "recent development of large-scale biologic databases, powerful methods for characterizing patients (such as proteomics, metabolomics, genomics, diverse cellular assays, and even mobile health technology) and computational tools for analyzing large sets of data" are now fueling the Precision Medicine Initiative (PMI), according to Francis Collins and Harold Varmus in "A New Initiative on Precision Medicine," a Perspective published in the New England Journal of Medicine in February 2015. This initiative will revolutionize healthcare and generate the scientific evidence needed to move the concept of precision medicine into clinical practice.[15] By considering genetic variability, these technologies are making personalized disease treatment and prevention viable.

CONCLUSION

Automated technology, including advanced data management software, is pushing the boundaries of what can be achieved in healthcare, from bench to bedside. New approaches to data generation, management, and analysis are enabling the use of enormous data sets, thereby empowering researchers and medical professionals to make faster and more reliable decisions. Similarly, data sharing and collaboration tools are making it possible to more rapidly determine the safety and efficacy of potential drug candidates for different patient populations, heralding an era of personalized healthcare. P

EDC SYSTEM ADVANTAGES

300
DAYS
AVERAGE STUDY
TIME SAVINGS

24%
COST REDUCTION

→ **COMPANY HIGHLIGHTS**

With eCOS, you:

- **Choose what you want:** Use our Clinical Configurator™ to build and budget your study, selecting only those features and services that fit your needs
- **Pay as you go:** Maximize savings as you only pay for the features you use when you use them, with no long-term contracts
- **Eliminate upfront capital costs:** Avoid extensive (read: expensive) technology investments through our secure cloud-based platform
- **Skip lengthy training:** Get in, get the know-how and get going — all within two weeks
- **Get ready access:** Log in to a single, secure URL from anywhere using any browser or mobile device running iOS, and your complete data set is right at your fingertips.
- **Learn only one interface:** Use one part of eCOS, and you're ready to master all the rest
- **Leverage data centralization:** Access a secure, centralized data repository along with advanced analysis and processing capabilities for improved compliance with reporting requirements
- **Avoid disruptive upgrades:** Continue with your work while Merge eClinical maintains and continuously updates all software in response to client needs, global/regional industry requirements, and regulatory guidelines
- **Tap the latest technology:** Seamlessly integrate a wide range of study functions, including endpoint adjudication, randomization, inventory management and dispensing, medical coding, translation, and more

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ENSURING THE INTEGRITY OF TEMPERATURE-SENSITIVE DRUGS ALONG THE COLD CHAIN

WHAT YOU CAN DO TO MITIGATE RISK

BY JAY MCHARG President, American Aerogel

Jay McHarg, CEO & President of American Aerogel, has 20 years of experience in engineering, operations, and strategy, and has dedicated his career to designing, building, and delivering customer-focused results. Since 2008, he has focused his business and engineering experience on the cold chain industry, leading innovative product development and developing strategic partnerships for American Aerogel, a company dedicated to providing the best products and services available to protect temperature-sensitive shipments. Jay leads a team of engineers and industry experts that are passionate about temperature control and work hard to provide the most innovative packaging solutions. Jay earned both a bachelor's and master's degree in engineering from McGill University and an MBA from Babson College.

ABSTRACT

Dramatic changes in the pharmaceutical industry are forcing manufacturers to find better solutions to ensure the integrity of temperature-sensitive products along the cold chain. From shipments of active ingredients to clinical trial materials and finished products, even a minor temperature excursion during transit can have dire consequences for drug sponsors, patients and other stakeholders. An excursion outside the acceptable temperature range can compromise product efficacy and patient safety, lead to product loss or costly quarantine for analysis, and damage company reputation.

For more than a decade, the global pharmaceutical industry has been aggressively upgrading its shipping practices and tertiary packaging (shipping containers) for safer transit of temperature-controlled pharmaceuticals and biologics. The urgent need for temperature-assured material distribution stems primarily from several industry trends: changing product pipelines, more-stringent regulatory requirements and oversight to mitigate risk, and escalating cost and time pressure to speed medicines to patients.

Clearly, the industry needs better solutions to protect temperature-controlled-product efficacy across supply chains. Realizing the traditional cold chain and tertiary packaging are inadequate to meet current industry demands, many companies are partnering with specialized container suppliers and shippers who have the expertise, technology, and resources to ensure safe product delivery.

TRENDS IMPACTING PACKAGING

The dramatic growth of high-cost biologics and specialty drugs is fueling the demand for temperature-sensitive packaging. Biologics are more structurally complex and temperature-sensitive than small molecule pharmaceuticals, and must be handled under specific temperature-sensitive conditions. From 2007 to 2013, the global biopharmaceutical market grew at a compound annual growth rate (CAGR) of approximately 14% and its current market value has reached $197 billion, approximately 20% of the total global pharmaceutical market. The market is expected to reach $344 billion by 2018, possibly accounting for approximately 27% of the market.[1]

Since temperature control can impact drug stability, biopharmaceutical companies must prove to the Food and Drug Administration (FDA), their product is maintained at its required temperature: frozen at -65°C, refrigerated at 2°-8°C, or controlled room temperature at 15°-25°C. If the temperature is not maintained, the drug product must go back to the manufacturer to check its stability data and determine if the product is within the acceptable temperature range.

Another strong trend impacting drug product shipping is more-stringent regulatory requirements and oversight, as products are increasingly being shipped to global destinations. As a result, comprehensive temperature control has replaced the traditional cold chain perspective. In 2013, the European Union codified its Good Distribution Practices (GDPs), which are rapidly becoming the required guidance worldwide. The GDPs expanded oversight to medicines such as controlled-room-temperature products. Global authorities now require proof that products remain within an approved temperature range during transportation. Unlike a decade ago, regulatory authorities as well as container manufacturers now have temperature-monitoring devices.

ADVANCES IN TEMPERATURE-SENSITIVE PACKAGING

Vendors of temperature-controlled packaging products have responded to the changing state of the industry and heightened regulatory expectations with new materials and technologies to transport pharmaceutical and biopharmaceutical products safely. Partnering with a highly qualified vendor you trust with the safety of your temperature-sensitive products and choosing the most reliable tertiary packaging for your needs are critical to the safety of your shipment. Trust is essential in forming a long-term, collaborative partnership for dependable shipping solutions.

Many companies are rethinking their strategies for shipping temperature-sensitive products, seeking packaging suppliers with considerable design and industry-specific expertise, and a high-level understanding of regulatory requirements, advanced technologies, and the capability of delivering efficient, cost-effective, risk-appropriate solutions.

GLOBAL BIOPHARMACEUTICALS MARKET VALUE

$197B
CURRENT VALUE

$344B
2018 EXPECTED VALUE

Shippers of temperature-sensitive drug products have a wide selection of packaging options. The choice is a matter of balancing the risk, cost, and benefits of each option, and considering the value of the payload, the regulatory requirements, and the potential consequences and costs of a temperature excursion.

Manufacturers should look for shipping containers that are the smallest and lightest for the payload size, contain high-performance insulation, and have been prequalified to stringent standards in an International Safe Transit Authority (ISTA)-certified testing laboratory. They should be able to maintain the payload temperature throughout any ambient profile. Modular designs simplify the preparation and provide flexibility, allowing use of the same box for several shipping durations and temperature ranges.

Packaging with high-performance insulation, such as that in American Aerogel packaging, can extend

> In 2013, the European Union codified its Good Distribution Practices (GDPs), which are rapidly becoming the required guidance worldwide.

Protecting Temperature-Sensitive Shipments

American Aerogel offers a packaging product solution that will deliver the performance and value to best address your temperature-sensitive shipping needs. Your recommended solution is developed from our standard product lines, custom services, and reuse programs. Minimizing your risk is our goal. The American Aerogel design team engineers risk out of temperature-sensitive shipments. Combining high-performance vacuum-insulated panel (VIP) insulation with advanced phase-change material (PCM), we design, manufacture, and prequalify packaging that performs to the highest standards. With our packaging and services, you minimize the risk of temperature excursions and redefine how you transport valuable payloads — you can ship more, with less coolant, in smaller containers, and over a longer period of time.

- Whether you are shipping payloads or using ground transport, our insulated packaging solutions will protect your temperature-sensitive material from unpredictable, harsh, and seasonal outside temperatures
- With a variety of sizes and durations to choose from, you can easily select the right ready-made solution to fit your needs
- Our in-house thermal engineers and packaging designers efficiently build and test customer-specified, temperature-controlled, reliable packaging solutions based on any needs
- American Aerogel products are insulated with Aerocore VIP patented, high-performance insulation, enabling smaller and lighter packaging using less thermal regulation material
- Our frozen shipping packages require 50% less dry ice than most other options, yet they keep payloads at or below -65°C for extended durations
- For refrigerated packages, we ensure your payload temperature remains in the 2°-8°C range, regardless of outside conditions
- Our standard product line for controlled room temperature (CRT) maintains a payload temperature of 15°-30°C
- Aerogel, a PCM, reduces the size and weight of the package and extends the duration of temperature control
- FlexSystem allows for size and temperature range to be adjusted based on payload requirements
- All AeroSafe shippers use the same size modular PCM plate, making preparation error-proof and simplifying SOPs for multiple shipments
- With our ISTA certified laboratory and multi-chamber testing facility, we have complete control over the design and prequalification process
- Offering rental and reuse programs as a more economical option

the delivery window, keeping contents at the required temperature for a few days after arrival. This is especially valuable when shipping temperature-sensitive material to an overseas destination or to a hospital, since it eliminates concern about having to remove the product immediately upon arrival to put in a freezer, and gives physicians and hospitality greater scheduling flexibility.

With high-performance insulation, less thermal regulation material is needed, making the package smaller and lighter than many other prequalified solutions. American Aerogel develops standard and customized packaging solutions for temperature-sensitive shipping, using aerogels and related materials in vacuum-insulated panels for thermal regulation.

To ensure strict temperature control, it is important to understand the options for thermal regulation material, including gel packs, dry ice, water, and advanced phase-change material that will freeze or thaw. The most commonly utilized packages for temperature-sensitive shipments are made of polystyrene or polyurethane, which are the least effective and require large amounts of thermal regulation material. Phase-change material, such as aerogel, reduces the size and weight of the package and extends the duration of temperature control. Aerogel-based insulation has a unit of thermal resistance (R-value) of more than 10 times that of polystyrene.

2°-8°C
PAYLOAD TEMPERATURE RANGE

For refrigerated packages

For greater flexibility, some packaging companies offer rental and reuse programs. For many companies, renting packaging is highly beneficial as a more affordable option. After shipping temperature-sensitive material, the packaging company recovers the empty containers, refurbishes them, and can redeliver them to the manufacturer for its next shipment.

LOOKING FORWARD

Over the past decade, the pharmaceutical industry has been rigorously seeking advances in shipping practices for temperature-sensitive pharmaceuticals and biologics to keep pace with significant changes in the industry. Suppliers of temperature-controlled packaging have responded with technologically advanced materials to ensure the integrity of valuable medications during shipping and to effectively manage risk while meeting more stringent regulatory requirements and preserving drug manufacturers' reputation. These industry trends are expected to continue, reshaping packaging options in the future for the safe delivery of medication to patients. P

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CHOOSING THE OPTIMAL DRUG DELIVERY SYSTEM TO MEET PATIENT NEEDS

BY KEVIN HAEHL General Manager, North America, Unither Pharmaceuticals

Kevin Haehl is responsible for developing and growing Unither Pharmaceutical's contract pharmaceutical manufacturing business for North America in niche fields such as sterile unit dosage forms using Blow-Fill-Seal technologies and Unistick® single-dose liquid stick-packs, and the strategic leadership of the newly acquired manufacturing site in Rochester, NY. He has over 25 years of broad experience across pharmaceutical manufacturing, sales support, engineering, process development, financial, quality, and supply chain. Prior to Unither, Mr. Haehl held management positions at Evonik and Eli Lilly & Company, and worked in engineering at DuPont.

ABSTRACT

For the last three decades, the challenge of poor medication adherence has been discussed by the healthcare industry, while the rates and associated costs of non-adherence continue to rise. Medication non-adherence is a significant risk to patient safety and substantially elevates the cost of care. Children, seniors, and many chronically ill patients are more prone than others to use medications incorrectly. The healthcare industry continues efforts to improve medication use, developing innovative drug delivery systems and packaging to ensure that patients take the right dose at the right time. Recent advances in drug delivery systems to meet the needs of today's lifestyles include user-friendly single-dose packaging with blow-fill-seal and stick-pack technologies.

Lack of patient adherence to their prescribed drug regimen is a common problem that compromises patient safety and escalates costs to both patients and healthcare systems. In the US, more than 50% of prescribed medications are taken incorrectly or not at all.[1] Failing to take medications as prescribed can increase the chances of severe medical complications or even death. Yet a 2013 survey of 800 American adults showed that nearly two-thirds of those who take prescription medications do not take their medication properly. The same patients also report poorer health than those who take medicines properly.[2]

Many other studies have shown additional negative consequences of non-adherence, and the statistics are surprising. For example, one- to two-thirds of hospital admissions resulting from drug-related adverse events are related to poor medication compliance,[1] up to 40% of nursing home admissions can be attributed to non-adherence,[3] and as many as 125,000 Americans die each year due to non-adherence.[1]

On the other hand, compliance with a drug regimen typically improves or maintains an individual's health. Taking an antibiotic may prevent a more severe infection, and adhering to a drug regimen for a chronic condition such as diabetes or high blood pressure may prevent complications. Either situation can avert hospital admissions, which in turn, reduces the use and cost of medical services.

Poor patient adherence also contributes significantly to rising healthcare costs. Remarkably, Americans incur avoidable costs of more than $200 billion each year as a result of irresponsible use of medications, according to a 2013 report by IMS Institute for Healthcare Informatics.[4] Non-adherence leads to $47 billion in drug-related hospitalizations each year, according to the National Council on Patient Information and Education (NCPIE).[5]

Taking the incorrect dosage is a common non-adherence error. Other reasons patients fail to take their medications as prescribed include forgetting to take a dose, having difficulty measuring the right dose because of frailty or tremors, taking higher doses than prescribed in an effort to improve their health condition faster, failing to pick up medication from the pharmacy, taking less than a prescribed dose to save costs, and stopping use of the medication early.

Every patient demographic segment can benefit from improved delivery methods to assure precise doses. This approach provides many benefits for patients who self-administer medications and for caregivers, as well as for pharmacists and clinicians.

Children and seniors are significantly more prone than other demographic segments to use medications incorrectly. Young children require the assistance of parents or other caregivers to ensure they receive the proper dose at the right time, but children often resist, causing a spoonful of medication to spill. A recent study of data from the US National Poison Database System revealed that during the period 2002 to 2012, 696,937 children under six years old experienced out-of-hospital medication errors, which is equivalent to one child every eight minutes. The majority (80%) of incidents involved liquid doses, and the causes ranged from "inadvertently taking or being given medication twice" (27%), "incorrect dose," and "confused unit of measure," to "wrong medication taken or given."[6]

Seniors who live independently often struggle with administering their own medicines. Some are vulnerable because they typically use multiple medications, and may have declining vision, memory, and functional abilities. Nearly 20% of community-dwelling seniors (65 years and older) take ten or more medications,[7] contributing to adherence challenges. Common medication errors for seniors include taking an incorrect dosage, forgetting, and mixing up medications or taking out-of-date ones. Elderly patients often forget to take their medications, and unwittingly may take a medication again.

Chronically ill patients are another vulnerable population, whose medication adherence drops after the first six months of treatment. Approximately half of patients with chronic illness do not take medications as prescribed.[8] These patients are more prone to suffer poor health outcomes if they do not adhere closely to their medication regimen, which can lead to more outpatient medical visits and hospitalizations,[5] driving up the costs of healthcare.

Today, an active lifestyle is the norm for children, teenagers, adults, and seniors alike. All of these patient segments – including patients who have careers, travel frequently, and engage in sports outings such as biking and hiking – need safe, accurate easily portable dosing options.

How is the pharmaceutical industry addressing the issue of non-adherence? What are good medication practices for patients on the go, in the care of others, or dealing with sensory shortcomings?

For manufacturers, single-dose technology assures greater consistency of results in clinical trials and full-scale manufacturing, distinguishes their products, and can extend product lifecycle.

LEVEL OF PATIENT NON-ADHERENCE

$47B
DRUG-RELATED HOSPITALIZATION EACH YEAR

696,937
OF CHILDREN UNDER SIX YEARS EXPERIENCED OUT-OF-HOSPITAL MEDICATION ERRORS 2010-2012*

***80%**
OF INCIDENTS INVOLVED LIQUID DOSES

Drug manufacturers, as well as physicians, are seeking more patient-centered solutions, looking at delivery systems and packaging options that are most likely to encourage patients to take their medicines as directed. Accurately measured doses and easy-to-handle packaging with clear labeling are essential to meet today's needs for self-care. The packaging must also have child-resistant features and provide deterrence to counterfeiting.

Unit-dose packaging in innovative forms is increasingly being adopted as a solution to improve patient adherence to their prescribed drug regimen. A single-dose package or container is accurately filled to hold only the quantity of drug intended for one dose. Single-dose packages are meant to be opened only once, and are typically clearly labeled. These features reduce medication error because the identity of a drug is easy to confirm, and the packaging ensures patients are taking the proper dose. Other benefits of single-dose packaging include reduced risk of contamination, less drug waste, and greater convenience for patient self-administration. Drug-makers are now focusing on drug delivery systems that provide ease of use, portability, and a level of comfort for patients taking medicine outside of their home.

Additional benefits of single-dose packaging are reducing or eliminating the preservatives, which can cause allergic reactions; dispensing a single dose in a more sanitary manner; and reducing concern over contamination of the drug because of the protective packaging around each dose.

Packaging medications in a unit-dose format is also the solution for most hospitals in the US and many in Europe. Both hospitals and pharmacies benefit by saving dispensing time, ensuring better dose accuracy, and often reducing waste due to better management of medication dispensing operations. For manufacturers, single-dose technology assures greater consistency of results in clinical trials and full-scale manufacturing, distinguishes their products, and can extend product lifecycle.

Oral, topical, and injectable medications in the form of tablets, capsules, creams, and liquids can all be packaged in unit-dose containers, which come in many sizes and shapes. Blister or pouch packages are widely used for tablets, capsules, and other oral solid formulations. Single-dose packaging units for liquid medications are available for oral administration, and as injectables in the form of plastic syringes with rubber tips and squeeze tubes. Typical unit-dose containers for injectable drugs are prefilled syringes and cartridges.

Unither Pharmaceuticals, which specializes in the development and contract manufacturing of sterile single-dose pharmaceutical products, offers a range of dosage forms and delivery systems that are convenient and easy to use. Forms include single-dose vials using blow-fill-seal (BFS) technology, stick-packs, and effervescent-tablet technologies. For vials, many different shapes are possible, and with premolded, presterilized inserts, it is possible to achieve different methods of drug delivery.

Stick-packs are another type of single-dose package that is convenient, portable, and easy to open and administer. The premeasured sticks can be filled with powders or liquids. Liquid stick-packs reduce the likelihood of spilling a spoonful of medication while trying to gain a resisting child's compliance or when administering liquids to geriatric patients with tremors. Recently, liquid stick-packs were introduced for solutions, suspensions, and gels for both the oral and topical administration of liquids as an alternative to glass bulbs, tubes, sachets, and conventional bottles. The portable, easy-to-carry packs are appealing because no device is required for delivery. Also, the strength of the stick-pack material ensures their safety and security throughout the supply chain.

CONCLUSION

Medication non-adherence is a significant issue that is likely to grow as the US population ages and patients take more medications to treat chronic conditions.[10] The issue is a growing concern to clinicians, healthcare systems, and payers. Reducing dosing errors saves lives and reduces massive costs to governments and other stakeholders. Single-unit dosing offers significant potential to improve patient adherence and reduce medication errors. Drug delivery systems using blow-fill-seal and stick-pack technologies help ensure accurate dosages and provide a safe, more convenient, portable way for patients to comply with their treatment regimen. For manufacturers, these single-dose systems offer the benefits of distinguishing drug products and extending product lifecycle. P

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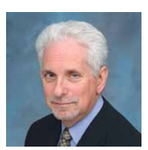
INNOVATIVE STRATEGIES TO MEET TODAY'S CHANGING EQUIPMENT NEEDS



→ **BY LARRY KADIS** CEO & President, Federal Equipment Company

Larry Kadis is CEO, President, and Co-Owner of Federal Equipment Company, founded in 1957. Along with his cousin, Michael Kadis, they have built the business into a global leader in the processing and packaging equipment industries. Larry's father Abe and uncle Morris founded Federal Equipment Company, where Mr. Kadis has worked for more than forty years. He has focused recently on creating strategic partnerships for the business with multinational corporations like Pfizer and BASF.

ABSTRACT

Dramatic changes in the pharmaceutical industry are driving pressures to lower the time and costs of drug development, manufacturing, and packaging. Manufacturers and their contract service providers are looking to improve efficiency, eliminate redundancies, and rapidly increase pipelines. Significant company consolidation is resulting in considerable surplus equipment, driving growth for the used -equipment market. Contractors and companies producing highly specialized drugs need new types of equipment at the best prices. As a result, asset management is having a growing impact on businesses with surplus equipment while offering ideal scale-up opportunities for contract manufacturers and emerging pharmas. In turn, the role of trusted, experienced equipment dealers to help determine asset value and optimal strategies for decommissioning operations and to provide support for the buying of equipment is critical.

As the pharmaceutical industry undergoes significant change, manufacturers, contract research organizations (CROs), and contract development/manufacturing organizations (CMOs, CDMOs) are striving to adapt. They are seeking new ways to respond to changing needs and mounting pressures to increase productivity while keeping costs down and to decrease time to market while ramping up pipelines. Additonally, there is a need to elevate quality and meet more rigorous regulatory guidelines calling for use of the latest manufacturing and packaging tools and technologies. This also calls for acquiring efficient equipment that meets current needs to produce new, highly specialized products, including biopharmaceuticals and biosimilars, while reducing production time, containing costs, and minimizing the required number of operators.

Increasingly, pharmaceutical and biopharmaceutical companies are relying on strategic outsourcing partners to deliver high quality development, manufacturing, and packaging services in the most efficient way, as well as provide the specialized expertise, regulatory understanding, and resources they need. In terms of equipment and technologies, manufacturers want easy-to-use processing systems that can manufacture and package increasingly complex drug products in short start-up times and with easy changeovers. CROs, CMO/CDMOs, and equipment suppliers, in turn, are striving to meet the growing demand from their clients for cost-conscious ways to meet changing equipment needs.

The continuously rising pace of industry mergers and acquisitions has resulted in redundant infrastructure and equipment, which can typically be reused or repurposed to meet current needs. As a result, the used pharmaceutical equipment market has experienced significant growth, offering benefits for drug manufacturers, CROs, and CMO/CDMOs.

Consolidated manufacturers can sell the equipment, enabling other industry companies and outsource organizations to gain immediate access to lower-cost, high quality machines. Generics producers and contractors require very robust, flexible machinery with high output. The trend to more complex formulations for targeted treatments has driven a higher demand for sophisticated technologies with flexible platforms that can handle small batches and ensure the highest safety for operators and products.

The trends of increased manufacturer consolidation and the greater use of outsourced services are driving growth in the used pharmaceutical-equipment market. The strong growth continues due to the increased availability of high quality equipment and demand for low-cost solutions. Continuous processing equipment, commercial-scale single-use technology, equipment that can handle potent substances, and adapting lines for personalized medicine are key drivers of pharmaceutical manufacturing and bioprocessing today.

For equipment sellers or buyers, the best way to realize the benefits of used equipment is to work with a trusted partner who knows the industry market; understands pharmaceutical laboratory, processing, and packaging equipment; has an established network across the industry; and can provide comprehensive customer support. Experienced dealers provide an avenue to resource recovery for sellers, as there are multiple strategies for dispensing of different types of equipment, which can also translate to capacity access and cost savings for buyers.

EQUIPMENT SOURCING STRATEGIES: SELLING

Equipment sellers can benefit from a reliable, well-known dealer who has a broad, established network of potential buyers and warehouse space where equipment can be viewed and tested by prospective customers, and stored until it is sold. The dealer should also have extensive experience assessing and appraising the equipment and understand the regulatory requirements involved in the sale of used pharmaceutical equipment. Sellers must be aware of laws and regulations regarding sales of certain drug-manufacturing equipment, such as tablet presses and capsule filling equipment. They should also be aware of both domestic and international import and export compliance laws and regulations. The laws often require considerable technical knowledge to properly classify an export.

The sale of equipment that is no longer in use will recover some of the initial capital expenditure. When considering the potential of your equipment to sell, the type and condition of the machinery as well as the cost of removing it are key considerations to determine if it should be sold immediately, or stored, or scrapped. Another consideration when selling equipment is, which types are in demand? Some equipment is in much higher demand than others. For example, for solid-dose manufacturing, high quality tablet presses and capsule fillers from recognized manufacturers are highly desired and generally sell quickly. Other factors to consider for selling equipment are: Have more advanced versions replaced the type you want to sell? Can your equipment be upgraded to perform faster or provide a greater yield, and at what cost? Even if the machine is in excellent condition, is it so highly specialized and customized that it is unlikely to attract any buyers?

KEY DRIVERS OF PHARMACEUTICAL MANUFACTURING & BIOPROCESSING

- **CONTINUOUS PROCESSING** EQUIPMENT
- COMMERCIAL -SCALE **SINGLE-USE** TECHNOLOGY
- **POTENT** SUBSTANCES EQUIPMENT
- ADAPTING LINES FOR **PERSONALIZED MEDICINE**

Some sellers are better off if they move their equipment to a dealer's warehouse to open up floor space and prepare for an optimal sale. In that case, it should be stored under appropriate conditions, ideally in a clean, climate-controlled building.

BUYING USED EQUIPMENT

Purchasing used equipment offers significant benefits for pharmaceutical manufacturers, particularly smaller and generic companies, CROs, and CMO/CDMOs, who can realize tremendous savings and reduce lead times. The cost of used assets is often as little as 40-50 percent and sometimes as low as 20 percent of the price of new systems. That is a significant savings over the capital investment required for new systems. Another important advantage is that used equipment is immediately available, eliminating waiting time for the delivery of new equipment, which can take weeks or months. The time savings can be a significant benefit for contract organizations bidding on projects that require specific pieces of equipment.

When equipment failures occur, surplus assets are valuable for both branded drug manufacturers and contractors. An experienced used-equipment dealer can help manufacturers quickly find appropriate replacement equipment, allowing production processes to continue and avoiding lost revenues and potential supply shortages. Used equipment can also be stored on site as a cost-effective option for backup to mitigate downtime in case of an equipment problem or a period of planned maintenance.

For maximum time and cost savings, used equipment should be considered as early as possible in the process design stage to allow for greater flexibility in equipment options and avoid time-consuming, costly design and specification stages of new equipment purchases.

Federal Equipment customers routinely seek both new and used equipment, depending on their manufacturing mix. New products require time for installation, and there may be delays for training and delivery if the equipment is custom-built or modified. With a short time frame to get a new product launched, used equipment becomes a more viable option over new equipment. If a company needs spare machinery, replacement equipment, or additional capacity with similar equipment, used equipment is a viable, lower cost-option.

When making purchasing decisions about new equipment, quality, and performance are the leading considerations of pharmaceutical manufacturers, according to a 2015 Nice Insight Pharmaceutical Equipment Report. Based on a global survey of 560 purchasing decision makers at manufacturing and outsourcing organizations, the report concludes that companies seek equipment that will outperform current pieces in quantity or efficiency. Price ranks lower in priority, following equipment durability and reliability. Equipment must be dependable, and enable manufacturers to comply with regulations and provide validation support.

RANK OF PURCHASING CRITERIA

1. QUALITY & PERFORMANCE
2. DURABILITY & RELIABILITY
3. REGULATORY & VALIDATION
4. PRICE

> When making purchasing decisions about new equipment, quality and performance are the leading considerations of pharmaceutical manufacturers...

PARTNERING TO LEVERAGE THE BENEFITS OF SURPLUS EQUIPMENT

Finding a trusted experienced partner who is highly qualified to provide strategic management services regarding the buying, selling, and global redeployment of equipment can save companies considerable time and costs. Whether to manage this function in house or through a qualified partner depends on the size and type of company, the quantity of assets to be managed, the available resources, and the company's expertise in equipment management.

An effective used-equipment dealer can facilitate the entire process, from the evaluation of resource-recovery needs to the development and implementation of a customized plan. A qualified dealer should help evaluate a client's equipment needs and determine whether used systems will be appropriate or new and possibly customized equipment is needed. Used-equipment management requires the ability to make certified appraisals, provide optimal resource-recovery solutions, and find suitable replacement equipment – new or used – that will allow rapid restoration of operations. Dealers who are trusted sources of pharmaceutical processing and packaging equipment can help realize both maximum recovery to sellers and optimum cost-savings to buyers, while ensuring the equipment is high quality and that all transactions are transparent and compliant with relevant regulations. P

COMPANY PROFILE

Federal Equipment Company

For more than 50 years, Federal Equipment Company, a large used-equipment dealer with an inventory of thousands of machines and a broad knowledge of equipment values, partners with companies who buy or sell surplus machines and consults with them on the most efficient, economical strategies. Serving as a strategic partner, Federal Equipment can develop and implement a strategic management plan to support efficient manufacturing with high quality equipment — typically at lower prices.

CULTURAL COMPETENCE IN PHARMA

MULTICULTURAL MARKETING IS NO LONGER INNOVATION, IT'S COMPETITIVE ADVANTAGE

BY RHEA KIM, Ph.D. Chief Research and Development Officer

Dr. Rhea Kim brings unique expertise with more than 20 years of leadership experience in creative management, targeted market research, branding, and strategic marketing and PR, working with global companies. Dr. Kim held the position of Creative Director at multiple marketing and advertising agencies, and also provided leadership for branding and high-level product development. Dr. Kim earned a bachelor of fine arts degree in studio arts, a master's, and a doctorate degree with emphasis on qualitative research, all from University of Southern California. Dr. Kim also serves a professor at her alma mater working with doctoral students and has a book scheduled for publication.

CUSTOMER EXPERIENCE "THE GATEWAY TO GROWTH"

The healthcare industry is in the midst of a turbulent global transformation, and with the advent of technology and the ability to reach consumers across country boundaries, cultural-value-based strategy and messaging is more important than ever before. Multicultural influence will be driving trends in the pharmaceutical industry and personalized medicine. CMOs will have to stay ahead of these trends and adapt to these influences, culture shifts, and demands on medicine.

MULTICULTURAL DIFFERENCES IN PATIENT OUTCOMES

One of the most important aspects of pharma marketing is the understanding of the patient journey and how this journey may differ across patient types.

The rich ethnic diversity we call "multicultural" or "cross-cultural" constitutes the largest, fastest-growing consumer segment in the US market, creating significant treatment gaps across therapeutic areas that not only represent potentially millions of new scripts, but also create a strong brand upside as well as a reputation boost from the opportunity for pharma to improve patient outcomes on a national scale.

The number is staggering – the sale upside can be anywhere from $100 million to over $1 billion per brand. This means a brand-specific, incremental sales upside. As an example, in 2012, looking at the top 50 spenders in the US Hispanic market alone, the investment range is $30 million to nearly $300 million per company annually, none of which were pharma companies. Why? Multicultural marketing models driven by nonpharma industries did not apply as effectively to pharma due to the other industries, different stakeholder mix, specialized analytics, highly restrictive regulations, and unique consumer insights and behaviors. Due to these differences, the business case built for pharm brands was not sufficient to persuade managers to invest. Populationwise, the US Hispanic market alone is larger than Spain, and it's expected to more than double by 2050. It's an emerging market in our backyard. So why not invest?

LEVELS OF AWARENESS OF MULTICULTURAL PATIENTS

The multiethnic segment is also in the vanguard of the consumer movement when it comes to digital, mobile, and social media use, and when communicated to in a relevant way has a higher promotional response. In an effort to gain first-mover advantage, the number of pharma companies investing in multiethnic marketing has tripled within the last decade (PharmExec.com, Volume 35, Issue 5). However, this pivotal group is not being reached and impacted effectively with the tools of engagement currently employed.

Within the difference in the patient journeys for Hispanics, Asians and African Americans in therapeutic areas such as cardiovascular and metabolic, vaccines, oncology, hematology, respiratory, Alzheimer's disease, rheumatoid arthritis, hepatitis, multiple sclerosis, and others, there is a common thread, which points to significant gaps across cultures within diagnosis, treatment, and adherence rates. These gaps are also known as health care disparities.

Researchers argue that at times, the gap is in awareness levels, or perhaps the treatment rates across cultures compared to the non-Hispanic white patients is a lot lower. These gaps can be quantified in financials down to a brand level with the idea that if the gap can be closed, there is immediate financial upside to the brand. To close some of the gaps, an incremental investment is needed to specifically target these audiences.

SIGNIFICANT EVENTS IN THE PATIENT JOURNEY

Three major events in the past seven years have significantly heightened awareness and opportunity within the multicultural health segment overall. First, in 2008, the US presidential campaign showed the power of marketing to and building brand loyalty with US minority populations. Second, in 2010, the US Census came out with the latest population projections highlighting the tremendous growth of minority ethnic and cultural communities. Third, the Obama administration's Affordable Care Act (ACA) further heightens the opportunity specific to the multicultural health field (PharmExec.com, Volume 35, Issue 5).

Five to eight years ago, a few of the major pharma companies started taking a closer look at these market segments. Companies such as Pfizer, Novartis, and Merck & Co. launched a multiethnic or multicultural corporate strategy, while additional firms have made isolated brand investments in a given year. In 2015, we have at least fifteen pharma companies now consciously investing into multicultural markets on a brand level; at least 40% of these companies are either exploring or already have a corporate strategy across brands. Hence, labeling multicultural as an exploratory innovation is no longer the case for the industry, but is instead a competitive advantage.

A similar dynamic occurred in the retail space, and interestingly enough, over the past five years, Walgreens, CVS, Target, and Wal-Mart have all established multicultural operations internally with targeted investments in various cultural segments.

In addition, personalized medicine is a new healthcare paradigm where proper medication and dosage are customized to special characteristics of

Companies such as Pfizer, Novartis, and Merck & Co. launched a multiethnic or multicultural corporate strategy, while additional firms have made isolated brand investments in a given year.

THREE MAJOR EVENTS

2008 US PRESIDENTIAL CAMPAIGN BUILDING BRAND LOYALTY WITH US MINORITY POPULATIONS

2010 US CENSUS POPULATION PROJECTIONS — GROWTH OF MINORITY COMMUNITIES

2010 AFFORDABLE CARE ACT (ACA)

a patient and his/her disease. Individuals respond differently to drugs. A growing list of genetic polymorphisms in drug-metabolizing enzymes, drug transporters, and drug targets have been linked to the efficacy, dosage, and toxicity profile in humans.

CURRENT IN THE HEALTHCARE INDUSTRY:

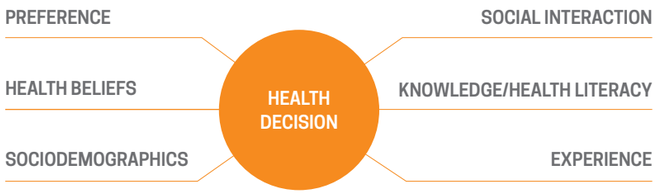
+ With the advent of technology, ability to reach consumers across country boundaries
+ Need cultural-values-based messages to reach consumers
+ New studies reveal healthcare decision making
+ Increased complexity in cultural landscape for consumers worldwide
+ Alternative healthcare methods more prominent
+ Healthcare reform and fiscal restraint with unsustainable cost trajectory
+ Healthcare disparities among different racial groups
+ An increase in diversity that has been accompanied by a sharp decrease in white Caucasian "mainstream" culture
+ Increasing demand of services by expanding pool of consumer-patients
+ US alone seeing more dynamic changes in its demographics – nonwhite US population will reach 47.2% by 2050
+ Each culturally diverse group defines health and illness differently
+ Growth in personalized-medicine needs as the culture change affects consumers, demand for pharmaceuticals and medicine
+ Personalize Your Care Act of 2013 (only relevant in US)

WHY MULTICULTURAL AWARENESS IS IMPORTANT

+ Multicultural influence forms the driving trends for personalized medicine

INSIGHT

Health Decision Model



There needs to be continued effort in contextualizing the customers within their cultural setting through different marketing efforts (print and online), staff training, and leadership profiles and in putting the consumer at the center and radiating outward.

CHANGES IN DEMOGRAPHICS

47.2%

NON-WHITE US POPULATION BY 2050

+ Manufacturing to stay ahead of these trends and adapt to these influences, culture shifts, and demands on medicine, and specific needs by consumers that will have to be met by manufacturers which include adapting new ways of manufacturing; i.e., portable manufacturing, producing orphan drugs, etc.
+ Personalized medicine drives innovations in manufacturing
  – Multicultural influences are at the root of the demand for personalized medicine and other upcoming trends for pharmaceuticals
+ Global growth and expansion strategies in need
+ Need to integrate Medicine and Healthcare – Digitally Accelerated
+ Need to redefine market access

WHAT IS CULTURAL COMPETENCY AND HOW DOES THAT TIE TO MARKETING STRATEGIES?

There is no one definition of cultural competence. Definitions of cultural competence have evolved from diverse perspectives, interests, and needs, and the definition has been widely adapted and modified during the past fifteen years.

Cultural competence is a set of congruent behaviors, attitudes, and policies that come together in a system, agency, or among professionals, and enable that system, agency, or those professionals to work effectively in cross-cultural situations. It is about responding to the different ethnic and racial groups with sensitivity, going beyond "awareness."

The word *culture* is used because it implies the integrated pattern of human behavior that includes thoughts, communications, actions, customs, beliefs, values, and institutions of a racial, ethnic, religious, or social group. The word *competence* is used because it implies having the capacity to function effectively.

There needs to be continued effort in contextualizing the customers within their cultural setting through different marketing efforts (print and online), staff training, and leadership profiles, and in putting the consumer at the center and radiating outward. P

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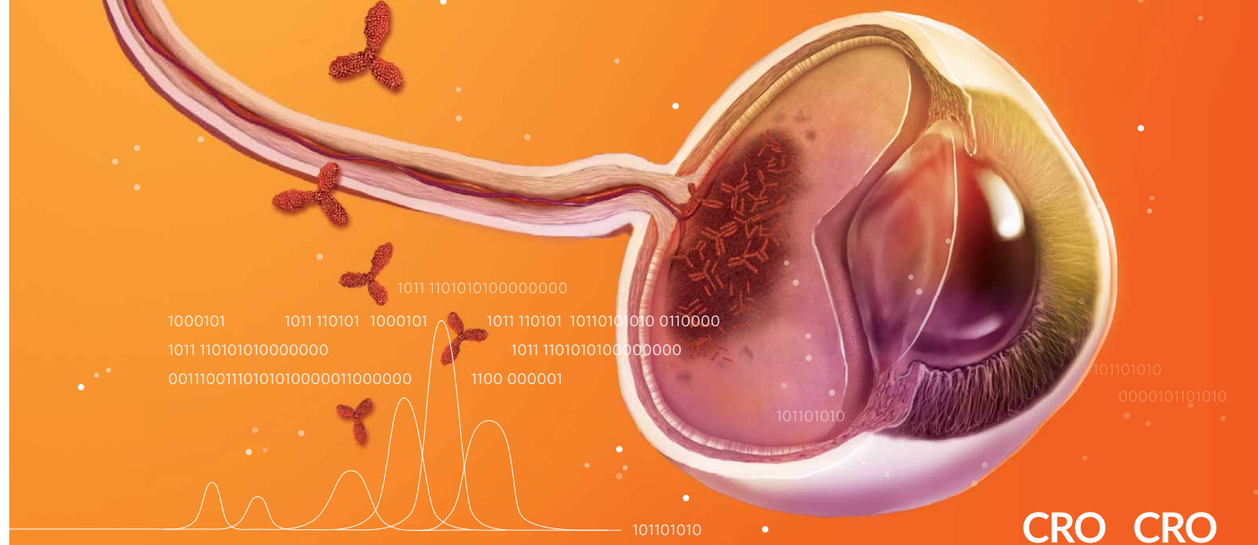

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