pharma's almanac

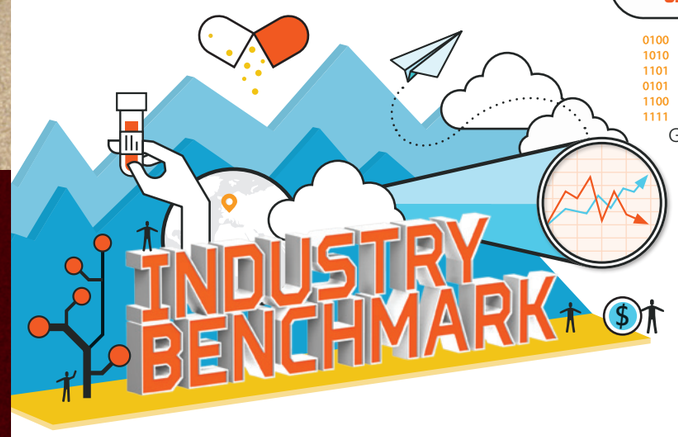
A NICE INSIGHT SUPPLEMENT

Q1 2017 EDITION

GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS

MARKET LANDSCAPE

GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS Q1 2017 EDITION



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SPECIAL FEATURE

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Industry Benchmark: Findings from 7 Nice Insight Global Industry Surveys

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→ A NOTE FROM THE EDITOR

COPING WITH THE DATA AVALANCHE

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

One of the most memorable compliments I received in my 14 years as editor of *Speciality Chemicals Magazine* came from an American executive at a trade show. He told me he had boarded a plane with a pile of about 15 chemical industry magazines and when he got off, he binned all but two – of which mine was thankfully one. I'm not telling you the other one. I'll never hear the end of it if I do...

If anything, the pharmaceuticals industry has even more written about it than the chemicals industry. I, too, come back from every show with a pile of rival magazines about 20 deep that it takes me three weeks to digest. And I have an essential need to keep up with what's going on and with what the competition is doing. For those who have days filled with meetings and projects, the information challenge must seem insuperable.

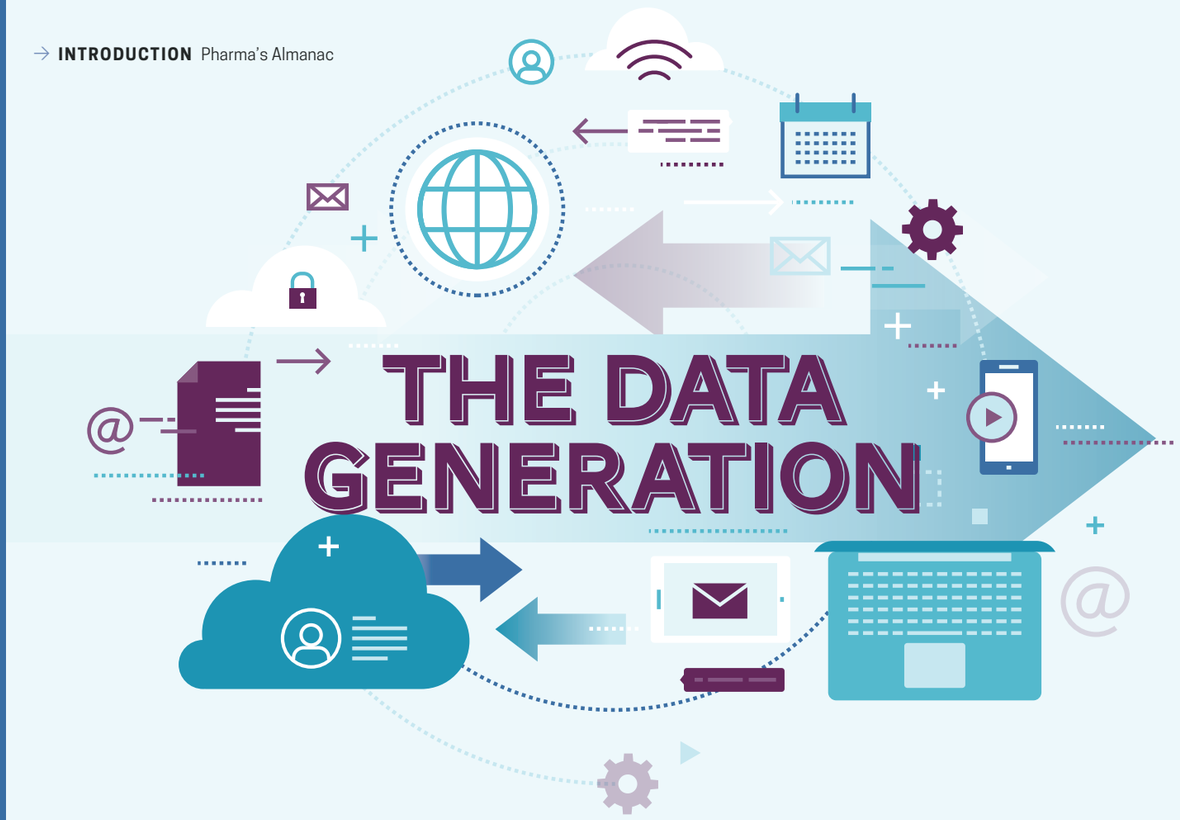
Indeed, information overload may be the biggest issue of our time. It is likely this will only increase. As Nigel Walker notes in this issue's lead feature on 'big data' in the pharmaceutical industry, the world's technological per-capita capacity to store information has roughly doubled every 40 months since the 1980s, is now doubling every 18 months and, by 2020, it may be doubling every three months.

The concept of big data itself generates, well, big data. Googling 'big data' plus 'pharmaceuticals' itself yields over 1 million hits, as we found when compiling the article. Huge amounts have been written and said about this. The challenge is so mind-boggling that burying your head in the sand is an understandable response. But that response simply won't do.

The pharmaceutical industry faces as great a challenge as any from big data. The reasons for this, put very simply, are that no industry is so awash in and so reliant on data, not least to satisfy ever-more stringent and complex regulations. Big data touches every corner of what the industry does, and the savings potential from coming to grips with it is immense. Yet at the same time, pharma is years behind most industries of comparable sizes in how it manages this data.

Our own commitment to helping you through the morass of information out there remains unchanged. That's Nice, the publisher of *Pharma's Almanac*, has at its heart a giant research operation. Every year the Nice Insight annual surveys go out to thousands of companies in the pharmaceutical, biopharmaceutical and related sectors to reveal what they are seeking from suppliers in multiple fields.

Pharma's Almanac also seeks to bring you real insight into the most important emerging trends and technologies by speaking to those on-site. In this issue, we look at continuous manufacturing for both drug substance and drug product, asking why it has taken so long to emerge and if things really are different this time around. The word count was a bit higher than expected but, hey, it's a fascinating subject and this is the age of big data, after all. P



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

The pharmaceutical market landscape remains tremendously dynamic in 2017. Outsourcing practices for drug discovery, product and process development, clinical trials and manufacturing continue to evolve as well. Data — 'Big Data' in particular — is facilitating much of the changes, from the effectiveness of outsourcing to paradigm shifts in manufacturing.

The first issue of Pharma's Almanac in 2017 explores the current market landscape and the impact of Big Data and covers a whole host of other topics:

The Industry Leader Insight article by Don Barbieri, Technical Products Manager for Excipient and Drug Delivery Systems with SPI Pharma, touches on the importance of patient-friendly formulations in addressing patient noncompliance.

The pharma industry needs to address poor patient adherence with improved user experiences to help patients and improve public perception, according to Kevin Haehl, General Manager of Unither Pharmaceuticals.

Nigel Walker, Founder of That's Nice LLC/Nice Insight, looks at the impact Big Data is having on the life science industry.

Our feature story highlights preliminary results from Nice Insight's seven industry surveys on CDMOs, CROs, intermediates, excipients, equipment, the clinical supply chain & logistics and life sciences private equity/venture capital investments.

Our Roundtable discussion encompasses new regulatory requirements impacting the excipient supply chain, the evolving role of cloud computing in pharma, and what service providers need to do to provide global yet local support.

The concept of enhancing CDMO responsiveness through embedded flexibility is explored by Gwenaël Servant, Managing Director of Servier CDMO.

Virtual Panelists explore the potential of continuous manufacturing as reported by Nice Insight's Executive Content Director Andrew Warmington.

Stephen Sirabian, Executive Vice President, E/E Division and Ed Godek, Manager, Process Technology for Glatt Air Techniques, Inc. describe the pharma industry's growing capabilities for continuous solid dose manufacturing.

Ronak Savla, Ph.D., Scientific Affairs Manager and Stephen Tindal, Director of Scientific Affairs from Catalent Pharma Solutions discuss bioavailability and particle engineering in oral solid dose formulation.

Márcio Temtem, Associate Director for Particle Design and Formulation Development and João Vicente, Team Leader for Particle Engineering & Solubility Enhancement with Hovione, discuss alternatives to amorphous solid dispersions (spray drying and hot-melt extrusion), including an effective coprecipitation technology.

The importance of operational excellence and the ability to deliver high-performing, variation-free processes in achieving successful production of oral solid dosage forms is discussed by Adam Covitt, VP of Federal Equipment Company.

Arne Grumann, VP of R&D at Fermion, reviews the increasing role that CDMOs with knowledge and experience in optimizing crystallization and particle engineering are playing in solid dosage drug development and formulation.

Marga Viñes, Business Development Manager with Grifols Partnership, outlines the requirements for successful tech transfer of sterile injectable fill-finish projects to CDMOs.

Christa Myers, Senior Pharmaceutical Engineering Specialist and Todd Vaughn, Senior Process Specialist & OSD Expert with CRB discuss the need for introducing new processing concepts, analytics and control in OSD facilities of the future.

Catherine Hanley, Director of Marketing and Syed T. Husain, Chief Commercial Officer with Alcami outline their company's strategy for supporting small and medium-sized pharma and biotech innovators.

Drivers for growth of the sterile injectibles market and the opportunities for CDMOs with the right tools, skills and experience are explored by Nick Bykerk, Director of Finance, Supply Chain and Business Development and Val Dittrich, Business Development Manager with Grand River Aseptic Manufacturing.

In an Executive Q&A piece, Catherine Hanley, Director of Marketing for Alcami, highlights the keys to achieving successful cultural integration following a merger or acquisition.

The "Quarterly Review" covers notable news, while "Trends Trading" by Emilie Branch, Nice Insight's Strategic Content Manager, looks at investments in companies leveraging the microbiome.

The key attributes of CDMOs providing high-quality support for the manufacture and distribution of controlled substances are reviewed by Patrick Hatem, VP of Manufacturing and Kim Noll, Commercial Project Manager and DEA Liaison with UPM Pharmaceuticals.

Ariette van Strien, Chief Commercial Officer and Daniel Bell, VP of Regulatory Compliance and Technical Affairs at Marken discuss the importance of offering personalized services when supplying logistics solutions to the pharma industry.

The importance of considering the design intent, necessary single-use systems, and acceptable risk when designing single-use facilities is reviewed by Carl Carlson, Director, Bioprocess Design and Technology with M+W U.S., Inc.

Tim Tyson, Chairman and CEO of Avara Pharmaceutical Services, discusses building a quality CDMO through the acquisition of human and physical capital.

Icagen VPs Anil C. Nair, Kenneth F. Wertman, Marcel Patek and Paul R. August explore the 'growth pharma' model in which drug discovery programs are obtained via acquisitions.

Steve Kuehn, Executive Content Director at Nice Insight, introduces the latest offering at www.Pharmasalmanac.com — Pharma's Almanac TV — another channel providing valuable insights from thought leaders in the industry.

In this issue's In Conversation piece, Oskar Gold, Sr. VP Key Account Management and Marketing/Corporation Communications at Vetter Pharma International, discusses how outsourcing the fill-finish of aseptically prefilled syringe systems can help companies of all sizes.

Mark R. Bamforth, President and CEO and Richard O. Snyder, Chief Scientific Officer with Brammer Bio outline the significant investments their company is making to support the commercial manufacture of viral vectors.

Finally, we say thank you to the sponsors of our first Nice Symposium OSD and outline two symposia planned for 2018. P

This issue of Pharma's Almanac is packed full of valuable information, but there are endless topics to explore. Let us know what interests you!

ABOUT THE AUTHOR

Cynthia A. Challener, Ph.D.
Scientific Content Director

Dr. Challener is an established industry editor and technical writing expert in the areas of chemistry and pharmaceuticals. She writes for various corporations and associations, as well as marketing agencies and research organizations, including That's Nice and Nice Insight.

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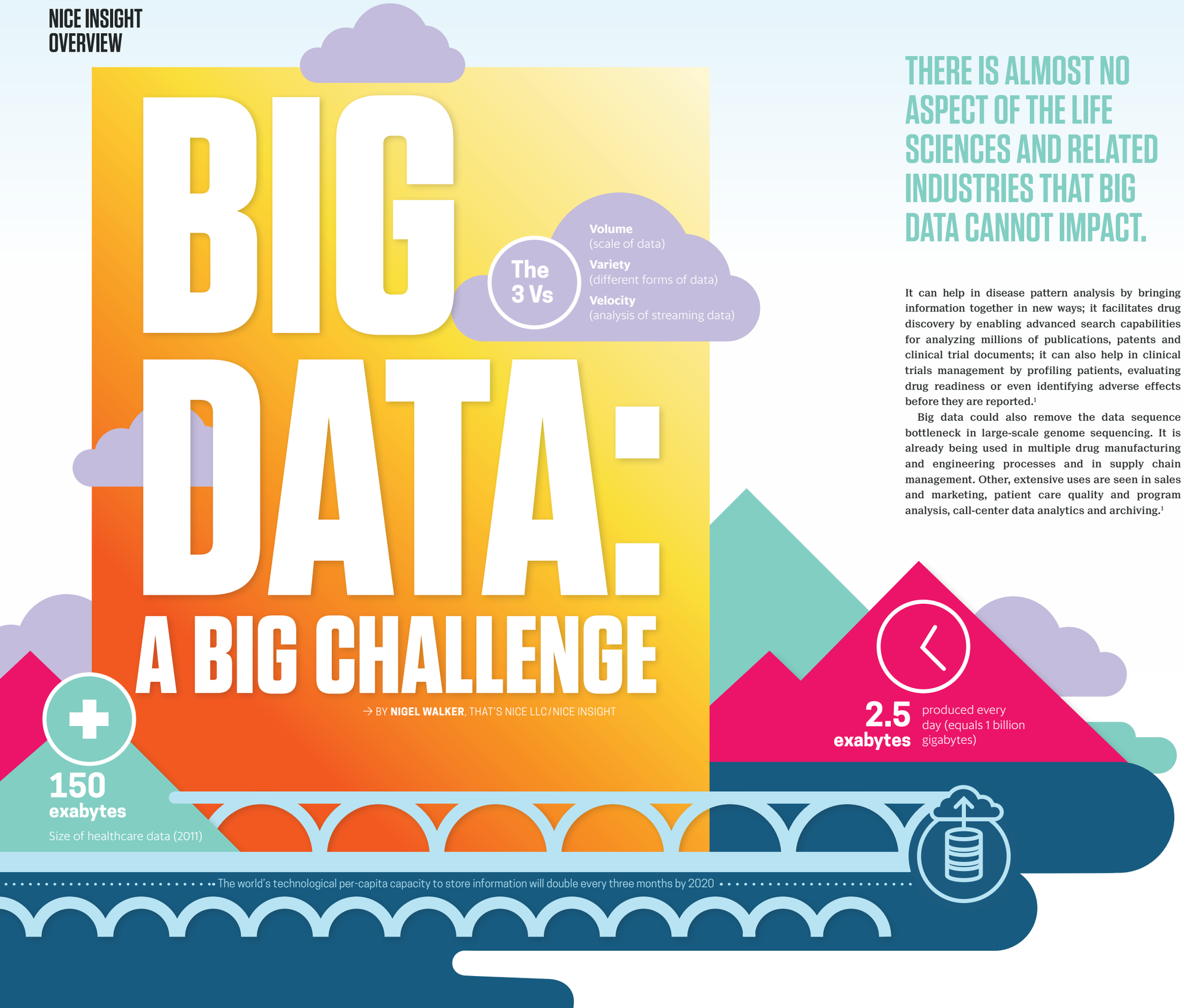
BIG DATA: A BIG CHALLENGE

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



THERE IS ALMOST NO ASPECT OF THE LIFE SCIENCES AND RELATED INDUSTRIES THAT BIG DATA CANNOT IMPACT.

It can help in disease pattern analysis by bringing information together in new ways; it facilitates drug discovery by enabling advanced search capabilities for analyzing millions of publications, patents and clinical trial documents; it can also help in clinical trials management by profiling patients, evaluating drug readiness or even identifying adverse effects before they are reported.[1]

Big data could also remove the data sequence bottleneck in large-scale genome sequencing. It is already being used in multiple drug manufacturing and engineering processes and in supply chain management. Other, extensive uses are seen in sales and marketing, patient care quality and program analysis, call-center data analytics and archiving.[1]

Big Savings

Some of the potential savings are mind-boggling. One analysis projects that applying big-data strategies to inform decision-making could generate up to $100 billion/year in value across the U.S. healthcare system, while another, from a 2011 baseline, puts the "opportunity of the value pathways" at $300 billion to $450 billion, 12% to 17% of the $2.6 trillion baseline in U.S. healthcare costs.[2,3]

The adoption of big data by the pharma industry also has important implications for suppliers. Both consultants agree that for greater use of big data to yield value, pharma companies will need to collaborate more with trusted partners of all kinds by sharing information and working together to make sense of it.[1,2]

In Translation

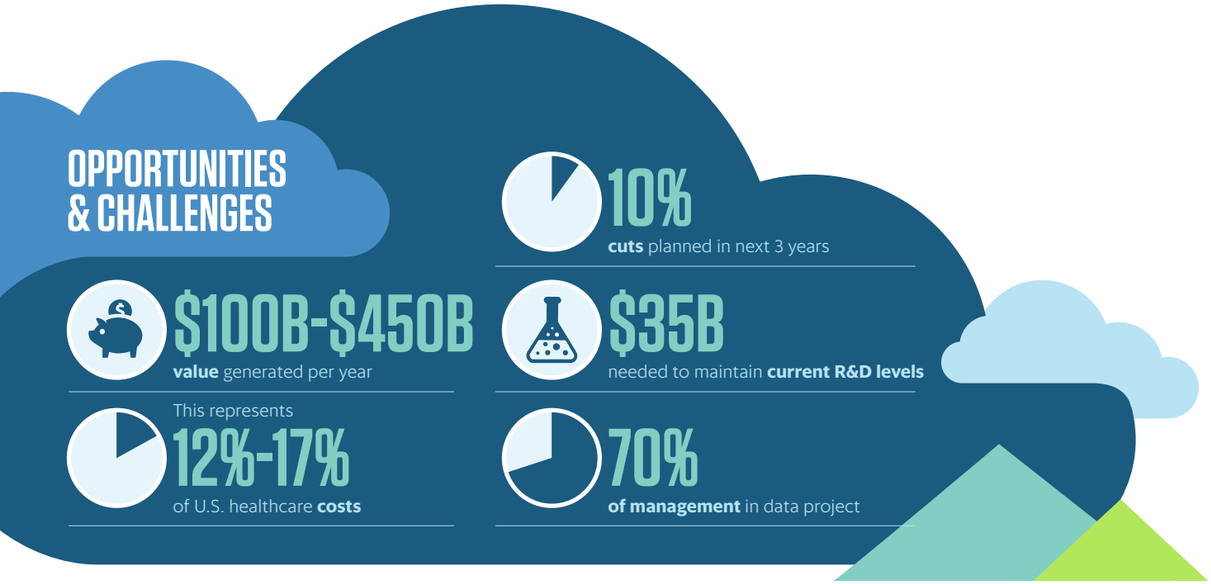
So what does it all mean? The term 'big data' was coined in the 1990s, but its origins lie in the digitization of knowledge that began even earlier and was accelerated by the computer revolution. This has been accelerated by several orders of magnitude in recent years by mass networking, cloud computing and, specifically in healthcare, the move to electronic record-keeping.

Big data is generally applied to data sets too large or complex for traditional data-processing methods to cope with in terms of analysis, capture, data curation, search, sharing, storage, transfer, visualization, querying, updating and information privacy. Big data is generally characterized by the 'three Vs' coined as volume, variety (structured, unstructured and semistructured) and velocity. It is also used to refer to the methods used to derive value from the data.[4]

Putting the Data in Pharma

The term has been used enough to become a cliché and be satirized. Yet the challenges big data pose are clearly real enough. The world's technological per-capita capacity to store information has roughly doubled every 40 months since the 1980s. By 2012, according to IBM, 2.5 exabytes (2.5×1018) of data was being generated every day. The amount of data is now doubling every 18 months. Some estimate that by 2020, it will double every three months.[5,6,7]

Every industry faces challenges from big data, but none more than the pharmaceuticals and wider healthcare industries. Why? Put simply, no industry is more awash in and dependent on data. With drug discovery programs, clinical trials, sales data, healthcare records, medical test results and now genomics research and social media, the industry has masses of data at hand. Indeed, it relied on analytics long before the concept of 'big data' was widely used.



Now the volume of data is growing exponentially, posing ever-greater challenges of managing it before analysis can even start. According to software development firm Informatica, 70% of any data project in pharma involves simply managing the data.[8]

At the same time, pharma has not really progressed with using data when compared to, say, the banking, electronics and retail sectors. Yet, given the massive and ever-growing cost and timelines of developing new drugs, the high odds against success, cost-reduction pressures and ever-more-stringent regulation it faces in bringing new products to market by comparison with these industries, no industry has more to gain from the cost-saving and growth-driving opportunities big data might bring.

According to a recent IMS Institute IT survey, large drug manufacturers need to make over $35 billion in savings from 2016 to 2017 just to maintain current R&D levels and operating margins. Nearly half are planning cuts over 10% in the next three years.[9]

To date, most of pharma's big activity has focused on R&D. Observers generally agree that it is doing better here than further downstream, where it continues to use inexact methods – such as focus groups, one-on-one interviews and basic segmentation – on which to base decisions that can cost hundreds of millions of dollars. The pharmaceutical supply chain is miles behind the curve in terms of knowing where its products actually are at any given point, something that the consumer goods industry would never tolerate.

Understanding Value

Above all, information in the pharmaceutical industry, like the industry as a whole, is organized in silos and hard to integrate. As Shannon Fitzhugh-Mengers and Mark Diamond point out, pharma remains rooted in legacy systems, particularly when it comes to pharmacovigilance. It has a difficult balancing act to achieve, with patient safety on the one hand and the needs of doctors, regulators and other stakeholders on the other. Nonetheless, it has to address the problem that its traditional method of incremental improvements will not even begin to address the explosion of (mostly unstructured) data.[7]

> **“The pharmaceutical supply chain is miles behind the curve** in terms of knowing where its products actually are at any given point, something that the consumer goods industry would never tolerate.

Another part of the problem is that, with times seemingly good in recent years, there has not been a compelling reason to change the business model. Moreover, many pharma companies have outsourced data management along with so many other functions they deemed noncore. All too many simply do not understand the volume and value of the data they actually have.

Industry executives recognize the problem. A recent survey by PwC shows that two-thirds of pharma professionals believe that their companies could do better in leveraging big data, while in another by Capgemini, nearly all pharma executives ranked their firms as below average for personalization, analytics and responsiveness.[10,11]

Seeking a Chief Data Officer

So what can they actually do? Accenture recommends starting by appointing a Chief Data Officer (CDO) to work across traditional functions and champion data collection, prioritization, distribution, analysis and security. A CDO should have very wide-ranging management authority across multiple cross-functional tasks.[12]

This would change some power structures within companies and, undoubtedly, feathers will be ruffled because optimizing analytics will require true collaboration across the whole enterprise. “Executives and management must encourage disruption of the status quo, moving beyond traditional organizational boundaries. Accept no objections (and there will be plenty). The organizations that best harness and share data will become leaders with distinct competitive advantages,” says Valtech.[13]

To address the challenge of big data, says Bill Drummy, CEO of Heartbeat Ideas, “pharma needs to cultivate the skills and – more critically – the courage to change its management and compensation systems so that risk-taking is rewarded, ‘playing it safe’ is penalized and latent talent is unleashed.” Be more like the “new value creators,” such as Google, in other words – something that is easier said than done.[14]

Fitzhugh-Mengers and Mark Diamond recommend the concept of ‘human-centered design,’ which is based around “understanding people’s needs using in-depth behavioral research.” It will use current technology and additional data from wearable devices and other sources to automate database translation and bring together all stakeholders “with common goals and a common approach to solutions,” including those from other sectors that translate to pharma.[7]

The Difference Maker

The big challenge will remain how to manage the data, how to decide what is and is not relevant, how to access it, and how to draw actionable insights. Many IT companies are touting specific solutions in the drug discovery fields, such as Integrichain, Medvivo, Medmeme, twoXAR, Cyclica and Schrodinger, to name but a few. But analysts concede that there will not be a one-size-fits-all answer to this.

Some pharma companies are shying away from acting due to incomprehension at the sheer scale of the challenge, wariness of the limitless potential costs, or fear of pioneer disadvantage. Tata Consulting's Sanita Garg says that the challenges “are as much cultural as technological.” Some are particular to pharma; others reflect the need for entirely new skill sets that “cannot be acquired in silos or through traditional training methods.”[1]

AstraZeneca has had a four-year partnership with HealthCore – using HealthCore data alongside its own to guide investment decisions relating to multiple chronic illnesses – and has also used the patient-driven data of PatientsLikeMe to guide its R&D on respiratory diseases, and worked with Practice Fusion to aggregate data on asthma patients. Roche has similarly worked with sequencing and diagnostics firm Foundation Medicine to use genetic data to guide its R&D.[3,15]

Roche has also teamed up with U.S. technology firm Qualcomm, as have GlaxoSmithKline and Novartis, which used the partnership in developing the Internet-connected emphysema inhaler, Breezhaler. Novartis has also worked with IBM on cloud-linked devices, while Sanofi is working with Google's life science business. Nine major firms, including Pfizer, Bayer, Sanofi and AstraZeneca, are part of Project DataSphere – built by analytics giant SAS – to share clinical data for cancer research.[15,16]

All of these are baby steps. Longer term, the stakes could hardly be higher. As Teradata says: “The bottom line: For pharmas, biotechs and other life science firms, the ability to handle Big Data is a difference maker – both on the bottom line and for the billions of people who rely on their products.” This may be the single challenge that will define the pharma industry's whole future.[17] P

ABOUT THE AUTHOR

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

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ADHERENCE

ENERGIZING CLIENT PORTFOLIOS WITH PATIENT-FRIENDLY DOSAGE FORMS

→ BY **DON BARBIERI**, SPI PHARMA

Patient noncompliance is extremely costly in terms of reduced patient health and lost revenue opportunity. SPI Pharma offers excipient technologies and drug development services supporting the formulation of patient-friendly oral dosage forms designed to address this crucial issue.

Patient noncompliance costs the pharmaceutical industry approximately $564 billion annually.[1] Despite the fact that patients typically prefer oral administration, one of the biggest contributors to medical nonadherence is dysphagia, or the inability to swallow traditional tablets and capsules. Dysphagia significantly affects the geriatric population, for example, as much as up to 68% of nursing home residents, 7% up to 30% of elderly admitted to the hospital, 8% up to 64% of patients after stroke, and 13%–38% of elderly living independently.[2] Other factors leading to poor medication adherence include bad taste and inconvenient dosing.

In fact, administering oral medications to pediatric, geriatric and mentally ill patients can be challenging. With children, there is a choking concern with solid dosage forms. Liquid medications are therefore often preferred, but dosing accuracy can be a problem with these products since a calibrated cup or device is needed to ensure uniform dosing. They may also contain undesirable additives, such as preservatives and dyes, and the stability of the API can be an issue. Geriatric patients in acute care facilities who are bedridden or suffer from conditions that affect swallowing often struggle taking their oral medications. Patients who are mentally ill often use a technique called “cheeking” to avoid swallowing medication, which can significantly affect their treatment results.

“Interventions to improve medication adherence should be a top priority for the pharmaceutical industry and will prove beneficial to all stakeholders,” according to Capgemini, the international consulting firm. “Increasing adherence rates by only ten percentage points would translate into a $41 billion pharmaceutical revenue opportunity in the U.S. ($124 billion globally), accompanied by improved health outcomes and decreased healthcare spending.”[3]

SOLVING FOMULATION CHALLENGES

Orally Dispersible Technologies

Offering ease of use and convenience, orally disintegrating tablets (ODT) and powders (ODP) have become a preferred dosage form for consumers worldwide for medications in a variety of therapeutic areas.

Antacid & Laxative Ingredients

Antacid suspensions can be made from viscous pastes, pumpable gels, powders or preformulated products. Antacid tablets can be made from powders, directly compressible (DC) ingredients or DC preformulated products.

Chewable Tablets and Lozenges

Chewable tablets and lozenges are often a preferred dosage form for children and adults who cannot swallow traditional tablets. Ideally these dosage forms should have a smooth, creamy texture and a pleasant taste.

Taste Masking

The success of your orally administered tablet may depend on how easy and pleasant it is for patients to take.

Nutraceuticals

Highly engineered materials and expertise in functional core excipients have made us a valued partner in the formulation of dietary supplements and nutritional products. Our products help you achieve superior organoleptic properties.

Swallow Tablets

Traditional swallow tablets are the most widely used solid oral dosage form. Their main advantages are ease of formulation and good chemical and physical stability. They tend to be the most economical to produce.

Soft Gel Capsules

The use of softgel capsules is increasing across a wide range of applications, including prescription medicines, consumer health, vitamins and mineral supplements.

Vaccine Adjuvants

SPI Pharma supplies Alum vaccine adjuvants to enhance and help the ability of your antigen to stimulate the immune system

Effervescents

Effervescence has been used for many years as an oral delivery system and has widespread acceptance in the pharmaceutical and nutritional markets.

PATIENTS ARE MORE LIKELY TO TAKE THEIR MEDICATION AS DIRECTED **WHEN THE DOSING REGIMEN FITS INTO THEIR LIFESTYLE AND IS CONVENIENT AND DISCRETE.**

THE ORALLY DISPERSIBLE SOLUTION

Patients are more likely to take their medication as directed when the dosing regimen fits into their lifestyle and is convenient and discrete. Ease of administration is also important for the caregiver for pediatric, geriatric, non-ambulatory patients and the mentally ill.

Orally Disintegrating Dosage Forms (ODDs), such as tablets and mini-tablets, disintegrate rapidly on the tongue within 30 seconds without the need for chewing or use of liquids, while powder forms rapidly disperse in the oral cavity. As a result, they are advantageous for all patient groups and comprise the fastest growing segment of the drug delivery market.[4] Indeed, market research studies have shown that patients prefer orally disintegrating tablets over conventional tablets and would ask their doctor for, or purchase, this type over regular tablets or liquids.[5]

Furthermore, dispersion in saliva in the oral cavity may result in pre-gastric adsorption for some drugs, bypassing first-pass liver metabolism and leading to a faster onset of action, which can be particularly advantageous for certain indications such as migraines. Avoiding first-pass metabolism also enables a much larger proportion of the dose to reach the desired site of action, potentially allowing for lower dose requirements and, in turn, reduced side effects.

The most promising area of development for ODDs is in Pediatrics; the European Medicines Agency's Committee for Medicinal Products for Human Use described orally dispersible dosage forms as "having great promise for children."[6] Studies have shown that orally disintegrating mini tablets are well accepted by children as young as two years old.[7]

FORMULATING ORALLY DISINTEGRATING TABLETS

Specifically, an Orally Disintegrating Tablet (ODT) should have an *in vitro* disintegration time of approximately 30 seconds or less using United States Pharmacopeia disintegration test equipment. ODTs should also have a good mouthfeel without grittiness, be good tasting and appeal to the target patient group. They must be robust and not crumble when being removed from the package, and must also have sufficient physical and chemical stability for adequate shelf life without the need for overly expensive packaging.

While pediatric applications are the most promising, there are additional requirements that must be considered when formulating ODDs for this group. Size and fast disintegration are particularly important, not only to reduce choking, but also to prevent the patient from expelling the dose. Taste and texture are extremely important to ensured compliance; however, the types and quantities of sweeteners and flavors used, particularly artificial ingredients, must be carefully determined. For some excipients, there may also be established limits for use due to lack of safety data in pediatric products, or limits have been established in the Inactive Ingredient Guide. Finally, ODDs for children often require a wider range of dosage strengths, particularly at the lower end. Orally disintegrating mini-tablets have been shown to be effective in providing low-dose accuracy and the ability to accommodate a wide range of doses.

LIFE CYCLE MANAGEMENT AND PATIENT-FRIENDLY DOSAGE FORMS

Life Cycle Management opportunities represent another key element of the appeal of patient-friendly dosage forms. Companies can use these dosage forms as a way to enter new markets, extend product lines and expand into previously unsupported patient populations, while also extending their patents and trademarks, as well as the lives of their products. All of these activities contribute to increased revenues.

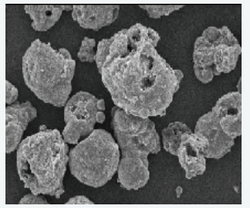
Orally disintegrating technologies can be a particularly valuable life-cycle management strategy for both branded and generic drug manufacturers. These dosage forms can help companies establish innovative leadership positions in a crowded marketplace, especially for over-the-counter products.

FORMULATION OPTIONS FROM SPI PHARMA

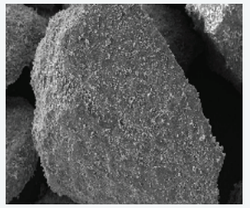
The success of an orally administered tablet or powder may depend on how easy and pleasant it is for patients to take. At SPI Pharma, we understand this relationship and focus on assisting our customers in developing patient-friendly dosage forms.

With core expertise in polyol chemistry, SPI has developed several Mannogem® mannitol products (spray-dried, granular and powder), for use in multiple patient-friendly oral dosage forms. Mannitol offers a pleasant, cooling effect and a smooth mouthfeel without being overly sweet (50% as sweet as sugar) in orally dispersible and orally disintegrating formulations. It also is a strong, durable binder with high compactability, low friability, minimal sensitivity to over-lubrication, a high dilution capacity and low hygroscopicity. As a result, Mannogem mannitol is suitable for use with a wide range of APIs and is used extensively in swallow, chewable, and orally dispersible applications. Its high solubility may also help to facilitate rapid dissolution and improve the solubility of poorly soluble drugs.

Mannogem® Mannitol Products



SEM Mannogem EZ (100X Magnification)



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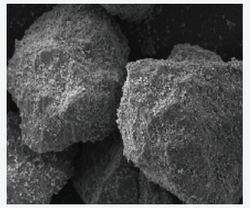

SEM Mannogem 2080 (100X Magnification)

MEET SPI PHARMA

SPI Pharma is a major supplier of specialty ingredients and excipients to the pharmaceutical industry, dating back over 75 years. Headquartered in Wilmington, Delaware and with R&D and production sites in the U.S., France and India, we offer multiple products and platforms based on core technologies geared to the development and manufacture of patient-friendly dosage forms.

SPI Pharma is best known as the world market leader in immediate-release antacid actives, supplying multiple aluminum-, magnesium- and calcium-based products in gel, paste and powder forms, plus preformulated suspensions and tablets. We also offer data packages to support the development of commercial antacids. Other key SPI products include directly compressible calcium carbonate powders, a wide range of functional excipients for all dosage forms and a strong line of vaccine adjuvants based on aluminum hydroxide chemistry.

Our full spectrum of specialty excipients, orally disintegrating products, services and technologies support every stage of the drug product life cycle. Our fully formulated and optimized Pharmaburst® and Pharmasperse® systems are ready to use and provide excellent organoleptic properties for any patient population. Our Actimask® taste-masked ibuprofen and acetaminophen products, Effer-Soda® surface-modified sodium bicarbonate and Mannogem® line of mannitol excipients are designed for the formulation of multiple dosage forms that meet the diverse needs of your patient population.

PATIENT-CENTRIC FORMULATIONS ARE **ALSO TRULY DIFFERENTIATED MEDICATIONS THAT OFFER REAL COMPETITIVE ADVANTAGE,** PARTICULARLY IN A CROWDED MARKET.

Effer-Soda® is, like Mannogem, part of the wide range of functional excipients that SPI offers. It is a highly stable, surface-modified sodium bicarbonate that is used in effervescent tablet and powder formulations. Effer-Soda–containing products, when dropped into a glass of water, create patient-friendly dosage forms that dissolve readily, are easy to take and taste pleasant.

Demonstrating true innovation in the formulation of patient-friendly ODTs, in 2002 SPI introduced Pharmaburst®, the first coprocessed drug delivery platform for the manufacture of robust, rapidly disintegrating tablets using standard tableting equipment. Approximately 60 drug products have been commercialized worldwide to date using this technology.

Use of Pharmaburst 500 (our latest product) streamlines formulation development by reducing both time and cost. Customers only need to blend in the API, flavors, sweeteners and lubricants to meet their specific needs. SPI recommends the use of sodium stearyl fumarate as the lubricant of choice, which SPI supplies under the trade name Lubripharm®, because studies have shown that there is a measurable reduction in ejection force when compared to magnesium stearate.[8]

The coprocessed Pharmaburst 500 system possesses optimal compactability with rapid disintegration (<30 seconds) along with a high carrying capacity that enables the formulation of ODTs, even at higher dosage levels. It is also designed with attractive organoleptic properties. Notably, Pharmaburst is not only cost-effective, but also provides reduced time to market for product line extensions and entry into new markets and patient populations.

Pharmasperse® from SPI is designed for the formulation of patient-friendly orally disintegrating powders and can be combined with SPI's Actimask® taste-masked acetaminophen and ibuprofen actives. Powder formulations are easily poured from sachets or pouches into the mouth where they readily disperse and can be swallowed within 15 seconds without the need for water. ODPs are attractive because they allow higher dosage formulations that cannot be achieved with ODTs' oral administration. Pharmasperse has particular applicability in pediatric medicines and for geriatric use in sachets and stick packs, removing the need to measure out a liquid dose.

It is also worth noting that taste masking in SPI's Actimask products is achieved using gelatin in an aqueous, solvent-free coating process. In addition to acetaminophen and ibuprofen, SPI is developing the technology for other APIs. As mentioned above, Actimask can be combined with the Pharmaburst and Pharmasperse platforms to create formulations that can offer better therapeutic efficacy and bioavailability, improved stability in certain drugs, as well as obvious improvements in patient acceptability and compliance.

COMPREHENSIVE SERVICE

To help customers achieve the most effective and optimal oral dosage form solutions, including patient-friendly formulations, SPI has introduced Pharmasolutions, a comprehensive drug development service. SPI works closely with drug manufacturers to develop drug delivery platforms and/or dosage forms on a fee-for-service basis. With Pharmasolutions, SPI is seeking to become a formulation partner to the pharmaceutical industry.

In addition to improving healthcare and serving patients, SPI sees huge potential for savings to the industry through the development of patient-friendly dosage forms. Patient-friendly dosage forms fulfill the diverse needs of today's patients and allow formulators to be creative and develop tailored products that are highly differentiated in the marketplace. P

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Don has worked in the pharmaceutical industry for over 30 years with responsibilities in a number of different areas, including manufacturing, technical services, and process and formulation development. Prior to joining SPI Pharma in 2015, Don was with Patheon in Cincinnati, Ohio as the Associate Director of Formulation and Process Development.

He is a graduate of the Rutgers College of Pharmacy in New Jersey and is currently a registered pharmacist in New Jersey, Wisconsin and Pennsylvania.

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VIRTUAL PANEL

CONTINUOUS MANUFACTURING: TO BE CONTINUED…

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

CONTINUOUS MANUFACTURING OFFERS OBVIOUS ADVANTAGES TO THE PHARMACEUTICAL SECTOR BUT HAS NOT YET EVOLVED INTO A MAJOR ALTERNATIVE TO BATCH. ARE THINGS ABOUT TO CHANGE?

DR. ANDREW WARMINGTON SPOKE WITH SOME OF THE LEADING CDMOS AND API MANUFACTURERS TO FIND OUT HOW THE LANDSCAPE IS SHIFTING.

"I don't know why it's not more widely used… this is the future," said Janet Woodcock, director of the Center for Drug Evaluation & Research at the U.S. Food & Drug Administration (FDA), when asked to explain the benefits of continuous production in pharmaceutical manufacturing.[1]

Woodcock was speaking to members of Congress in May 2015 during hearings on a bill calling on the FDA commissioner to award grants to academic institutions and not-for-profit organizations for "studying and recommending improvements to the process of continuous manufacturing of drugs and biological products and similar innovative monitoring and control techniques." She has been calling for more manufacturers to switch from batch to continuous since at least 2013.

THE JOURNEY TO CONTINUOUS CONTINUES

Shortly afterwards in July 2015, the FDA approved the use of continuous manufacturing in Vertex's new cystic fibrosis drug Orakambi (lumacaftor, ivacaftor) at a 4,000 ft^2 (370 m^2) facility in Boston. It is a wet granulator product and is manufactured on a production line developed in-house.

In March 2016, Vertex signed an agreement with Portuguese CDMO Hovione, a long-term collaborator, to install a commercial-scale continuous manufacturing facility at Hovione's site in Windsor, New Jersey. Due for completion in early 2018, this will also be open to third parties. It will include continuous blending, wet and dry granulation, fluid bed drying, tableting and coating operations.

Meanwhile, a few months back in December 2015, the FDA issued its draft guidance 'Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base,' with a view towards helping manufacturers implement various technological advances.[2] The agency believes that this facilitated another breakthrough: In April 2016, Janssen Supply Chain

→ **ABOUT THE PANELISTS**

Ian Muir, Ph.D.
Managing Director, Aesica

Mark Griffiths
Global CEO, Dishman Group

Roger Viney, Ph.D.
Senior Director, Off-patent APIs, Hovione

→ ABOUT THE PANELISTS

Matt Hanson
Head of API Franchise,
Millipore Sigma

Lukas Utiger, Ph.D.
President of Drug Substance,
Patheon

Bal Kalirai, Ph.D.
R&D Business Manager,
Robinson Brothers Ltd.

> COMPANIES CAN BE FORWARD-LOOKING BUT THEY ARE TIED TO THE EQUIPMENT THEY HAVE, AND FROM A SCIENTIFIC PERSPECTIVE THIS IS A BIG OBSTACLE.
>
> Roger Viney, Ph.D., Senior Director, Off-patent APIs, Hovione

(JSC), a division of Johnson & Johnson (J&J), received the first approval to switch from batch to continuous processing for the HIV-1 treatment Prevista (darunavir).

JSC can now produce 600 mg tablets on a continuous manufacturing line at its site in Gurabo, Puerto Rico, which integrates weighing, milling, blending and compression. The ultimate aim for J&J and JSC is to manufacture 70% of their highest-volume products using continuous manufacturing within eight years.

PRODUCT VS. SUBSTANCE

Both of these approvals refer to drug product rather than drug substance, but industry insiders say that the technological possibilities and the economic case are fundamentally similar in both fields. Contract development and manufacturing organizations (CDMOs) active in both fields are invariably interested in applying the technology to both.

Immediately afterwards, Lawrence Yu, Deputy Director of the FDA's Office of Pharmaceutical Quality, said in a blog: "Although it is not easy for drug manufacturers to transition from batch to continuous manufacturing, there are significant rewards. FDA encourages others in the pharmaceutical industry to consider similar efforts."[3]

The potential advantages of continuous production are well understood: reduced costs, shorter production times (in some cases reducing many weeks to a single day), greater flexibility (especially when responding to increasing levels of growth), reduced waste and environmental impact, reduced factory size, fewer locations and more efficient capacity utilization. Some also see it as a way to bring drug manufacturing back to the West.

LOOKING OUTSIDE PHARMA

For some perspective on this prospect, however, Google 'continuous processing' and 'small molecule'; the first hit will be an excellent article by Dr. Matthew Mollan and Dr. Mayur Lodaya of Pfizer, reviewing the potential of continuous processing to replace or complement batch in pharmaceutical manufacturing. The authors point to the plethora of other industries which have moved in that direction, FDA support, the pressures from rising costs and the growing need for customized smaller- volume drugs.

Mollan and Lodaya conclude: "The pharmaceutical industry is poised to change radically in the next 5-10 years in response to a changing marketplace. New risk models will need to be implemented to stay competitive and rapidly respond to these changing dynamics... The level of ongoing research activity and the partnership approach signaled by the FDA suggest that the changeover from batch to continuous processing in the pharmaceutical manufacturing environment will happen soon."[4]

This article was published in 2004! To point this fact out is not to be wise after the event at the expense of other authors. Yet continuous processing has taken an awfully long time to arrive in this industry. Why, given the obvious advantages and the continued encouragement from the regulators? And on what basis can we say that it will be different this time?

THE CHALLENGES TO CONTINUOUS MANUFACTURING

The main reason continuous processing has struggled to gain any traction is that manufacturing processes are virtually set in stone when a drug is patented. For the vast majority, the cost of validating a technically superior continuous process and then seeking marketing approval outweighs any reduced cost from a better process, particularly if registrations have been filed in multiple regions. Indeed, the same applies to a better batch process.

There has also been a perception that continuous manufacturing can only compete at very high volumes, though some dispute it. Then there is also simple inertia. Drug makers, CMOs and CDMOs have large investments in batch reactors that have already been written down. And to change to continuous means a change in mind-set about how process R&D is done.

"What has held us back has been an asset-heavy industry," says Dr. Roger Viney, Senior Director for Off-patent Products at **Hovione**. "Companies can be forward-looking but they are tied to the equipment they have, and from a scientific perspective this is a big obstacle too. Thousands of scientists are used to batch production, and this is another big reason why it has taken longer than expected."

Perhaps predictably, given that his firm is actually installing continuous processing equipment at one of its sites, Viney is an optimist when it comes to the potential for the technology. "The real advantage is speed of development," he says. "We have gone in with a partner and will work with them, but we also have free capacity to sell to the market or use for our own projects."

The new rig allows Hovione increased capabilities at commercial scale, including direct compression and both wet and dry granulation in continuous mode for the production of coated tablets. All of these processes are rapid, so the advantage is accelerated development. The company has also been working on applying continuous processing to drug substances at lab scale.

"We now, as of fairly recently, screen all our development projects to see if continuous processing is applicable to them," Viney says. Equally important, is the appointment of Nuno Matos to take full charge of continuous processing for both drug product and drug substance.

"We have recently worked on screening criteria to see if continuous processing is applicable to specific projects; there are technological ones but also commercial ones. When we start a drug substance project, we ask if there is an advantage to using continuous processing. One criterion would be cost – but it is also necessary to ask if there is actually a *need* to reduce costs. So we try to pick products where there is a need, and this kind of process can give an advantage.

"Another is purity of product – could continuous processing lead to a purer product? A third is IP – is there potentially something a continuous process could yield that would lead to greater IP generation? Other possible advantages include whether it might lead to greater product differentiation, or the possibility of reengineering after the product development phase."

> CONTINUOUS PROCESSING IS IDEALLY SUITED TO HIGH-VALUE, LOW-VOLUME NICHE MOLECULES WHERE CONSERVATION OF THE API IS A CRITICAL ELEMENT OF VALUE.
>
> Ian Muir, Ph.D., Managing Director, Aesica

COMMERCIAL WITHIN REACH

U.K.-based CDMO **Aesica**, which now belongs to Consort Medical alongside drug device development and manufacturing firm Bespak, has also been a pioneer in continuous processing for finished dosage forms and believes that it had the first commercial rig available for continuous processes.

"We worked with customers and equipment suppliers to develop it," says Managing Director Ian Muir. "The rig has been in place at our Queenborough site near London for just over four years. This was triggered in the first instance by a special customer relationship with a Big Pharma company that was interested in looking at continuous processes for finished dose manufacture."

Muir believes there are equally strong possibilities in drug substance too. "Continuous processing is ideally suited to high-value, low-volume niche molecules where conservation of the API is a critical element of value. Thus, smaller-volume therapeutic classes with high-value molecules makes the economics of continuous processing as attractive in APIs as in finished doses. These classes include orphan drug classifications and others which target themselves at particular subsets, as well as high-potency drugs."

CAPABILITY FOR CONTINUOUS

Patheon, another multinational, multi-site CDMO, draws on a long DSM heritage in working with microreactors – Lukas Utiger, President of Drug Substance, remembers using disposable glass microreactors back in 1998. The company has worked on continuous processing for both drug substance and drug product and is ready to manufacture at a scale into the tons when the market is ready.

"We already do continuous tableting at our site at Greenville, North Carolina, and our site at Linz in Austria has continuous capability for drug substance at all three levels, from lab to pilot plant to commercial production," he says.

Another U.K. CMO, **Robinson Brothers** (RBL), has only a small proportion of its activity in pharma. Nonetheless, both Managing Director Adrian Hanrahan and

> WE ARE ALREADY WELL SET UP, WE CAN PRODUCE SEVERAL TONS OF MATERIAL OUT OF OUR EXISTING FACILITIES, WE HAVE NUMBERED UP, DEVELOPED PROOF OF CONCEPT.
>
> Lukas Utiger, Ph.D., President of Drug Substance, Patheon

Bal Kalirai, Ph.D., R&D Business Manager, are strong advocates of being proactive in adopting new technologies.

RBL started work a year ago on an Innovate U.K. project with flow reactor maker AM Technology to see if a pharmaceutical process of several tons could switch from batch to continuous hydrogenation. This, he says, has been completed successfully, showing not only that the switch could be made but that an additional purification step needed in batch was not needed in continuous.

More recently, RBL has begun involvement in the Advanced Manufacturing Supply Chain Initiative (AMSCII) project led by GSK and covering all areas of pharmaceutical supply from formulation to clinical trials, in one of four "Applications," covering continuous hydrogenation, a continuous carbon disulphide reaction, and microwave chemistry.

There have been promising results in some areas, and AstraZeneca and Pfizer are expected to get involved too. "I am optimistic for the outcome and believe that

at least one supplier will launch a drug at large scale using it, and that RBL will within five years have a large-scale continuous processing rig producing one or two products at large scale, coupled with the use of process analytical technology (PAT)," Kalirai says.

WAITING FOR A VIABLE PATHWAY

Matt Hanson, Global Head of the API Franchise at **Millipore Sigma**, who was involved in work on continuous flow reactors at R&D scale when the business was still part of Sigma-Aldrich, cautions that there has been a lot of interest in the technology, "but until there is a viable alternative pathway and the FDA has approved a lot of development candidates, there will be a reluctance."

It is easy to spend a few hundred thousand dollars playing in the space, Hanson adds, but making this part of the supply chain for a drug is quite another matter. There is also a circular problem: Where the process could most usefully have continuous processing investigated, in the very early stages, is also where financial imperatives tend to lead to the lock-in of a batch process with its own impurity profiles. The alternative is likelier to be more viable once the project reaches phase II, but when the money is likelier to be available the options are diminishing.

Muir also points to the regulatory framework and having controls in place. "One advantage of batch is that it is easy to segregate parts of the process and see exactly where issues arise. The other part is to do with the technology: There has been a lot of work to put the hardware – the reactors – and the software together and ensure that they work together well. It has taken companies time to get from concept to commercial."

NUMBERING UP

Most regard the two recent FDA approvals as a significant moment in terms of the acceptance of continuous processing and possibly the start of something more substantial. Hanson, for one, says that they "will help move the technology forward," while Viney agrees that FDA support is crucial in driving acceptance. None, however, sees it as the opening of the floodgates so much as the start of a trickle.

"Five years ago we knew what continuous processing was, but now we have got a rig and processes in place and are now in a place where academic ideas can come to industrial fruition," Viney says. "I think other companies are in a similar position, in that the equipment is there and they can consider continuous processing as an option at the start of a project."

As well as depreciated assets and the innate conservatism of the pharmaceutical industry at all scales, Utiger points to the need for very reaction-specific conditions in continuous processing, particularly during crystallization. 'Numbering up' is cheaper than scaling-up, but many complexities are involved, he notes; it takes far more than adding another pump and another microreactor.

Kalirai of RBL says: "Pharma companies were held back mostly by concerns about the FDA accepting continuous processes, partly on the basis that it can very quickly generate a lot of off-spec product if something goes wrong. But in practice we find less variability when using continuous. It takes someone to take a bold step, validate the equipment and go to the FDA with the process."

> WHAT WE ARE SEEING NOW IS TYPICALLY WORK UP TO CLINICAL PHASE II, BUT THERE IS A RELUCTANCE TO INVEST TO MAKE MATERIALS FIT IN WITH FLOW CHEMISTRY.
>
> Mark Griffiths, Global CEO, Dishman Group

Muir, meanwhile, sees the approvals as the culmination of longer-term movements. "All of the regulatory agencies have traditionally regarded pharma as a batch process, so all of the process controls and final releases have been assumed to be built around a segregated batch system," he says. "They have been doing a lot of work behind the scenes with companies and built up a body of knowledge to show that products made through extended processes can be controlled."

CREATING A FIT

Mark Griffiths, CEO of the Swiss-based CDMO **Carbogen Amcis** and of its parent company the **Dishman Group**, is more skeptical, at least where it comes to heightened expectations. The company has, however, been working with microreactors and continuous flow chemistry for over ten years, and currently has its first GMP prep project at phase II under way for continuous flow chemistry.

"This is a piece of work for a U.S. client where there were challenges and this fit very well – the chemistry was energetic, it was low volume and the low residence time made it suitable, so we suggested this alternative to the client," Griffiths says.

Nonetheless, he adds, "What we are seeing now is typically work up to clinical phase II, but there is a reluctance to invest to make materials fit in with flow chemistry. We have done quite a bit of work with clients towards parallel development but [find] reluctance where clients are trying to get the chemistry 'fixed' and the NDA done. Speed is critical in the early phases."

Having seen many fads come and go, Griffiths draws an analogy with what was said back in the 1990s about chiral chemistry or more recently about biocatalysis. Some people, he thinks, see continuous processing as a panacea rather than just another part of the toolbox.

There is a general consensus as to where in the chemistry set continuous processing will have its most immediate viability: in large volumes, where the ability to run 24/7 gives cost advantages, and/or where energetic chemistry leads to exotherms that cause safety issues to arise in batch.

As Griffiths says, "When you have 500 grams of explosive and expensive material in a pot and the process safety considerations put you on the ragged edge in terms of costs, you can go to the customer and suggest a cost-benefit analysis." It is probably less useful, he adds, with complex molecules that require complicated assembly.

"You still need a chemist in a lab with a 500-liter reactor. This is a nice-to-have for a CMO and enables us to offer benefits to customers, but will it be 25% of the market in ten years' time? No," Griffiths concludes. Muir adds that the technology will be increasingly better understood, "but I don't see established products going wholesale over to continuous processing."

It is striking, though, that the more optimistic advocates do not fundamentally disagree with this figure. Few put a figure on the proportion of reactions that might use it but Viney suggests 10% to 20%. Utiger, most cautiously of all, does not yet see a reason to depart from the figure of 1% to 5% that he first guessed in the late 1990s. Only gas and liquid reactions with rapid kinetics are suited to it at the present state of technology, in his view.

THE CONTINUOUS BELL CURVE

Companies that already have a large amount invested in traditional batch processing, Viney adds, will be slower to change: Continuous processing will be more suited to virtual companies and/or those which have already outsourced a large amount of their manufacturing. It will also be less suited to those working in niche areas where there is limited access to API in the development stages, because they cannot afford to buy more API than they need to use.

Adapting to continuous processing on a large scale is about more than equipment and software, however – it is also about the mind-set. For a start, says Muir, producing in continuous mode means testing during the process instead of at the end. To keep a process within the requisite parameters requires the use of Quality by Design (QbD) and using many sensors that were not needed before.

He and Griffiths both note that more analytical chemists and an enhanced technical analytical capability are required because more samples need to be taken during the development stage, and there are more process controls. This is also tending to bid up the cost of analytical chemists, who are not always easy to find.

Adding that continuous processing goes hand in hand with QbD, Viney adds that the way batch processes have historically been validated is very inexact – typically making three batches and examining a couple of parameter changes. This should no longer be acceptable because it means that the full parameters of the reaction are often not sufficiently understood, even when it is set in stone.

> IN PRACTICE WE FIND LESS VARIABILITY WHEN USING CONTINUOUS. IT TAKES SOMEONE TO TAKE A BOLD STEP, VALIDATE THE EQUIPMENT AND GO TO THE FDA WITH THE PROCESS.
>
> Bal Kalirai, Ph.D., R&D Business Manager, Robinson Brothers Ltd.

Hovione now employs mathematicians and data scientists, some of who have worked with petrochemical companies, who can evaluate such things as the feedstock input and explore all the parameters and process questions. "This is a very different science to traditional organic chemistry, but once you have it in place and use it, it generates a lot of other possibilities," Viney says.

"Design of Experiments is very powerful because it gives you a complete understanding of what is critical to the process. You can map critical parameters and even generate a 5D model showing what will happen to any of them if one is varied. This is a completely different level of understanding to the one you get from making three batches."

ANTICIPATING THE NEW WAVE

With the technology increasingly understood and the regulatory authorities encouraging adoption, what will actually drive the next wave of progress? For Griffiths, the real challenge is looking at the product life cycle and seeing where the sweet spot is where flow chemistry could add value. In some cases, he says, it might be possible for the customer to file with a traditional manufacturing route, then look at flow chemistry.

"Probably the dynamic will be driven by larger pharma companies, who are a bit braver and likelier to have more direct experience, as well as deeper pockets, than smaller companies," he suggests. "There is a better chance that they will take a look at options like continuous processing before taking a project to a CMO." The biotechs are more driven by speed, generally speaking. He also sees potential with older products, "especially generics, where drug companies are trying to drive every dollar they can out of the process and want to get the costs of raw materials down too."

Having worked on both sides of the fence, Kalirai says that, while CMOs are able to move quicker to implement new technologies like this, they have actually been slower to adopt it than larger pharma companies because they lack the resources to invest – or are simply stuck in their comfort zone in relatively good times

> WE TRY TO EDUCATE CUSTOMERS TO LOOK AT THE APPLICABILITY OF CONTINUOUS PROCESSING FOR A SPECIFIC REACTION AND ASK IF THEY WOULD LIKE US TO DO SOME ADDITIONAL DEVELOPMENT. THIS MEANS ASKING THEM TO TAKE A CHANCE – THOUGH THAT IS WHAT WE, AS A CMO, DO ANYWAY.
>
> Matt Hanson, Head of API Franchise, Millipore Sigma

when their batch reactors are fully occupied. Passionate advocates of the technology will be vital.

Kalirai also believes that many more pharmaceutical companies are using continuous processing in-house but staying silent about it, meaning that some suppliers are in for a shock when it takes off. "The future is continuous and those who don't grasp the nettle will have a limited life span," he says. Anecdotally, plenty of continuous equipment has been sold in China – "We will struggle to compete if we do not adapt."

Another big challenge will be skills, in Kalirai's opinion. As more and more companies adapt to continuous processing, so universities will need to teach skills related to it, including PAT. At the moment, very few do. AMSCII is also looking at that.

"More successes," is Hanson's simple answer. "The more you have, the more people can tangibly understand it. We are mostly trained as batch chemists, and one of the other challenges is that you have to develop an alternative flow process alongside the batch process. This is often not really viable for small companies who have only one or two drug compounds that have a high chance of failure."

Millipore Sigma, he adds, has worked on the technology for some time and developed expertise, so it understands a lot about designing the equipment it can apply to certain chemistries at the Milwaukee, Wisconsin site, carrying them out on a larger scale at Sheboygan, Michigan. Mostly this has been non-GMP. Now the company is looking to expand to GMP-capable processes that customers would be interested in.

"We try to educate customers to look at the applicability of continuous processing for a specific reaction and ask if they would like us to do some additional development. This means asking them to take a chance – though that is what we, as a CMO, do anyway," Hanson says.

Utiger agrees that getting the right portfolio of reactions and flexibility on both sides are crucial. It will also require cross-disciplinary work because of the different mind-set needed. "Chemists know about kinetics but they don't know about reactor design in the way an engineer does," he says. They will have to learn to work together.

Nonetheless, Patheon is in place for a big switchover, should it come to fruition. "We are already well set up, we can produce several tons of material out of our existing facilities, we have numbered up, developed proof of concept. From that point of view we are ready and we will have plenty of capacity when customers are ready for it," says Utiger.

"Now there have been a couple of approvals, more companies will want to go down this path," says Muir. "I believe that continuous processing does indeed play well to the strengths of CDMOs like us. The kind of compounds that suit it do not come on all the time. Similar to technologies like spray drying and lyophilization, companies will want to access them as and when they need them rather than being captive to them."

There have been some false dawns on this road before but, says Viney, "I believe it is different this time. We have a rig, we have a man and we are looking at continuous processing for all our operations, so it does feel different to me now. With the two recent approvals, the chances are that it won't be a damp squib, though it will also not happen overnight." P

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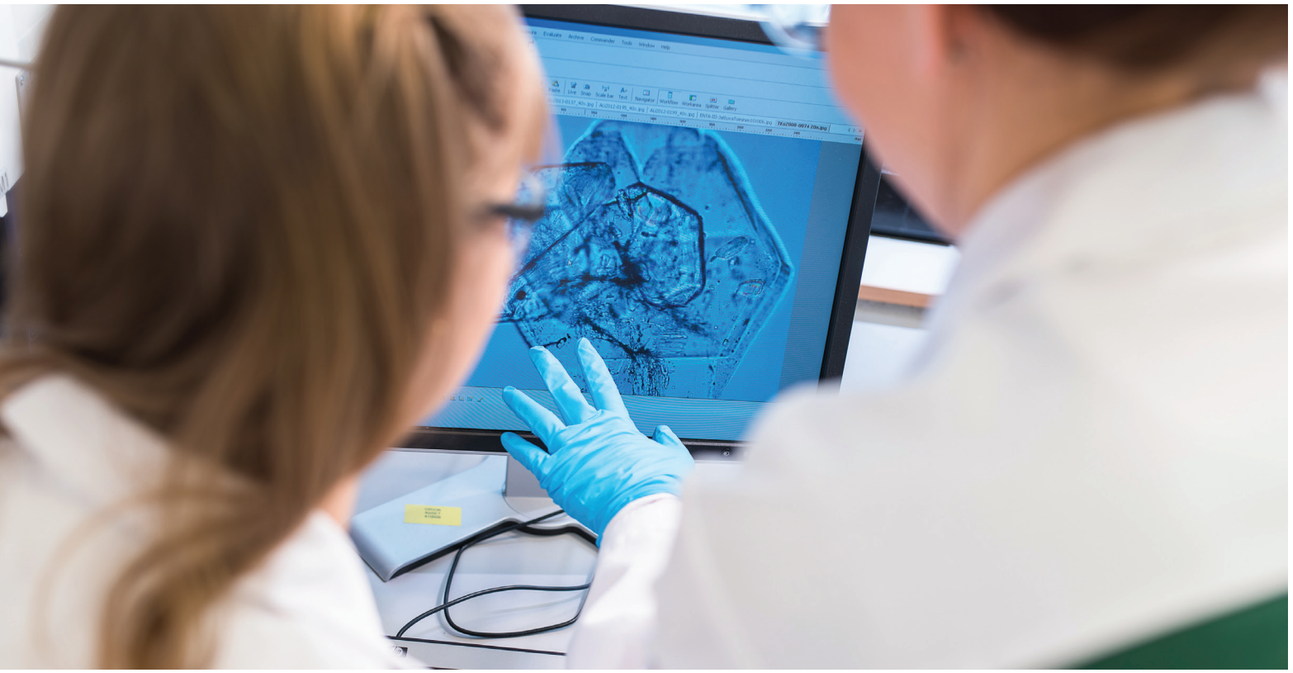

ACHIEVING SECURITY OF SUPPLY WITH EFFECTIVE PARTICLE ENGINEERING

→ BY **ARNE GRUMANN**, FERMION

Targeted particle engineering for solid dosage drug formulations has become an imperative given the challenging compounds in the pharmaceutical pipeline, the growing interest in inhaled delivery, and the move to continuous manufacturing. Contract development and manufacturing organizations (CDMOs) with extensive knowledge and experience with optimization of crystallization and particle engineering processes provide customers with improved product quality, lower costs, and accelerated development and commercialization timelines.

MULTIPLE DRIVERS FOR ENHANCED PARTICLE ENGINEERING

A number of changes occurring in the pharmaceutical industry are creating a significant need for the development of advanced particle engineering technologies for solid dosage drugs, regardless of their route of administration.

The biggest driver is the growing percentage of drug candidates that suffer from poor water solubility and consequently poor bioavailability – various estimates range from 40%-70%. The use of high-throughput and combinatorial chemistry capabilities in drug discovery has led to the identification of novel compounds with attractive therapeutic benefits, but challenging pharmacokinetic properties. Different strategies, from the straightforward (particle size reduction) to the more complex (preparation of amorphous solid dispersions or incorporation in lipidic vehicles, complexation with cyclodextrins and salt, or cocrystal formation), have been developed to enhance water solubility and ultimately improve dissolution rates and bioavailability. Most of these approaches require expertise in particle engineering.

While oral delivery remains the preferred route of administration, interest in delivery via inhalation has recently attracted attention as an additional approach to overcoming poor water solubility/bioavailability. Delivery first to the lungs, followed by absorption into the bloodstream, provides an alternative mechanism for making the active pharmaceutical ingredient (API) available to the body. APIs for inhaled drug products require specific size, shape and surface properties, thus effective particle engineering is crucial to their successful development and manufacturing.

EFFECTIVE PARTICLE ENGINEERING EFFORTS THAT LEAD DIRECTLY TO PRODUCTS **WITH THE DESIRED PSD CAN ELIMINATE MILLING COSTS.**

In addition to poor water solubility, many new drug candidates are classified as highly potent APIs (HPAPIs). These drug substances are effective at very low doses. In addition, formulated oral solid dosage (OSD) drugs based on HPAPIs typically contain very low concentrations of the active substance. Appropriate particle engineering is important to ensure that the HPAPI is evenly distributed throughout the formulated OSD and exhibits acceptable release profiles.

Finally, continuous manufacturing of OSD products has become a reality. FDA has approved the use of continuous processing for the manufacture of two different drug products in the last two years and actively encourages its adoption. Effective implementation of continuous processes for final product formation – such as grinding and tabletting – requires APIs with excellent flow properties. Application of particle engineering technology is therefore essential for developing solid APIs with appropriate particle characteristics.

A LITTLE ABOUT TARGETED PARTICLE ENGINEERING

Effective particle engineering depends on the successful achievement of three primary activities: target identification, knowledge gathering and process control. Appropriate target identification ensures a high yield of a high-quality product that is produced as the desired polymorph with the desired particle properties. Successful knowledge-gathering generates information about various particle characteristics, solubilities, the metastable zone, and the supersaturation properties of an API. Implementation of appropriate controls leads to the development of an optimal solvent system, crystallization and/or milling/micronization processes, and the establishment of appropriate physical analytics.

In all three cases, systematic development work is required. For target identification, thorough polymorph screening and evaluation of crystallization habits and limitations are essential. Systematic studies are also required to fully characterize API particles, including crystal form and flowability; particle size, shape and habit; specific surface area, purity and stability; bulk and tapped densities; and processability. Intellectual property considerations can also be identified. To obtain this information, a range of analytical techniques are used, including in-line particle size measurement during crystallization, metastable zone determination, particle size distribution analysis, x-ray diffraction for polymorph determination, scanning electron microscopy, microcalorimetry and more.[1,2]

NOTABLE ADVANCES

Advances in particle engineering technologies in three particular areas are worth noting, because they have had significant impact on the development of solid dosage drugs.

First, micronization increases the dissolution rate of poorly soluble APIs due to the increase in surface area. Water solubility and dissolution rate of drugs are key drivers for their absorption in the GI tract. For a therapeutic effect, a sufficient amount of drug needs to be absorbed at a sufficient rate. As the majority of new drugs under development are poorly soluble, the challenge of low solubility occurs more and more often in drug development, as does the need for micronization.[3,4]

Second, nanomilling results in the production of an intermediate that can also be considered a formulated product. API manufacturers that perform nanomilling are thus also producing formulated products in some cases, which impacts their regulatory status. Nanomilling aims to produce particles in the size range of a few nanometers to a few hundreds of nanometers. After production, a nanosuspension is obtained. For oral administration, the liquid of the nanosuspension needs to be removed to obtain a solid oral dosage form or formulate accordingly for an oral liquid nanosuspension. Therefore, nanomilled drug substances become formulated intermediates rather than API.[5]

Third, large porous particles have been shown to have aerodynamic properties comparable to those of small particles, but due to their larger size, they are not attacked by macrophages in the alveoli. The ability to engineer these types of large particles is facilitating the formulation of solid dosage drugs for inhalation delivery.[6] In order to achieve a therapeutic

effect, locally in the lungs or systemically, inhaled drug particles need to reach the site of absorption in the tiny alveoli. To make this journey, the particles need to possess a very narrow range of aerodynamic diameter (related to geometric diameter and density). The aerodynamic diameter window of 1-3µm is referred as ideal for inhalation drugs. Particles of this size range are targeted by phagocytosis of macrophages, thus removing the drug particles from their absorption site. By engineering drug particles with large size and low mass, the absorption site in lungs can be reached and phagocytosis avoided.[7]

CDMOs MEET TECHNICAL NEEDS

Particle engineering is a specialized field that requires specialized knowledge and expertise as well as specialized analytical and manufacturing equipment. Most (bio)pharmaceutical companies cannot justify the extensive investment required to establish the high level of capability required to achieve effective particle engineering. They therefore do not have the in-house know-how or resources needed to solve these types of problems. In other cases, sponsor firms may have the ability to perform particle engineering studies, but not for highly potent compounds, which require specialized containment solutions, or not for commercial manufacturing.

MEASURABLE IMPACT

Effective particle engineering at Fermion has been achieved by gaining a thorough understanding of crystallization processes combined with implementation of full automation in production. Crystallization and particle engineering issues are also considered at the very earliest stages of each project. The extensive crystallization know-how and wide range of particle engineering technologies, combined with the use of detailed R&D studies and a variety of milling capabilities, allows Fermion to rapidly develop processes that not only provide high yields, but also the desired product quality in terms of physicochemical properties.

One obvious advantage to this approach is a reduction in the variation of particle properties, which leads to a minimization of product quality variation. Low levels of variation have been achieved because our approach to particle engineering leads to the production of particles that consistently meet particle size distribution (PSD) specifications. One consequence: approximately 50% of products produced at Fermion do not require milling or micronization. Consistent PSDs are also highly beneficial to the milling process when milling is required because a smaller particle size is needed.

Skillfully designed crystallization processes are also very effective purification methods. In many cases at Fermion, well-designed crystallization processes have replaced laborious, multistep purification processes, including those that involve multiple but ineffective crystallization processes.

Cost reductions are also achieved through effective particle engineering. Higher yields and the elimination of purification steps are both possible through optimization of crystallization processes. Effective particle engineering efforts that lead directly to products with the desired PSD can eliminate milling costs.

CONCLUSION

With careful particle engineering, products have consistent quality and fewer deviations. Ultimately, particle engineering supports security of supply. Fermion recognizes the valuable role that particle engineering plays today and its increasing importance in future drug development and manufacturing. The company is therefore continually investing in expanding capabilities.

Recent additions have included the installation of different types of milling equipment for medium-scale processes (tens of kilograms) – including pin, hammer and jet mills that are also designed for the micronization of HPAPIs – and HPAPI micronization capabilities for large-scale production (up to 1000 kg). Fermion will also invest in Raman analysis capabilities in R&D scale in 2017. In addition, an online particle size distribution analyzer will be installed in 2017 in the expanded commercial production facilities at our site in Hanko, Finland.

The added equipment and analytical capabilities further enable Fermion to support our customers with the rapid development of tailored particle-engineering solutions for their challenging intermediates and APIs. P

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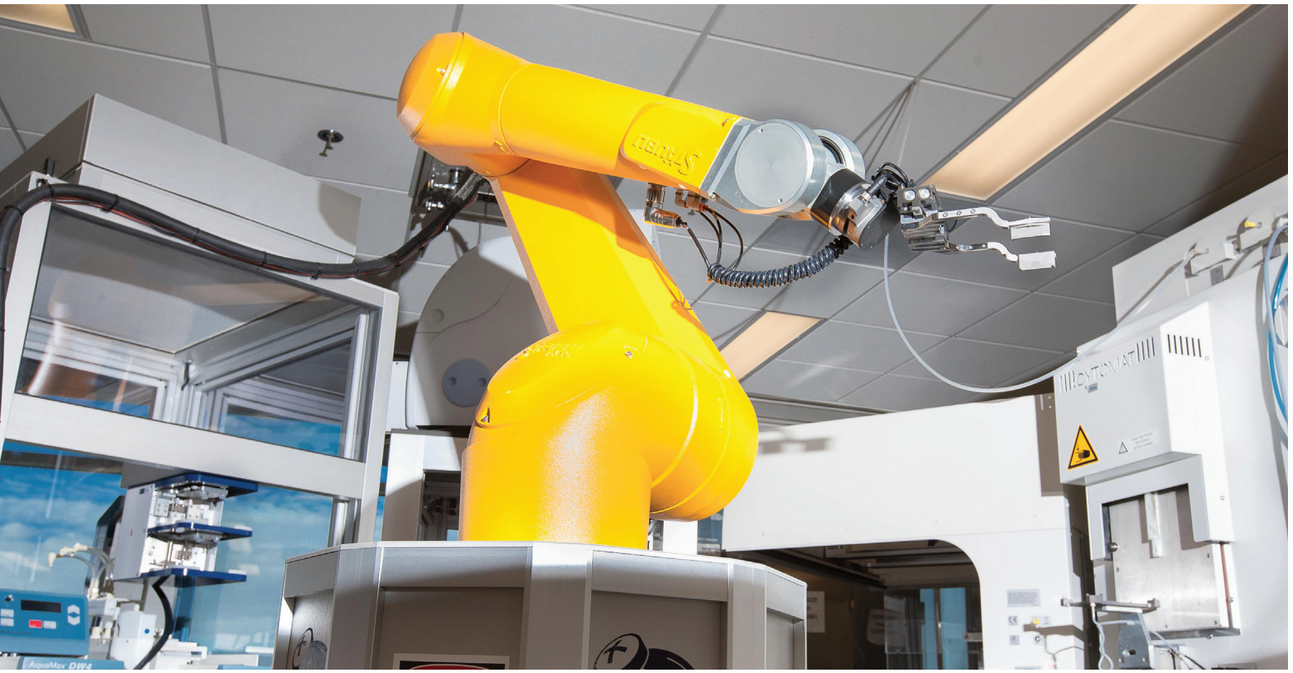


INTEGRATED INNOVATION: FOSTERING THE NEW GROWTH IN PHARMA

→ BY **ANIL C. NAIR, Ph.D.**, **KENNETH F. WERTMAN, Ph.D.**, **MARCEL PATEK, Ph.D.** AND **PAUL R. AUGUST, Ph.D.**, ICAGEN, INC.

The pharma landscape is constantly changing, especially as many players in the industry move toward slimmed-down in-house R&D. This includes embracing the "growth pharma" model in which drug discovery programs are obtained via acquisitions. Many big pharma executives have left their posts to spearhead lean, high-risk, high-reward biotech firms, start-ups and virtual companies, which lack wet labs and other means of obtaining experimental results.

A CHANGING INDUSTRY

Recent examples of plunging stock prices at several big firms portray an industry too reliant on blockbuster drugs to sustain growth. But clinical failures are only part of the story. Branded drugs have faced pricing pushbacks from consumers, and in several key areas are confronted with competition from generics and biosimilars.[1] On November 23 of this past year, the NYSE Arca Pharmaceutical Index was down 13% and the Nasdaq Biotechnology Index was 17% lower, all while broader market indexes remained up.[2] What this tells us about the industry as a whole is that investors are anticipating a tide change. Perhaps the best indicator of this is the numerous stories of big pharma executives changing careers and joining smaller biotech startups.[3]

But one can argue that the recent upsurge in smaller biotech firms came before the industry was adequately equipped to handle the substantial outsourcing these firms rely on.

These lean companies often lack rudimentary wet labs or any internal facilities capable of producing novel experimental results, and therefore face logistical challenges in which services of one drug discovery program are splintered into multiple organizations. To add to this, finding the best CRO can lead the search into different time zones, geographies and company cultures.[4]

To cope with difficulties these small firms face in terms of integrating different aspects of a drug screening program, other biotech startups have arisen to allow experiments to be designed in-house and carried out in robotic facilities elsewhere. Although these 'cloud laboratories' will certainly find a demand within an increasingly fractured industry, for companies looking for guidance alongside experimental results, they offer little.[5]

THE RISE OF GROWTH PHARMA

The shift in the industry was made clear when then-Actavis – now Allergan – CEO Brent Saunders coined the term 'growth pharma' as a differentiator to separate Actavis from a big pharma industry that was, and still is, having difficulties meeting investors' expectations. The growth pharma paradigm differs from the aging big pharma business model that does not rely on internal R&D but fosters innovations through acquisitions. Ultimately this has been a successful model, at least for Allergan, which saw a 4.5% revenue increase in the third quarter of 2016 when compared to the same quarter in 2015.[6]

What came of this was that 2015 saw a 20-year high in venture capitalist investment in biotech firms.[3] A market filled with high-risk, high-reward companies allows for an agile industry that quickly pivots to shirk selloffs that happen when potential blockbuster drugs fail in the clinical setting. To be sure, 2016 in particular saw a flurry of acquisitions, and the nix of the merger between Pfizer and Allergan has again solidified the growth pharma paradigm philosophically as well as economically (both Pfizer and Allergan have committed to more than $20b in acquisition since they went their separate ways).[7]

Icagen has been anticipating the industry's arrival of growth pharma over the aged big pharma model, and has uniquely positioned itself to be the industry's incubator: a one-stop shop with a *completely* integrated drug discovery program, one that moves beyond the fractured outsourced model of specialized CROs and into a true partnership for biotech firms looking to innovate and grow within the pharmaceutical industry.

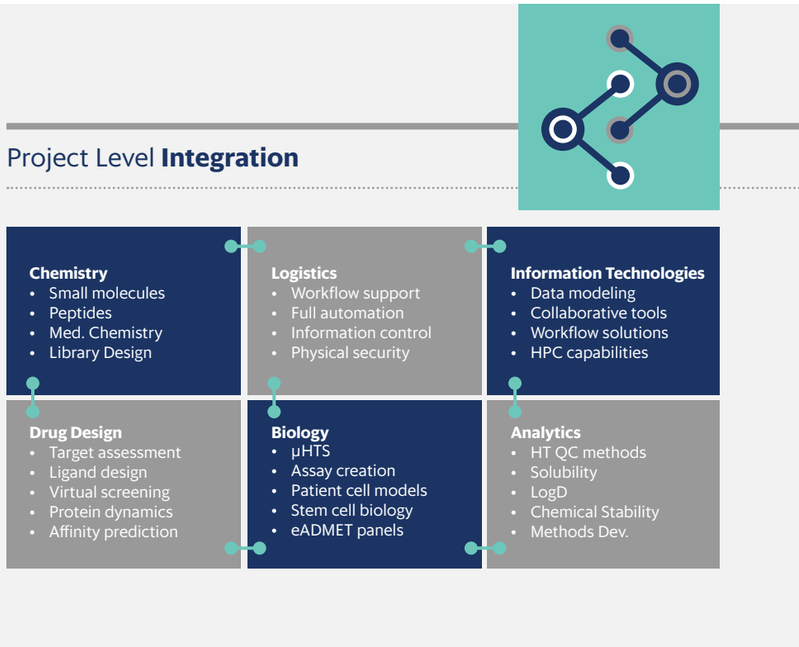
A TRULY INTEGRATED DRUG DISCOVERY PROGRAM

Icagen's acquisition of Sanofi's Tucson facility in mid-2016 changed the face of the company. This move transformed Icagen from a highly specialized CRO into North America's first truly integrated drug discovery contract research organization. This was achieved by introducing the broad scope of the Tucson facility's drug discovery program to the rigor of a highly specialized North Carolina site that has spent nearly a quarter of a century, with essentially the same core team, trying to unravel one of the more difficult drug discovery targets: ion channels and transporters.

The acquisition of the Tucson facility added chemistry, structural biology and in silico approaches for early drug discovery to the North Carolina site's top-of-the-industry biology. Adding Icagen's meticulous knowledge of ion channels and transporters to the Tucson facility's integrated approaches is already starting to transform the way the company pursues a wide range of targets. For example, Icagen's deep knowledge in ion channel biology is now married to an expertise in Tucson for patient-stem-cell–derived skeletal and cardiac muscle models.

THE ADVANTAGES OF REAL-TIME RESEARCH OPTIMIZATION

In the current fractured model of outsourcing, a company must rely on different



CROs to put together a drug discovery program. For example, a pharma company may contract one organization for early drug discovery via in silico approaches, and several others for medicinal chemistry and biology wet labs. At Icagen, all of these services are provided in a fully integrated drug discovery program that is capable of adaptive learning, as Icagen's lattice of biology, chemistry, structural biology and in silico modeling interface with each other continuously throughout the program.

Real-time research optimization not only increases efficiency, ultimately it enables Icagen to be a better partner – especially because of the crosstalk that happens between the sciences. Biologists thinking about chemistry, and chemists thinking about the implications for biology, create a unique form of translational science that cultivates novel approaches to drug discovery, one where in silico simulations turn into promising compounds. At Icagen, a partner will find everything they need under one roof, in addition to a different kind of scientist. Scientists at Icagen not only have strong expertise in their field but offer a unique translational knowledge of all fields, demonstrating that true integration leads to the discovery of strong drug candidates. In the fractured model, a company must wait on results from one CRO before moving to the next – at best creating 'white space' in programs, at worst missing key insights between disciplines. At Icagen, drug discovery occurs in a web of biology, chemistry, structural biology and in silico modeling, in which reevaluations and readjustments happen seamlessly and in real time.

BIOTECH'S NEW INCUBATOR

In a changing industry model that increasingly embraces 'growth pharma,' guidance and expertise are needed more than ever. In many ways, Icagen sees itself as this new industry's incubator. Not only is Icagen a fully integrated drug discovery CRO, Icagen is a think tank that houses industry leaders in every realm of drug discovery. This means better results in less time, especially when the real-time research optimization of the integrated drug discovery program at Icagen is compared to linear and other fractured models of CRO outsourcing. Furthermore, Icagen's two facilities – in Tucson and North Carolina – mean that it is not necessary for potential partners to maneuver time zones, language barriers and corporate cultures that can create costly disruptions in getting drug candidates to IND. P

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EXPERIENCE AND EXPERTISE FACILITATE CONTROLLED SUBSTANCE MANUFACTURING

→ BY **PATRICK HATEM** AND **KIM NOLL**, UPM PHARMACEUTICALS

Requirements for the manufacture of controlled substances impact all aspects of drug development, manufacturing and distribution. CDMOs that have an in-depth understanding of the regulations, long-standing positive relationships with regulators and a track record of successfully working with controlled substances can accelerate product development and commercialization so that treatments are made available more quickly.

PREPARING FOR LICENSURE

The Controlled Substances Act (CSA) in the U.S. is a federal regulation designed to prevent the diversion of certain potentially harmful substances for illegal use. Various narcotics, stimulants, depressants, hallucinogens and anabolic steroids, including plants, formulated drugs and specific chemicals, are assigned to one of five schedules depending on their medical applicability and potential for creating dependency and being subjected to abuse.

Schedule I substances are of no medicinal use, have a high potential for abuse and are considered too dangerous to be prescribed to the public. Substances in Schedules II through V (decreasing in potential for abuse) do have medical uses and can be manufactured, tested and distributed in compliance with U.S. Drug Enforcement Agency (DEA) regulations. Additionally, there are "listed chemicals" that are chemicals used to manufacture illegal controlled substances and, as such, must be legitimately used in accordance with DEA regulations as well. According to the Congressional Research Service, controlled substances account for approximately 10% of all drug prescriptions written in the U.S.[1]

Manufacturers and distributors of any substances covered by the CSA must be registered with the DEA. Before beginning the licensing process, companies must not only become familiar with the various security and record-keeping requirements, but see that their facilities are fully compliant to ensure control, traceability and accountability.

For instance, larger quantities of a Schedule II substance must be stored in a vault in which all six walls are constructed of at least 8" of substantial masonry and the door and frame meet strict design specifications. Large quantities of Schedule III-V substances, on the other hand, can be stored in cages, but the walls and doors must be made out of a certain gauge wire, posts placed according to regulation, etc. Smaller quantities of a scheduled substance can be stored in a safe or steel cabinet, again, as long as certain construction qualifications are met. A record-keeping system must also be in place to provide traceability of any and all controlled substances either coming into or being shipped from the facilities.

Once it has been confirmed that all of the security and record-keeping systems are in place, the first step is to apply for a State Board of Pharmacy license, which requires completion of the state's application and on-site inspection. Once that license is received, a company can then submit an application for registration with the DEA. It is also important to note that separate registrations are required for manufacturing, distribution, analytical testing (in specific situations), importing and exporting.

THE QUOTA SYSTEM CHALLENGE

Manufacturers of controlled substances – both active pharmaceutical ingredients (APIs) and formulated products – receive quotas from the DEA that dictate the quantity of controlled substance that can either be made (API) or procured (for use in finished product manufacturing) during a given year. The purpose of quotas is to limit production to the amount required to meet legitimate medical needs.

By April 1 of each year, those companies wishing to procure controlled substances for manufacturing use must submit their application indicating their quota needs for the following year, including estimates of the quantities of each controlled substance they will produce and raw materials they will use. Manufacturers of bulk controlled substances must submit their quota applications by May 1 of each year.

From the submitted quota applications, the DEA establishes Aggregate and Procurement Quotas. The Aggregate Quota dictates how much controlled substance can be manufactured in the U.S. Procurement Quotas establish the amount of a controlled substance a finished dose manufacturer may purchase for manufacturing use.

To purchase controlled substances as raw materials (such as an API for production of a formulated product), the purchaser must provide the supplier with its DEA certificate, as well as a Certificate of Available Procurement Quota confirming that it has unused quota available to cover the quantity being purchased.

If projects come to a contract development and manufacturing organization (CDMO) later in the year, it is possible to apply for quotas for controlled substances at that time. It is also possible to apply for an increase in quota if the assigned quotas turn out to be insufficient. As part of an application for quota increase, a company must provide detailed information as to how the previously granted quota was used, i.e., testing, waste, finished product. It takes approximately four weeks for the DEA to process an application for an increase in quota – a time frame that cannot be accelerated.

The use of the quota system, with aggregate annual quotas for each controlled substance, in essence results in a fixed market. However, although it can be more difficult for newer products, manufacturers are very good at predicting the quantities needed. To date we are unaware of any time when an aggregate quota was insufficient.

There can be significant production delays, however, if additional quota must be requested. Perhaps the most challenging situation is the receipt by a formulated drug manufacturer of API that doesn't meet specifications and must be returned to the supplier. In most cases, the supplier must first apply for additional quota in order to receive the rejected material back into its facility. Then, if unused quota is not sufficient, the drug manufacturer must apply for additional quota in order to receive a new batch of the API. It is a four-week process for both applications, resulting in a possible project delay of eight weeks.

MANAGING REPORTING REQUIREMENTS

Preventing diversion of controlled substances is the main goal of the CSA. Traceability and accountability at manufacturing and distribution facilities are the ultimate goals of the control and reporting requirements of the regulation. Extensive record-keeping is therefore essential. Manufacturers can choose to report on a monthly or annual basis. UPM Pharmaceuticals elected to report monthly in order to achieve a higher level of accountability, helping to identify any issues more quickly. For manufacturers, these monthly or annual reports include overall production information – what material came into the plant and how it was used.

UPM: **30 Years** of Positive DEA Inspections

UPM's Tennessee facility has had a controlled substance license for more than 30 years with no negative DEA inspections since at least 1987. The move from Baltimore to the current facility significantly expanded our capabilities for controlled substance manufacturing. The acquisition also included a large warehouse (for which UPM has a separate license) with vault and cage storage of pre-launch quantities of controlled substances. Importantly, we are a full-service CDMO that serves as a true partner for our customers. With our rich history and qualified personnel, we accelerate the movement of controlled substance projects through all phases of development.

WHEN SEEKING CONTRACT SERVICE PROVIDERS FOR PROJECTS INVOLVING CONTROLLED SUBSTANCES, **IT IS ESSENTIAL THAT SPONSOR FIRMS SELECT THE RIGHT PARTNER.**

Detailed biannual inventories are also required by the DEA. In these reports, manufacturers provide a snapshot of all controlled substances currently held under each registration. Year-End Worksheets are also required to be filed by January 31 of each year. Each worksheet acts as a reconciliation of the yearly activity for each controlled substance for which a quota had been granted. A worksheet reflects what was on hand at the end of the previous year, plus all the incoming and outgoing during the reporting year, after which, like a checkbook, everything must balance.

Choosing the right CDMO

The consequences of noncompliance with the regulations of the CSA can be immediate and severe. If the DEA finds evidence of substantial diversion, the agency can order a facility to cease operations immediately. When seeking contract service providers for projects involving controlled substances, it is essential that sponsor firms select the right partner.

A reliable CDMO will have a long, successful track record of compliance with controlled substance requirements, including meeting reporting requirements. Strong controls, effective handling and maintenance procedures and an excellent record-keeping system are also essential. As important is an in-depth understanding and working knowledge of the regulations and requirements stemming from a long-term, positive relationship with the DEA.

FULL-SERVICE SUPPORT

UPM Pharmaceuticals has a long history of manufacturing and distributing many different types of controlled substances. Our highly qualified and experienced personnel have always taken a proactive approach when dealing with the DEA. Our in-house training program ensures that operators and other employees who handle controlled substances understand the importance of following company procedures to ensure compliance with the CSA and avoidance of any diversion of controlled substances.

As a client-focused CDMO, UPM is vested in providing more than just capacity for the production of controlled substances. We work closely with our customers to make sure they understand all aspects and implications of the CSA. In addition, with an analytical laboratory approved to handle Schedule I-V controlled substances and listed chemicals, we can support our clients with formulation development and stability/degradation testing. Our R&D group also investigates abuse deterrence solutions for controlled substances that both DEA and the U.S. Food & Drug Administration have interest in.

The ability to support controlled substance projects in-house from the proof of concept stage through to commercialization/product launch, including formulation development, process and method development, validation and warehousing, does away with the need for technology transfer of these challenging projects off-site to other vendors. Clients save both time and money while getting their products into the hands of patients more quickly.

CONCLUSION

When dealing with controlled substances, avoiding diversion through the use of appropriate controls and record-keeping is absolutely crucial. Sponsor firms need to identify reliable CDMO partners with a proactive approach to managing controlled substance projects and a successful history of completing them. P

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AN OEE APPROACH TO SOLID DOSE EQUIPMENT PURCHASING AND IMPLEMENTATION

BY **ADAM COVITT**, FEDERAL EQUIPMENT COMPANY

More than ever, the success of a particular OSD product rests on operational excellence and the ability to deliver high-performing variation-free process.

Acquiring pharmaceutical pro-cessing equipment and successfully integrating it into operations is not as straightforward as it may seem. Whether used or new, everything is up for consideration and evaluation: vendor, type, specifications, performance, reliability, capability, service life, price and, importantly, availability. Oral solid dose (OSD) manufacturing, especially at commercial scale, is particularly dependent on the operational efficiency of a familiar but increasingly complex train of processing equipment to mass produce tablets and capsules. More than ever, the success of a particular OSD product rests on operational excellence and the ability to deliver high-performing variation-free process.

Measuring the operational performance of process equipment has evolved over the years, and the methodology to determine overall equipment effectiveness (OEE) is gaining popularity. Focused on measuring equipment availability and reliable, as-designed functionality, OEE principles focus on 'losses' that can be generated from a whole host of issues related to equipment. At a macro level, OEE focuses on Availability Loss, Performance Loss and Quality Loss – it also takes into account idling and minor stops, one of the Six Big Losses to OEE that affect OEE performance (see Table 1).[1]

In a 2014 *Industry Week* article, senior consultant Ellis New, Business Practice Leader for Productivity Inc., explained that "OEE assigns numerical value to improvement opportunity. It factors in the availability, performance and quality of output of a given piece of equipment and asks you this: How much right-the-first-time product did this machine produce compared to what it should have produced in the allocated time?" In other words, the question and answer is this: Is a piece of equipment effective within its value stream? "Does it let you meet present or future customer demand? If not," says New (and this is critical), "OEE helps you analyze the reasons why, so you can address them systematically."[1]

MAKING EQUIPMENT ACQUISITION MORE STRATEGIC

Without sounding too simplistic, the primary reason pharmaceutical manufacturers purchase production processing equipment is to meet present or future demand for its products. Beyond that, there are hundreds of business and competitive drivers prompting equipment acquisition, and it's safe to assume that the better a company is at acquiring and integrating equipment into operations, the more economical, efficient and flexible those operations can be. Given speed to market, response to market demand, competition and all the other factors involved, OSD pharma processors are increasingly looking to head off OEE's six big 'losses' as early as possible and boost equipment value as soon as possible once a piece of equipment hits the books, and by necessity, must earn its keep for years to come.

Federal Equipment Company's long experience selling used equipment is similar to new equipment vendors; pharma's OSD manufacturers want to get the most value out of every dollar spent on capital equipment. Pharma manufacturers operate some of the most intensive processing environments and, after 40 years in the business, we understand customers engage us and return to us because we've developed a business model that provides a range of resources – not only optimal equipment selection, but its acquisition, installation and process implementation.

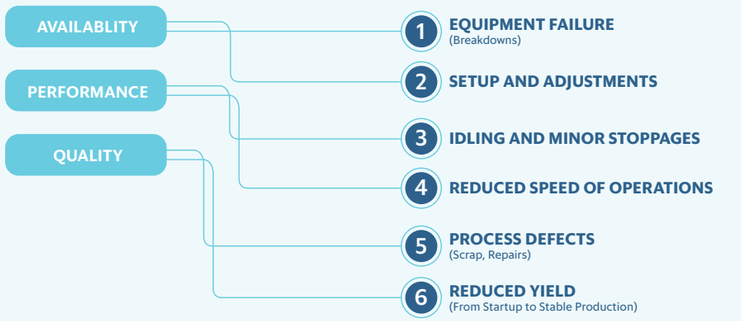
The process and manufacturing community understands OEE offers a solid foundation for measuring or scoring operational excellence. It also offers a guide on how we marshal company resources and key partnerships to support our customer's equipment acquisitions and integrations. Whether choosing from the extensive inventory of used OSD equipment that Federal Equipment Company maintains, or selecting new technology from prominent OEMs – many of them partners – we've created a unique equipment buyer's journey built around key equipment supply chain relationships, relationships that effectively support equipment acquisition strategies for some of pharma's most prominent branded, generic and contract OSD manufacturers.

FIRST THINGS FIRST

As mentioned, there can be hundreds of reasons prompting an equipment purchase, but first you have to find it. Acquiring the right machine for the job at the speed of business, and within often-severe financial constraint, has frustrated many a process engineer under pressure to extend a line in a hurry. New equipment is one answer, but manufacturers' timelines and other constraints can disrupt or delay critical equipment/process-related project timelines if delivery won't fit the schedule. The dynamics of the secondary equipment market can offer relief – and working with an experienced and knowledgeable broker, can locate and source affordable access to a particular machine or system and meet challenging project goals and deadlines.

TABLE 1

The Six Big Losses



OEE PHILOSOPHY IS **CENTERED ON FINDING IMPROVEMENT** OPPORTUNITIES.

In OEE circles, 100% performance means equipment in the manufacturing process is running at its theoretical maximum speed while operating. There are so many things that contribute to process performance (or the lack thereof) and, like any complex technical endeavor, require a comprehensive approach. Applying OEE strategy and a GMP-like process to equipment purchasing, uptake and acquisition is best practice. Because product quality is so tightly linked to equipment performance, pharma OSD manufacturers must gain mastery over all aspects of formulation, equipment condition and proper operation and maintenance. However, not every pharma processor has the resources or internal processes to accomplish this internally.

TODAY'S CURRICULUM: EQUIPMENT EXCELLENCE

OEE philosophy is centered on finding improvement opportunities. As Federal Equipment Company's experience with equipment acquisition has continued to grow, it became apparent that good customer experience and success with an equipment purchase is closely associated to how well an organization understands all the improvement opportunities that might be associated with their equipment purchase.

Addressing this knowledge gap and helping pharma's OSD manufacturers institutionalize better operational practices (in an effort to foster a more transparent and effective understanding of equipment and solid dose process) has been technical consultant Mike Tousey's mission for decades. Under the Techceuticals banner, Tousey has been schooling OSD equipment manufacturers, pharma processors and equipment operators on the finer points of tablet and capsule processing. Years of client referrals and cooperation created synergies that our mutual customers increasingly find valuable.

In 2012 Federal Equipment Company extended its relationship with Tousey, co-locating Techceuticals classrooms and labs adjacent to new environmentally controlled equipment staging and storage facilities that were acquired in a recent expansion. Combining lecture and hands-on training, Techceuticals Laboratory provides a perfect venue to address gaps in OSD process optimization and conduct equipment evaluations as part of a comprehensive equipment acquisition strategy. Tousey explains that not every company understands exactly what equipment or process specifics will suit their needs best or how to optimize formulation/equipment to curtail quality excursions and other things gumming up operations. The lab creates an opportunity to explore and evaluate alternatives and options without the financial commitment. The lab currently houses some of the most advanced solid dose manufacturing equipment now offered by the industry's biggest names, including Glatt, Ohara, Korsche, Fette, Globe, Vector and similar, popular OEMs.

Recently, Glatt installed two of its latest wet and dry granulators at the Cleveland lab, part of an ongoing relationship with Techceuticals, Federal Equipment Company and the pharmaceutical manufacturing industry. Quality OSD equipment can have an extended life (especially once it moves into secondary markets) and, whether acquired new or used, the closer equipment vendors can be to its users the better. "Our commitment to customers doesn't end with delivery," said Ed Godek, process technology manager for Glatt. "We want to connect with our users in meaningful practical ways; central to that effort is our direct support of Techceuticals training and optimization mission. Beyond that we offer factory support to Federal Equipment Company's buyers of used Glatt equipment – the relationship creates great synergies that all our customers value."

According to Tousey, the Techceuticals lab provides a real-world processing environment where students can evaluate the performance of their current and proposed formulations in machines they are looking to specify and acquire. "We provide the training and the equipment necessary for anyone looking to get better performance and quality from the solid dose products they manufacture," he says.

NEXUS FOR OPERATIONAL EXCELLENCE

Acquiring equipment and implementing it effectively is becoming a strategic imperative no pharma manufacturer can avoid. Equipment performance metrics like OEE can provide guidance and frame a best practice acquisition strategy. The synergies between Federal Equipment Company, Techceuticals and Equipment OEMs form a nexus for operational excellence and provide the means to effectively evaluate equipment, explore process optimization tactics to make equipment acquisition more strategic and extend the value of every equipment dollar spent. P

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

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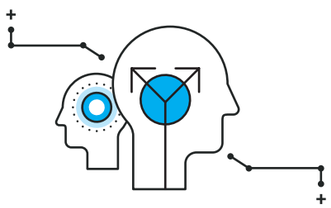
EXECUTIVE Q&A



WHY IS CULTURAL INTEGRATION FOLLOWING A MERGER SO IMPORTANT TO THE SUCCESS OF THE NEWLY FORMED ENTITY?

The impact on employee morale and turnover can be painfully high during and after a merger, and repairing it can be nearly impossible. If cultural integration doesn't happen, companies see significant and costly consequences. In order for a merger or collaboration to work, both parties must first agree on the same goals, values and culture for the future company. People must be aligned with the strategic goals of the new entity and come together as one, just as processes and systems that are in place on both sides of a company will need to be merged. Ultimately the success of the new entity depends on a successful integration and understanding of the company's direction from each and every employee. It is evident that being connected at every level is paramount.

WHAT HAVE YOU FOUND TO BE THE MOST CHALLENGING ASPECTS OF INTEGRATING THE CULTURES OF AAI PHARMA SERVICES AND CAMBRIDGE MAJOR LABORATORIES TO THE NEW CULTURE OF ALCAMI?

External perception of the brand was one of the most challenging aspects of integration. As we have changed and improved so much internally in a short period of time, it is difficult to gain back customers that may have felt wronged by one of the former companies. We are taking innovative approaches to bring our sites to customers via virtual tours and working to get clients — new, former and existing — back into our sites for a visit. The change of culture is palpable and we want them to experience it firsthand.

WHERE IS ALCAMI IN THE CULTURAL INTEGRATION PROCESS TODAY? WHAT ARE THE MAIN ISSUES YOU ARE TACKLING?

Communication. It sounds simple, but even with regular communication it is easy for people to become confused, frustrated and anxious if they don't know or understand the vision and direction that executives have for the company. We address this with regular business review meetings, town halls, communication calls and internal newsletters to share the bigger picture and how it filters into every part of the company. Most important is to have ambassadors within the company to drive home a consistent message.

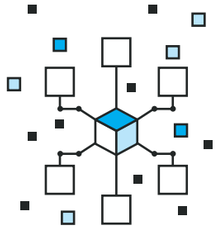
KEYS TO CULTURAL INTEGRATION

That's Nice sat down with Catherine Hanley, Alcami's Director of Marketing, to find out how to successfully integrate after a merger.

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

CAN YOU SHARE SOME OF THE MOST VALUABLE LESSONS YOU HAVE LEARNED WHILE GOING THROUGH THE PROCESS?

Before starting the rebranding project, we formed a "Branding Team" comprised of a cross-functional group of people from all businesses, sites and levels of the company to support the change. This was the first important decision made regarding cultural integration and a large contribution to our successful integration. By having people from across the company and from both former companies, we were able to discuss the differences between cultures and gain our own brand ambassadors to drive the change within the company. We have continued the emphasis on the brand with a Brand Awareness team that focuses on ways to maintain a strong brand both externally and internally. Without the buy-in of your employees, a brand is like an advertisement with nothing to back it. When customers visit our sites today, they can see and feel the cultural shift that has taken place. The accountability that is so important to success is there, and the energy of an innovative, thriving new company can be felt the moment you walk into our facilities. Employees feel and show ownership and pride in the brand, which sets the tone for the culture moving forward.



HOW DO YOU KNOW WHEN THE INTEGRATION PROCESS IS COMPLETE?

Integration and culture shift are difficult things to measure. We regularly measure employee engagement as an indication of cultural integration; however, we don't see the integration as ever being fully complete. As we continue to hire and expand our businesses, we need to continue regular exchanges across sites, businesses, and between commercial and operations groups to stay integrated and continue to work more closely.

EXPANDING THE COMMERCIAL OPTIONS FOR PREPARATION OF AMORPHOUS SOLID DISPERSIONS

→ BY **MÁRCIO TEMTEM, Ph.D.** AND **JOÃO VICENTE, Ph.D.**, HOVIONE

Spray drying (SD) and hot-melt extrusion (HME) are commercially proven and accepted amorphous solid dispersion (ASD) technologies for the enhancement of the dissolution and bioavailability of poorly soluble drugs. These approaches are not suitable for all APIs, however. Hovione, in addition to offering non-ASD solutions such as nanomilling and cyclodextrin complexation, is developing an effective coprecipitation technology platform to address this key market need.

ENHANCING SOLUBILITY WITH ASDS

Solubility in physiological fluids is a prerequisite for high bioavailability of drug substances. For many APIs that exhibit poor water solubility, bioavailability can be enhanced by preparing the product in an amorphous rather than a crystalline form. Amorphous compounds, because they lack long-range order, typically have higher apparent solubilities and faster dissolution rates than their crystalline counterparts. On the other hand, they present some challenges in drug formulation due to their reduced physical and chemical stability compared to crystalline materials.

Formation of a solid dispersion of an amorphous API in a polymeric matrix can often improve its stability. Amorphous solid dispersions (ASDs) therefore provide a means for preparing amorphous drug formulations with higher apparent solubilities and faster dissolution rates as well as the stability required for safe and efficacious medicines.[1]

ASDs are most commonly produced via spray drying (SD) or hot-melt extrusion (HME). A wide variety of approved polymer excipients are available for the formulation of ASDs. The specific polymer and preparation method are dictated by the characteristics of the API and the desired properties of the formulated product, including the dose and form (tablet, capsule, etc.).

DETERMINING THE BEST METHOD

As mentioned above, on the commercial scale, spray drying and hot-melt extrusion are the two main methods used to prepare ASDs. The solubility of the API in organic solvents and its melting point are the two key properties that are considered when determining the best method for ASD formation. HME applicability is limited to APIs with low melting points and non-thermal labile drugs, while SD is in practice limited only by API solubility in organic solvents. In some cases both technologies are applicable, and the formulator must consider additional factors in order to select the optimum solution.

There are also cases, however, where neither HME nor SD is ideal, particularly APIs with high melting points (>200 °C) and limited solubilities in volatile organic solvents. For these 'brick dust' compounds, which are increasingly prevalent in the drug industry pipeline, either an alternative method for ASD formation is required, or a non-ASD approach must be adopted (such as nanomilling or complexation with cyclodextrins; see Table 1).

Amorphous solids can be generated using a number of different techniques beyond SD and HME. Solvent-free methods include vapor condensation, supercooling of a material in the liquid state, and disruption of a crystal lattice in the solid state via grinding. Solvent-based methods involve precipitation of the API from solution, and include solvent evaporation via various methods and freeze drying. To date, these different methods have generally only been performed on smaller scales.

Coprecipitation of an API and a polymer is, on the other hand, an attractive option for problematic APIs that are also scalable. There has been in fact one drug (Zelboraf®, vemurafenib, from Roche) produced at large scale via a solvent-controlled precipitation process.[2]

PRACTICAL COPRECIPITATION

Improvement of the coprecipitation process is, however, needed to make the technology more attractive for commercial drug formulation and manufacturing. Hovione, a leader in spray drying, is developing new techniques for coprecipitation that will allow its use as a robust and reliable third-platform technology for ASD generation.

The approach we have taken involves the use of microfluidization.[3] In this solvent-controlled precipitation (SCP) process, the API and polymer are dissolved in one solvent and mixed with a second, antisolvent in which the ingredients are insoluble (alternatively, the polymer can be dissolved in the API antisolvent). The two streams interact under carefully controlled conditions in a microreactor. These conditions are selected to allow the formation of an API-polymer coprecipitate consisting of agglomerates of nanoparticles. The nanoparticles have very high surface areas and thus unique physicochemical properties.

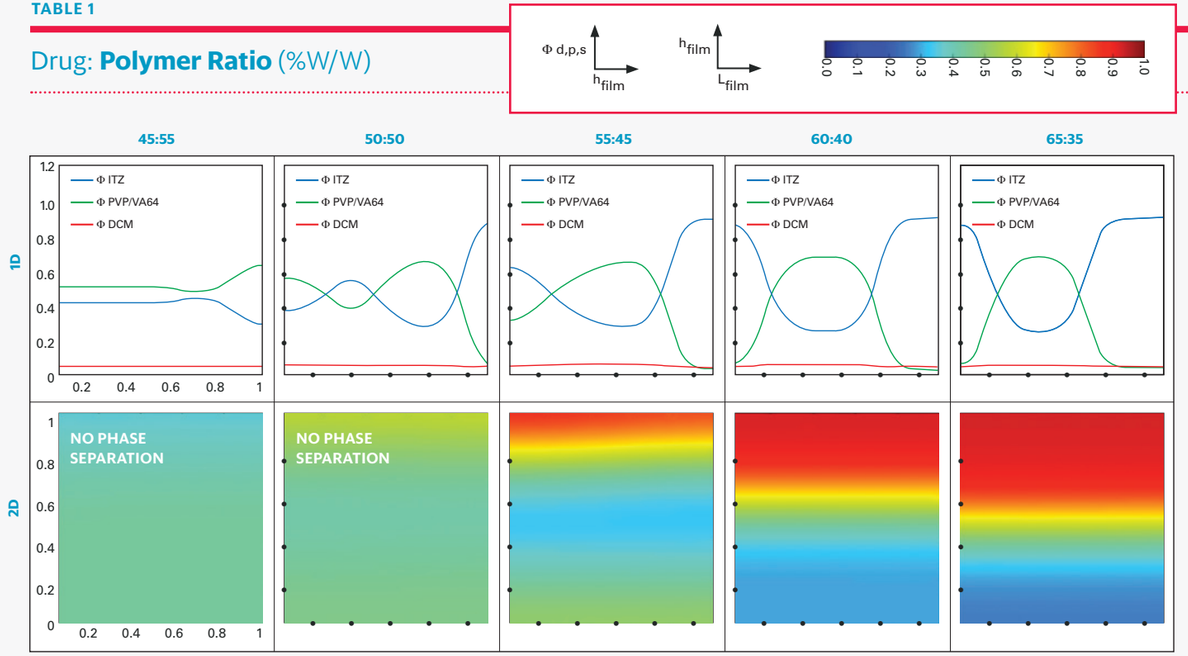
One advantage of the technology over spray drying is the ability to use polar, high-boiling solvents (dimethylacetamide and dimethylformamide, for instance). In addition, compared to HME, coprecipitation is a low-temperature process that can be used for thermosensitive APIs. The novelty of our approach to SCP at Hovione is the use of microreactors and microfluidization to promote the contact between streams. The feed concentrations and rates, API/polymer ratio, and mixing conditions (temperature, time, etc.) have a direct impact on the critical quality attributes of the materials produced.

Traditionally, coprecipitation processes have been performed in stirred reactors with shear mixing, which provides limited control over the actual mixing conditions. In our process, however, the particle size, size distribution and morphology, as well as the level of nanoparticle aggregation, can be finely controlled due to the uniform mixing conditions generated in the microreactor using an assisted microfluidization process. As a result, this new SCP technology is highly attractive for enhancing the bioavailability of BCS Class II compounds with poor solubilities. The suspensions containing the coprecipitates may be isolated by conventional means, as filtration or centrifuge or dried via spray drying to yield spray-dried nanocomposite microparticles.

THE USE OF MICROFLUIDIZATION TECHNOLOGY ALLOWS FOR FINE CONTROL OF THE PARTICLE SIZE, SIZE DISTRIBUTION, DENSITY AND OTHER CHARACTERISTICS CRUCIAL TO DRUG PERFORMANCE.

TABLE 1

Drug: **Polymer Ratio** (%W/W)



FORMATION OF A SOLID DISPERSION OF AN AMORPHOUS API IN **A POLYMERIC MATRIX CAN OFTEN IMPROVE ITS STABILITY.**

WHEN ASDS ARE NOT AN OPTION

Even with access to coprecipitation, there are times when solubility enhancement for APIs cannot be achieved through the preparation of an amorphous solid dispersion. There is consequently a need for non-ASD alternatives in such cases. Nanomilling and inclusion complexation with cyclodextrins are two additional options.

The nanomilling process at Hovione predominantly involves a step of microfluidization to produce the nanoparticles, followed by isolation via spray drying to isolate the materials or microencapsulate the APIs. As with the coprecipitation process, the use of microfluidization technology allows for fine control of the particle size, size distribution, density and other characteristics crucial to drug performance.

Inclusion complexation with cyclodextrins is another established method for increasing the solubility of poorly soluble APIs. Hovione has a license with Ligand to access their Captisol® technology (sulfobutyl ether β-cyclodextrin) for formulation screening; that provides access, at the proof-of-concept stage, to one of the most successful cyclodextrins in the field. As with the development of ASD solutions, processes based on nanomilling and inclusion complexation with cyclodextrins need to be developed with scale-up to commercial production in mind.

ACCELERATING FORMULATION DEVELOPMENT

While we have built a great reputation in particle engineering, particularly on our process development capabilities and the ability to take any process from the lab to commercial scale, we have also started developing strong foundations in formulation development. One example of the latter is our proprietary software (Ternarius) for the development of ASDs. Thermodynamics, diffusion and solvent evaporation kinetics were incorporated into a mathematical model, allowing formulators to identify promising formulations without the need to consume any API.[4] Additionally, this tool provides guidance to reduce the number of physical experiments that must be performed, therefore saving time and expensive API.

We are also developing methodologies for the rapid evaluation of the potential *in vitro* and *in vivo* performance of compounds formulated using different ASD and other platform technologies for enhancing bioavailability. These methods take into consideration the target tissue(s), formulation type, and dosage (among others) to predict the most appropriate solution.

CONCLUSION

The improvement of solubility has become a crucial subject for many drug candidates under development today. Access to the best solution for bioavailability enhancement ensures the highest likelihood for successful formulation of these challenging compounds.

Hovione is therefore continuing to extend its expertise and capabilities in spray drying while developing other enabling technologies such as hot-melt extrusion, a novel coprecipitation platform technology, and alternative techniques for APIs not suited to ASD formation.

Our extensive experience with many different types of poorly soluble compounds has also provided us with a great basis to develop state-of-the-art methodologies for accelerating formulation design and process development, allowing for more rapid and cost-effective identification of optimum solutions. P

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INVESTING FOR SUCCESSFUL ADVANCEMENT OF VIRAL VECTOR MANUFACTURING

→ BY **MARK BAMFORTH**, **MBA** AND **RICHARD O. SNYDER, Ph.D.**, BRAMMER BIO

The gene therapy sector is experiencing phenomenal momentum, with many new companies being formed, the number of clinical trials expanding, and growth in the number of products poised for commercialization.

Contract development and manufacturing organization (CDMO) Brammer Bio is responding to growing demand for phase III and commercial manufacturing support with significant investment in capacity and technologies designed to support the manufacture of viral vectors.

PHENOMENAL MOMENTUM

Gene therapies are designed to treat diseases by modifying genetic information, including correcting genes that function improperly or adding normal copies of defective genes. They have the potential to address and potentially cure a wide range of ailments, including various inherited and acquired diseases such as cancers, neurological diseases, infections such as HIV, metabolic diseases, ocular diseases and cardiovascular diseases.[1]

Recent successes in clinical trials, measured in terms of safety and efficacy, are driving interest in this area. According to a July 2016 report by Datamonitor Healthcare, gene therapy products in development (from preclinical to phase III and beyond) number 418, which is more than double what was in the pipeline in 2012.[1] In addition, the number of products in preclinical development has increased by a factor of four. At the time of the report, 24 products were in phase III or later development stages. Roots Analysis estimates there are over 500 gene therapy candidates in clinical development, with approximately 1,700 clinical studies underway around the world.[2]

Notably, eight gene and cell therapies have been approved to date: Gendicine, Oncorine, Rexin-G, Glybera, Neovasculgen, Imlygic, Strimvelis and Zalmoxis.[2] Strimvelis and Zalmoxis were approved in Europe in 2016. GlaxoSmithKline's Strimvelis is a gene therapy for the treatment of ADA-SCID, a severe immune disorder that is usually fatal within a few years after birth.[3] Zalmoxis is made of allogeneic T cells genetically modified with a retroviral vector given to transplant patients to help the body fight off infection, enhance the success of the transplant and support long-lasting anti-cancer effects.[4] The FDA in 2016 also awarded breakthrough designations (enabling accelerated approvals) for two gene therapies.[3]

Roots Analysis estimates that the market for viral vectors and plasmid DNA manufacturing will grow at an annualized rate of ~17% over the next ten years to reach a value greater than $1 billion.[2]

MANUFACTURING CHALLENGES

Most of the products identified by Datamonitor are *in vivo* gene therapies using vectors (viral or plasmid based), with viral vectors being most often employed, particularly adeno-associated virus (AAV), but also lentivirus and adenovirus.[1] Roots Analysis has identified over 90 active manufacturers of viral vectors and more than 30 producers of plasmid DNA, with an additional 14 companies capable of manufacturing both;[2] however, academic institutes and nonprofit organizations make up the majority of the manufacturers.

To date, demand has largely been for research-grade vectors and vectors for early phase clinical trials, but as products move to later development stages, demand is rapidly increasing for commercial-grade material at a scale that can support delivery to large populations and at high doses. However, a limited number of manufacturers have developed or are developing commercial-scale capacity for vector production.

Manufacturers taking on phase III and commercial production of viral vectors face numerous challenges, including the unsuitability of many existing vector production technologies with respect to efficiency, productivity, stability, etc. In addition, there is a need for both large- and small-volume manufacturing capabilities that require different technical solutions, as well as facilities that are suitable to support commercial manufacturing.

NEED FOR LARGE- AND SMALL-VOLUME MANUFACTURING

Phase III and commercial production of viral vectors can involve a wide range of process and product volumes due to the vast array of targeted diseases for which gene therapies are appropriate. Different combinations of dosages and the size of patient populations contribute to a significant span of product lot sizes.

For instance, gene therapies for muscular dystrophy, a disease that has a large patient population and requires large doses to treat the muscle groups in the body, would require the manufacture of very large product lots. Even though the doses would be smaller, treatments for Parkinson's and cardiovascular diseases would also require large lots due to the very large patient populations. Ocular diseases, on the other hand, can affect very small and very large patient populations and often require very small doses, and thus would drive the lot size.

The production technologies required for the manufacture of large and small viral vector lots can differ significantly. For instance, typical stirred-tank bioreactors up to 2,000 L are necessary for the production of the largest-product lots in suspension. Commercial quantities of the smallest-volume viral vectors can be produced in small stirred-tank bioreactors. Certain products are manufactured in adherent systems where the cells need to grow on a surface. These needs may be met using CellSTACK® or HYPERStack® multilayer cell culture vessels, while larger volumes can be supported, for example, with the largest surface area bioreactor being the Pall iCELLis® 500, which equates to almost 800 cell factories. Consequently, CDMOs committed to supporting the advancement of gene therapies through phase III and commercial launch must be flexible, versatile and offer a wide spectrum of production and purification capabilities.

NEED FOR MODIFICATION OF CONVENTIONAL PRODUCTION TECHNOLOGIES

Viral vector manufacturing processes are in some ways similar to the unit operations required for the production of monoclonal antibodies (mAbs) and other traditional biologic drug substances. The products are produced in bioreactors and subjected to harvesting and downstream purification, including chromatographic separation, depth filtration, etc. High-throughput analytical capabilities are needed to facilitate both process development and product characterization, as well as process characterization and validation.

However, viral vectors tend to be more fragile than protein-based products; for instance, for enveloped viruses, the envelop must be maintained throughout downstream processing in order to preserve

Selecting an **Effective Bioreactor Technology**

The large-volume production of viral vectors is typically achieved in bioreactors. However, the design of the bioreactor can have a significant impact on process performance. Brammer Bio therefore invested time and resources to evaluate different potential bioreactor technologies, both on paper and in the process development lab.

After careful deliberation, Pall upstream and downstream platforms have been selected, including the Allegro® STR Single-Use stirred-tank bioreactor line, and for adherent processes, the iCELLis® bioreactor system. The advantages of this reactor technology for viral vector production include ease of use, compatibility with the production cells used in vector manufacturing, cell growth and vector yield, reliable supply chain for consumables, and scalability to 2,000L. The bioreactors are being installed in Brammer's Cambridge and Alachua facilities.

Image supplied courtesy of **Pall Corporation**

potency. Consequently, buffer systems and process manipulations are designed to be compatible with the vector product being manufactured. Carefully selected methods are also required for viral inactivation; for example, nanofiltration is not applicable because the viral product would itself be removed. Manufacturing of open steps is performed in Class A environments, and segregation and containment of products is crucial.

Drug product manufacturing requires special consideration too, where filling lines are dedicated to viral vector production and nonviral products are not filled using these systems to avoid the risk of cross-contamination. In addition, filling of small-volume (micro liter) products can be challenging. State-of-the-art pumps typically have efficiencies of +/– 5%, but only with volumes of 0.25 ml or greater. Minimization of flow paths is essential to avoid product loss. Stability studies must also be factored in, since these can consume large quantities of product, depending on the fill configuration.[5]

Storage of viral vectors, which are typically liquid formulations, is usually at –80 °C (compared to –20 °C for mAbs) and also requires different container and packaging solutions. Vials and stoppers must maintain their integrity for extended periods of time at ultra-low temperatures, and materials commonly used for conventional biologics are often not suitable or compatible.

Despite these differences, expertise in traditional biologics manufacturing is applicable to the production, handling and manipulation of viral vectors.

SIGNIFICANT INVESTMENTS AT BRAMMER BIO

Brammer Bio provides development, manufacturing and testing services for cell and gene therapies through a range of platform technologies, including pre-clinical process development, clinical process optimization, process scale-up, process and analytical qualification, and commercial supply. They also provide logistics and warehousing support for in-bound and outbound biomaterials.

On January 1, 2017, the company acquired a 69,000-sq.ft. manufacturing facility in Cambridge, MA and nearby 49,000-sq.ft. warehouse, and on-boarded around 100 employees with experience in phase III and commercial biologics production. This facility is being converted for large- and small-scale phase III and commercial manufacturing of gene therapy vector products. The company is also doubling its clinical capacity in Florida. All of this expansion is in response to increasing demand from the industry. In addition, Brammer has a facility in Lexington, MA, where it is developing plans for phase III and commercial production for modified cell therapies.

Manufacturing investments are significant. While the existing infrastructure at the facility in Cambridge, including utilities (water-for-injection, clean steam, waste stream management, etc.) are appropriate for viral vector manufacturing, the HVAC system and clean rooms require extensive modifications. The new clean rooms with single-pass air and one-way flows for materials, people and waste meet Class 10,000 standards for drug substances. The plant is also being equipped with isolator fill-finish systems for viral vector drug product manufacturing.

Importantly, Brammer is purposely incorporating dedicated manufacturing capabilities for both large- and small-volume production of viral vectors that the Brammer team has over a decade of manufacturing experience with. Extensive capabilities for process and product characterization are also being established. Brammer has selected a high-throughput mini-bioreactor system with the option for 24 or 48 mini-bioreactors to allow scale-down modeling for efficient process characterization, qualification and to support process validation.

The significant experience of the Brammer team, together with the implementation of single-use disposable technologies at Brammer's multiproduct facilities, provides significant flexibility with respect to the types of projects that can be completed and project scheduling, all while ensuring product quality. P

ABOUT THE AUTHORS

Mark R. Bamforth, MBA
President and CEO, Founder, Brammer Bio

In 2015, **Mark** founded Brammer Biopharmaceuticals, a cell and gene therapy CMO, subsequently merged in March 2016 with Florida Biologix to create Brammer Bio. Previously, Mark founded Gallus BioPharmaceuticals, a premier CDMO delivering clinical and commercial mammalian-based biopharmaceuticals. Mark spent 22 years in the U.K. and U.S., running global operations and a pharmaceutical CMO business for Genzyme Corp. He has a BS in chemical engineering from Strathclyde University and an MBA from Henley Management College.

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Dr. Snyder was the founder of Florida Biologix, which was spun out of the University of Florida in 2015 and merged to create Brammer Bio. Dr. Snyder has been investigating virus biology, vector development, cGMP manufacturing and analytical technologies, and viral vector–mediated gene transfer for over 30 years. Dr. Snyder received his doctoral degree in microbiology from The State University of New York at Stony Brook, and obtained his BA in biology from Washington University in St. Louis.

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ENHANCING RESPONSIVENESS WITH EMBEDDED FLEXIBILITY

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

In today's pharmaceutical marketplace, speed to market is absolutely crucial. CDMOs with built-in flexibility are ideally situated to help drug companies shorten development and commercialization time lines. Flexibility can take many forms — from rapid tech transfer within an internal network to agile manufacturing configurations and use of automation, to the ability to rapidly respond to changing market and customer needs.

NEED FOR A NEW LEVEL OF FLEXIBILITY

Responsiveness has always been a key expectation for contract manufacturers providing services to the pharmaceutical industry. Today, however, with increased competition, the growing importance of evidence-based medicine, the expanding focus on orphan drugs and rare diseases and the rising use of accelerated approval pathways, responsiveness alone is insufficient for meeting the needs of sponsor companies. Flexibility combined with responsiveness has become essential.

CDMOs must, in fact, find mechanisms for providing flexibility in all aspects of their operations. Drug companies of all sizes are now seeking service providers that can offer flexible deal structuring. They also need outsourcing partners with the capability to implement adaptable manufacturing configurations and production schedules. Rapid and efficient technology transfer, including formulation and process development when necessary, is also crucial to shortening project timelines.

Some of these capabilities — particularly flexibility in manufacturing operations, including technology transfer — are established over time and can be found at CDMOs with track records of excellent service performance. Others require investment in innovative technologies, such as state-of-the-art automation solutions, advanced management systems and a culture that encourages efficiency without compromising on quality and safety.

LEVERAGING BUILT-IN FLEXIBILITY AT SERVIER

Servier is a highly respected, globally recognized French pharmaceutical innovator and manufacturer, developing patient-centric, targeted therapies using advanced technologies. The company invests nearly 25% of its yearly turnover in R&D to ensure the development of the most advanced drug candidates in oncology, cardiology, metabolic diseases, neuropsychiatry and rheumatology. Its 11 facilities located around the world form a wide-ranging manufacturing and research network that supplies even the most challenged markets and patient populations. Since 1995, Servier has also produced generics through its Biogaran business unit, which currently sells more than 200 specialties and holds a 25% market share in France.

Considering the various implications of the significant changes occurring in the pharmaceutical industry in recent years, Servier Group sought a new operational model that would allow the company to convert its manufacturing division from a cost center into a profit center. Reducing costs and implementing lean management and operational excellence would not be sufficient. Leveraging its experience in supplying contract manufacturing services to the Biogaran business unit, which Servier has done for over 10 years, seemed a practical solution.

In 2015, therefore, Servier Group began to pursue the formation of Servier CDMO, a business unit that would capitalize on Servier's expertise in the development and synthesis of APIs, formulated products and extensive global resources as a large pharmaceutical company. We have established aggressive revenue goals and anticipate achieving the switch for manufacturing from a cost to a profit center within the next five years.

DEAL MAKING, ACCOMMODATING AND STRUCTURING

As part of a larger pharmaceutical manufacturer with extensive financial resources, Servier CDMO has significant flexibility when it comes to deal structuring and project implementation. Many smaller pharmaceutical companies have limited resources across the board and operate under highly constrained financial conditions. Servier CDMO recognizes this issue and, because of its position within Servier Group, is able and willing to participate in tailored financial arrangements that include a wide range of unique financial parameters to accommodate the needs of its customers.

For instance, Servier has worked with companies that have minimal cash reserves and thus have difficulty committing to regularly scheduled payments, but are pressured to get their candidates into clinical trials. For these customers, Servier CDMO issues invoices to match funding schedules. Without financial pressures, these sponsor companies are able to focus on the important tasks required for the development and testing of their candidate drugs.

With the deep financial resources of Servier Group, Servier CDMO is also in a position to invest in new technologies for clients, depending on the specific project details and facility situation. Investments of this type have occurred, for instance, at the Servier Russia and Servier Ireland facilities. This approach not only helps meet client needs, it allows Servier to develop additional capabilities with high market demand.

PRODUCTION PLASTICITY

Flexibility in production capabilities is also crucial in today's pharmaceutical industry. Rapid development and fast commercialization are necessary to remain competitive. It is becoming increasingly important for CDMOs to offer customers support with activities across the entire drug development lifecycle – on a global basis.

In addition, sponsor companies are seeking CDMOs that can accommodate projects with minimal waiting time. With many drug candidates developed for small, targeted patient populations, they also prefer service providers with multi-product manufacturing facilities that have demonstrated the ability to rapidly and safely switch between products, whether intermediates, APIs or formulated drugs. CDMOs that provide efficient and cost-effective analytical services are in demand as well.

Servier's ANPHARM plant in Warsaw, Poland, which provides development and manufacturing support to drug companies in the region, has invested heavily in these types of capabilities and services. Systems have been automated to improve flow, resulting in significantly reduced lead times. Efforts to minimize product changeover times have also been highly successful. The improvements have not gone unnoticed. In a recent independent benchmarking study, McKinsey & Co. identified ANPHARM's performance as best-in-class in on-time shipment in full (OTIF) against that of nearly 500 other sites.

TRANSFER FLEXIBILITY

Within the last 15 years, Servier Group has expanded its facilities from just four to 11, including the construction of plants in underserved markets such as Russia, China,

Brazil and Morocco. Importantly, all of the facilities were designed and constructed to meet the specific needs of Servier.

As these facilities were completed, many of the processes developed at the French historical plant of Gidy (near Orleans) were transferred to them so that products of equivalent quality could be manufactured and provided to the local markets. One consequence of this activity was the development of a highly efficient and effective technology transfer process. Customers of Servier CDMO benefit directly from this capability as projects can be transferred rapidly to one or more sites within the global Sevier network. This can be achieved by a dedicated and skilled team that has exercised this specialty for many decades now.

PRODUCT DEVELOPMENT

With over 60 years of experience developing and producing intermediates, APIs and formulated drug products, Servier Group has the flexibility to support projects at all stages of drug development and commercialization across numerous therapeutic classes. Over the past decades, the company has launched more than 50 products, developed from scratch. Of course, this count does not include numerous projects that have been stopped in the preclinical or clinical stages. This considerable amount of knowledge (an average of 25 molecules under development per year) will help Servier to reach its goal of launching one New Molecular Entity every three years. Servier CDMO will use this experience to help its client's achieve their own success.

MARKET FLEXIBILITY

With access to several state-of-the-art, multiproduct facilities located in both mature and developing markets around the world, Servier CDMO offers its clients tremendous flexibility to reach their customers, whether they are distributors, hospitals or patients. Local experts at each facility also have extensive knowledge of regulatory requirements, from quality to import expectations.

Currently the top-producing sites for Servier Group include China, Russia, France and Ireland. Growth is anticipated in many of the younger markets, including Russia and Africa. In Russia, for instance, beginning in 2020, manufacturers must produce the drug product locally in order to be included on the government list of drugs approved for reimbursement.

Africa is also a rapidly growing market that Servier Group (and consequently Servier CDMO) are continually investing in. The company has plants in both Morocco and Egypt that supply all of Africa, including both branded products and products manufactured for Biogaran. Notably, all the same equipment and systems as those used in EU sites have been implemented at these facilities, which are inspected by French and other regulatory authorities.

EXPANDING CAPABILITY

Investments are not only taking place at global Servier sites. The company is moving into the biopharmaceuticals space with the construction of a biologics workshop at a cost of nearly $40 million for the development of monoclonal antibodies and cell therapies. A portion of the facility, which will be completed some time in 2019, will be dedicated to projects conducted in collaboration with universities.

WITHIN THE LAST 15 YEARS, SERVIER GROUP **HAS EXPANDED ITS FACILITIES FROM JUST FOUR TO 11, INCLUDING THE CONSTRUCTION OF PLANTS IN UNDERSERVED MARKETS** SUCH AS RUSSIA, CHINA, BRAZIL AND MOROCCO.

Expansion of capacity for the production of highly potent APIs and final drug products is also underway in France, Spain, Ireland and other sites around the world. The first projects will be completed in the beginning of 2017, with the remainder up and running by the end of 2017 and the beginning of 2018.

The addition of the biologics workshop and further high-potency capacity make Sevier CDMO an even more flexible outsourcing partner. These investments are intended to address clear gaps in the marketplace and designed to help our customers accelerate the development and commercialization of novel therapies that will meet significant unmet patient needs.

EMBEDDED FLEXIBILITY

Flexibility to meet changing customer needs is imperative for the success of CDMOs serving the pharmaceutical market. More than simple flexibility, Servier CDMO offers embedded flexibility – flexibility backed by the resources and operational, technical and regulatory expertise of an internationally recognized pharmaceutical manufacturer. Servier's embedded flexibility includes flexibility for deal structuring, flexibility within scheduling, flexibility of manufacturing technologies, flexibility to rapidly transfer projects and flexibility to support a wide range of products for both mature and emerging markets, including those where few other CDMOs operate. P

ABOUT THE AUTHOR

Gwenaël Servant, Ph.D.
Managing Director, Servier CDMO

Gwenaël has more than 18 years of experience in the pharmaceutical industry. He started as an R&D chemist at Servier's main API production site, then moved to the head office at the Industry Division of Servier to harmonize relations between the corporate level and the industrial site, for drug substance as well as drug product. Gwenaël has contributed to the creation of the business unit "Servier CDMO." He is now in charge of managing it.

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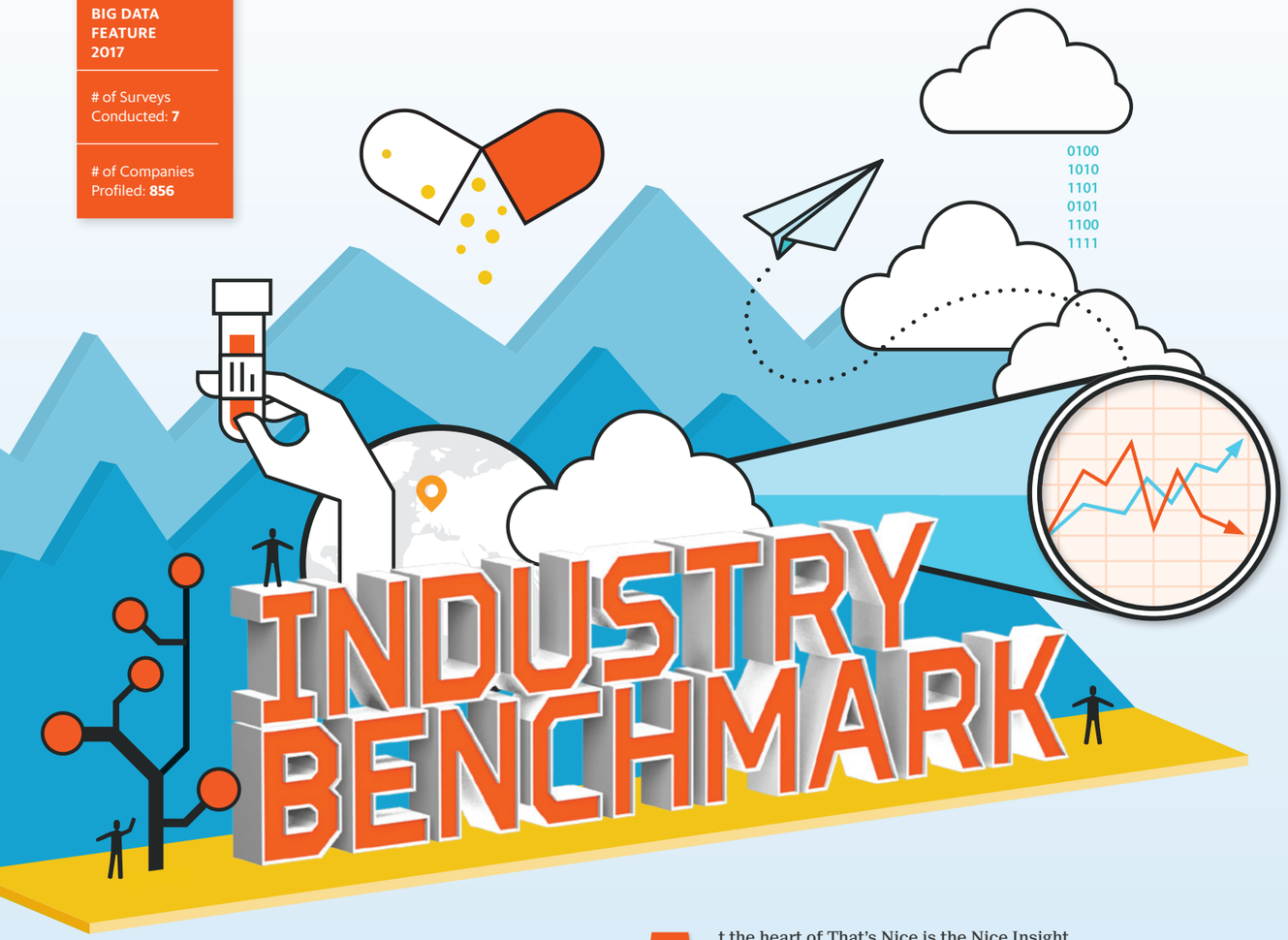
BIG DATA FEATURE 2017

# of Surveys Conducted: **7**

# of Companies Profiled: **856**



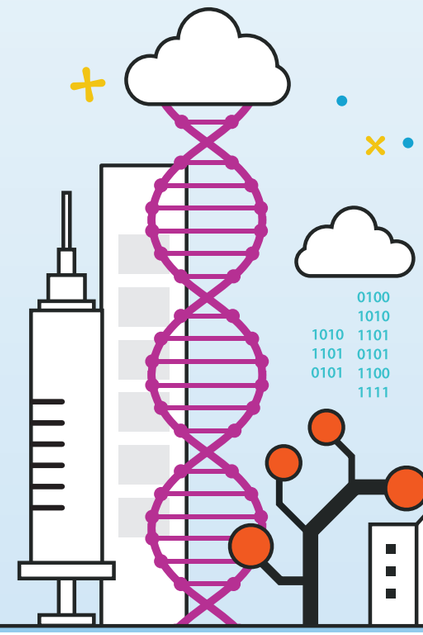
Findings from **7 Nice Insight global industry surveys** covering outsourced products and services, equipment, and private equity funding provided by over 440 different companies.

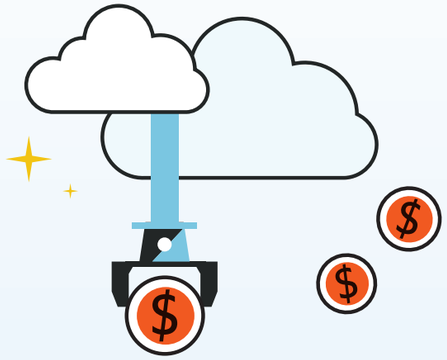
At the heart of That's Nice is the Nice Insight division, which provides data and analysis from proprietary annual surveys as well as custom primary and secondary research of many kinds. Nice Insight is tasked every year with conducting a series of surveys, which offer unique insight into what companies in the pharmaceuticals and biotechnology sectors see as the key trends and drivers in their business.

In this feature, we summarize the results – and 'summarize' is an understatement for the few words used to overview the vast array of data comprised in the reports, which cover over 856 providers of outsourcing services that we track. The longest-established surveys are now seven years old and we are continually adding to the list.

With the obvious exception of the 2017 Nice Insight Life Sciences Private Equity/Venture Capital Investment Survey, these draw on answers from a basically similar group of relevant senior executives to bring together a complete picture of the market landscape.

In each of the articles that follow, a survey profile is drawn from a representative sample of companies both geographically (North America, Europe and Asia) and size of company (large, medium-sized and small pharma/biotech companies). They are also rigorously profiled to ensure that every respondent has deep knowledge of the particular section of the market s/he is talking about.





In each case, too, you will learn what the key drivers are for assessing, then selecting and also evaluating suppliers, the kinds of products and services sponsors currently require, how they anticipate their needs will evolve over time, the stages of the development chain they are most prone to outsourcing, what attributes are most important in maintaining a relationship, the main reasons dissatisfaction may occur, and much more.

The full reports, of course, go into much more detail; for instance, do makers of small-molecule APIs expect their consumption of coloring agents to increase over the next three years? The answer is in there: 38% say it will increase, 45% say it will stay the same and 17% say it will decrease. And that is just one statistic.

Summarizing here what has already been summarized in the following articles would be to take things to the extreme. Suffice to say that the results are not always what conventional wisdom might say.

Demand for seemingly basic products such as excipients and intermediates remains surprisingly buoyant, and the 'CDMO' trend is far more than hype. Suppliers of preclinical and clinical contract research services face challenges to broaden their consumer base. Meanwhile, changes in the kinds of drugs being developed are greatly impacting the kind of equipment and clinical supply services the industry needs.

For a host of **greater insights**, please read on...

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Andrew Warmington, Ph.D.
Executive Content Director


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Scientific Content Director


Steve Kuehn
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Emilie Branch
Strategic Content Manager


Carrie Cao, Ph.D.
Scientific Contributor

CDMO SURVEY RESPONDENTS PROFILE

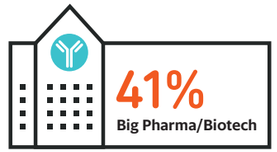
# of Survey Respondents: **702**

# of Companies in the Study: **163**

By Region

38% Europe
North America 33%
Asia 29%

By Company Size



Midsized Pharma/Biotech 36%
Small Pharma/Biotech 20%
Emerging Pharma/Biotech 3%

41% Big Pharma/Biotech

By Department

The Majority of Respondents Surveyed Were at the Executive Level.

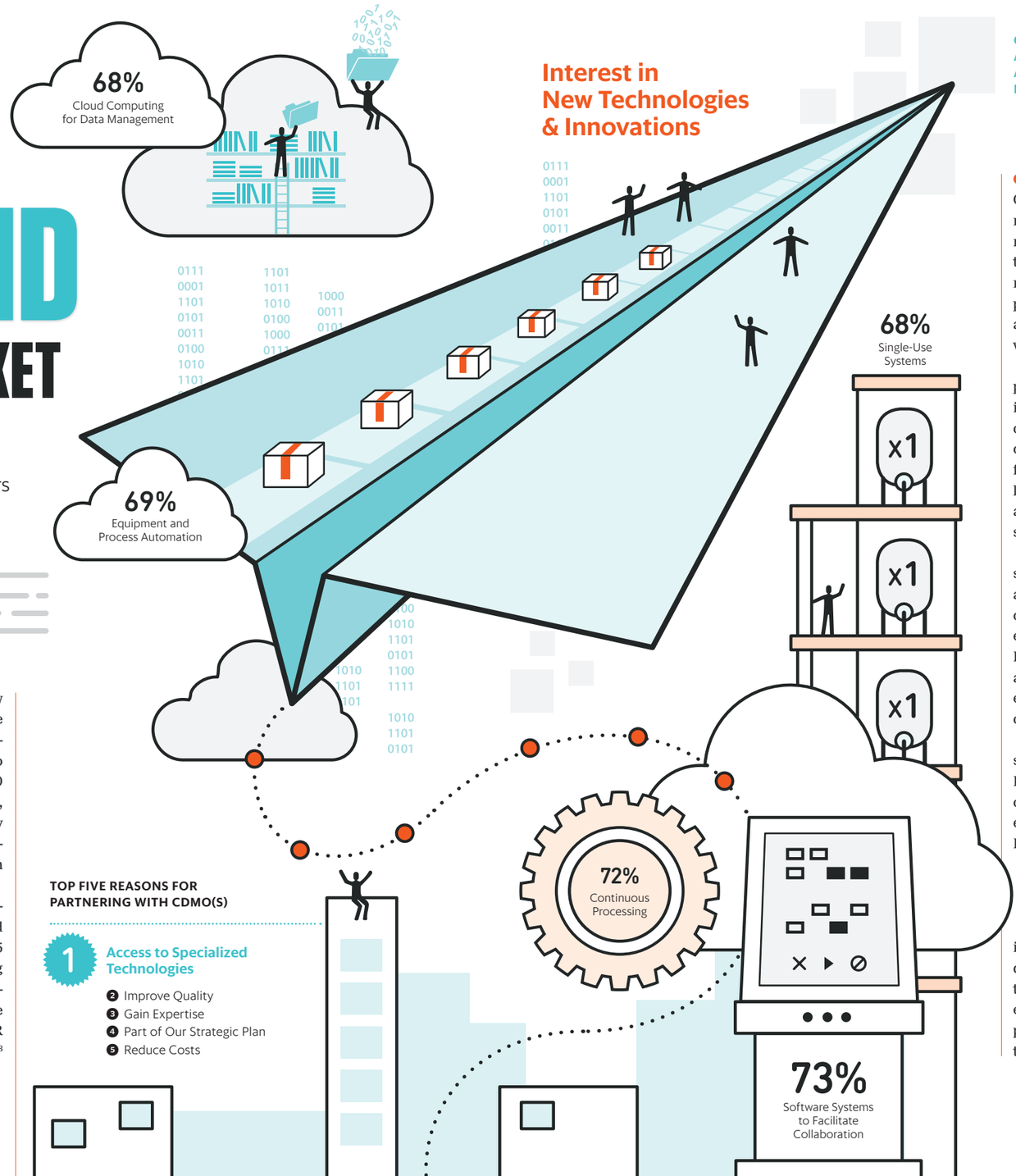
37% Corporate Management

17% Quality Assurance/ Quality Control

R&D/Formulation/Analytical	11%
Drug Development/Production/Manufacturing	11%
Operations/Engineering	8%
Contracting/Sourcing/Purchasing	8%
Regulatory Affairs	5%
Clinical Trials Operations/Management	2%
Preclinical Operations	1%

CHANGES IN THE WIND FOR THE CDMO MARKET

Demand for contract development and manufacturing services remains strong, but initial results from the 2017 Nice Insight CDMO survey suggest that service providers will find the marketplace increasingly competitive.



OVER TWO-THIRDS OF SURVEY RECIPIENTS ARE INTERESTED OR VERY INTERESTED IN A NUMBER OF NEW TECHNOLOGIES THAT IMPACT DAY-TO-DAY OPERATIONS.

The global pharmaceutical market continues to grow at a healthy rate. According to research firm Evaluate Pharma, the global drug market will expand at a compound annual growth rate (CAGR) of 6.3% from 2016 to 2022, with biologics accounting for 50% of the top 100 products by the end of the study period. Meanwhile, global R&D spending in the pharmaceutical industry will see a 2.8% CAGR. By 2022, half of the added revenues will be contributed by new products currently in the R&D pipeline.[1]

Strong demand for APIs is also expected. Mordor Intelligence estimates the global API market will expand at a CAGR of 6.5% from $154 billion in 2015 to $225 billion in 2021.[2] These growth rates are in turn driving growth in the global pharmaceutical contract manufacturing market, including APIs and finished dosage forms, which Mordor predicts will increase at a CAGR of 6.4% from $58 billion in 2016 to $84 billion in 2021.[3]

CHANGING CONDITIONS

Growth is not the only change occurring in the pharmaceutical industry or the contract development and manufacturing sector, however. Pricing pressures continue to mount as governments seek mechanisms for reducing healthcare costs by lowering the cost of expensive new (particularly biologic) medicines. Patients and payers are also looking for evidence of added value in new treatments.

Being first to market with the safest, highest-performing, most cost-effective products has become increasingly crucial to success for pharmaceutical companies and is creating the need for highly efficient and responsive contract development and manufacturing organizations (CDMOs) that can serve as long-term partners. Access to novel technologies for addressing drug delivery challenges is also a necessity today.

The top reasons for outsourcing to CDMOs are, not surprisingly, changing as a result. Initially, outsourcing activities were largely driven by the desire to reduce costs. That has changed significantly. Cost was not even a top-five factor for respondents to the 2016 Nice Insight CDMO Outsourcing survey.[4] Improving quality and efficiency, gaining competitive advantage and operational or technical expertise, and reducing the risk of supply shortages were identified most frequently.

In 2017, drivers are different yet again. The top reason for outsourcing for participants in the 2017 Nice Insight CDMO Outsourcing survey is access to specialized technologies.[5] Improving quality and gaining expertise remain important to survey respondents. However, the other two top-five reasons also changed: outsourcing has become a strategic activity, and cost has once again become a factor.

It is also interesting to note that over two-thirds of survey recipients are interested or very interested in a number of new technologies that impact day-to-day operations, including software systems to facilitate collaboration (73%), continuous processing (72%), equipment and process automation (69%), cloud computing for data management (68%) and single-use systems (68%).

Respondents expect to decrease (52%) rather than increase (39%) spending on contract development and manufacturing services over the next five years

Annual Outsourcing Expenditure

More than $100M	21%
$51M to $100M	35%
$10M to $50M	32%
Less than $10M	7%

The Most Popular Methods Used to Select an Outsourcing Partner

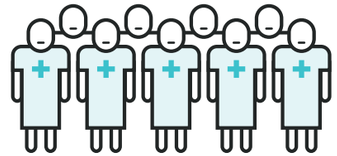
46% Industry Research

Consultants	41%
Trade Shows/Events	37%
Referrals/Colleagues	36%
Online Directories	34%
Web Searches	33%
Periodicals/Publications	33%

Use of Outsourcing Partners by Phase

47% Phase I

Preclinical	38%
Phase II	44%
Phase III	34%
Phase IV/Postlaunch	21%



Therapeutic Areas of Focus

42% Cardiovascular Diseases

Infectious Diseases	39%
Metabolic Disorders	38%
Respiratory Diseases	38%
Endocrine Diseases	34%
Oncology Diseases	34%
CNS Disorders	27%

The 2017 Nice Insight CDMO Survey results are based on input from over 700 pharmaceutical industry professionals representing all sizes of pharmaceutical and biotech companies (41% large, 36% medium-sized, 20% small and 3% emerging) from around the world (Europe 38%, North America 33%, Asia 29%). These companies are engaged in the development of all major forms of medicines.

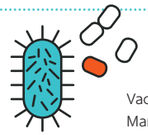
More than a third of the individual respondents (37%) hold management (CEO, COO, CSO, SVP, VP) positions. In addition, 8% or more of respondents serve in quality, R&D, development, manufacturing, engineering and sourcing.

CHANGING SPENDING EXPECTATIONS

Perhaps the most notable differences between survey results from 2016 and 2017 are the changes in the level of spending on CDMO services and the expectations for spending in the future. While 71% of respondents to the 2016 Nice Insight CDMO Outsourcing survey had outsourcing expenditures of $50 million/year or more, just 56% of 2017 survey participants indicated this high level of spending.

Furthermore, more respondents to the 2017 survey expect their companies to decrease (52%) rather than increase (39%) spending on CDMO services over the next five years; in 2016, 75% predicted higher expenditures, with just 4% forecasting reduced spending.

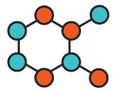
RESPONDENTS WHO OUTSOURCED BIOMANUFACTURING SERVICES



Microbial Cell Line-Based 48%

Vaccines	46%
Mammalian Cell Line-Based	43%
Cell and Gene Therapy	37%
Advanced Antibody-Based Products	23%

PRODUCTS OUTSOURCED TO CDMOs BY TYPE



Small-Molecule NCEs 25%

Large-Molecule NBEs	21%
Small-Molecule Generics	21%
Large-Molecule Biosimilars	17%
OTC Drugs	16%

RESPONDENTS WHO OUTSOURCED DRUG PRODUCT PACKAGING SERVICES

44% Commercial-Scale Primary Packaging

Clinical-Scale Secondary Packaging	39%
Labeling	38%
Clinical-Scale Primary	34%
Bottling	34%
Tubes, Pouches & Stick Packs	34%
Child-Resistance & Compliance Packaging	34%

RESPONDENTS WHO OUTSOURCED DRUG DELIVERY ENHANCEMENT SERVICES

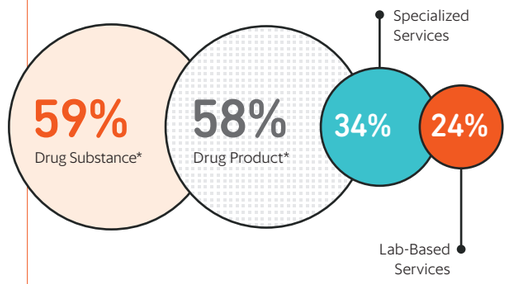
45% Develop controlled-release formulations

Bioavailability-enhancing excipients	42%
Solvent-capable rotor processors	34%
Fluid bed rotor processors	35%
Wurster column bead drying, layering and coating	36%

On the other hand, more than half (55%) of respondents to the 2017 survey expect their companies to increase the number of CDMOs they partner with. An additional 40% expect the number to remain the same. Respondents work for drug manufacturers that contract with as many as 30 CDMOs: 38% work with up to 10, 39% with 10 to 20 and 23% with 21 to 30.

% OF RESPONDENTS WHO OUTSOURCED EACH SERVICE CATEGORY

*R&D and Manufacturing – Both Small- and Large-Molecule



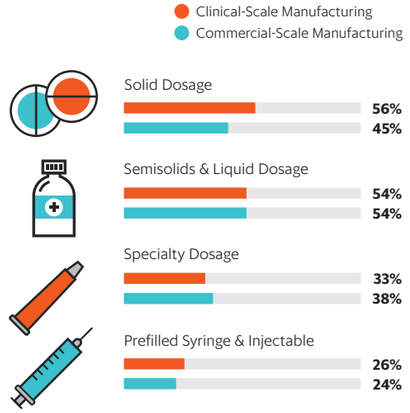
WHAT IS BEING OUTSOURCED?

Despite the reduced level of spending in 2016, drug manufacturers continued to outsource a wide range of project types. CDMOs were used most frequently for the development and manufacture of small-molecule APIs and final products, including both new chemical entities (25%) and generics (21%). New biological entities were also outsourced by approximately one-fifth of survey participants (21%). Projects related to biosimilars and over-the-counter (OTC) medicines were least likely to be outsourced (17% and 16%, respectively).

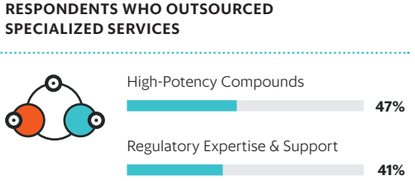
Outsourcing partners were engaged at all phases of development, with phase I and II projects most common (47% and 44%, respectively), followed by preclinical (38%), phase III (34%) and phase IV and postlaunch (21%) projects. This trend is not surprising, given the high attrition rate for drug candidates as they move further along the development cycle.

Outsourcing has become a strategic activity and **cost has once again become a factor.**

RESPONDENTS WHO OUTSOURCED DRUG PRODUCT SERVICES



RESPONDENTS WHO OUTSOURCED SPECIALIZED SERVICES



With respect to the types of services sought by survey participants, drug product (58% of respondents) and drug substance research, development and manufacturing services (59% of respondents) were equally in demand. Specialized services, including those required for highly potent compounds and controlled substances, as well as sterile or contained manufacturing and regulatory compliance support, were used by 34% of survey participants. One-quarter of respondents used laboratory services for analytical and stability testing, pre-formulation and formulation studies, process development, optimization and scale-up work.

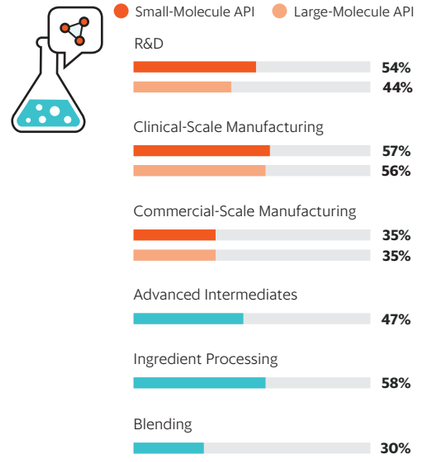
CDMOs used for drug product services were pursued most frequently for clinical- and commercial-scale solid, semisolid and liquid dosage manufacturing support (45% or more of respondents). Outsourcing of prefilled syringe and injectable dosage form manufacturing was conducted by approximately one-quarter of survey participants.

The most commonly needed services for drug substance development (more than half of respondents) included ingredient processing, clinical-scale manufacturing of small- and-large molecule APIs, and small-molecule API ingredient R&D. For projects related to biopharmaceuticals, CDMOs were most frequently obtained by survey participants for assistance with microbial cell line, vaccine and mammalian cell line development and manufacturing.

Both drug product packaging and drug delivery enhancement services were also widely cited. Commercial-scale primary and clinical-scale secondary packaging were the most commonly used services. At least a third of survey participants are seeking solutions for labeling; clinical-scale primary packaging; commercial-scale secondary packaging; the production of tubes, pouches and stickpacks; and the development of child-resistance and compliance packaging.

With respect to geographic location, outsourcing by respondents takes place around the globe. Slightly below or above one-quarter of survey participants have 6%–10% of their outsourcing projects in all regions and countries covered by the survey: Brazil and Argentina, China, Eastern Europe and Turkey, India, Japan, the Middle East, Singapore and Southeast Asia, the U.S. and Canada, and Western Europe.

RESPONDENTS WHO OUTSOURCED DRUG SUBSTANCE SERVICES



TYPES OF BIOLOGICS INCLUDED IN RESPONDENTS' PRODUCT PIPELINE

51% Vaccines

Antibody Drug Conjugates	42%
Blood Factors	46%
Hormones	44%
Growth Factors	44%
Interferon	37%
Monoclonal Antibodies	42%
Interleukins-Based Products	41%
TNF Factors	37%

RESPONDENTS WHOSE BUSINESS IS ENGAGED IN THE DEVELOPMENT OF BIOLOGICS

51% New Biological Entities (NBE)

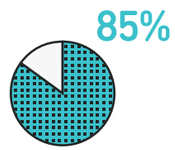
33% Biosimilars

75% of respondents felt it was likely that a preferred provider would become a strategic partner, while 66% agreed that a CDMO that started off as a tactical service provider would likely become a preferred provider.

Projects Contracted to Each Type of Outsourcing Relationship

Tactical Service Provider	32%
Preferred Provider	42%
Strategic Partnership	26%

85% of respondents based in the U.S. were either very interested or interested in becoming involved in a strategic partnership with a CDMO in the next 12-18 months.



WHAT MATTERS TO SPONSORS

Faced with solubility and bioavailability challenges for novel small-molecule drugs and a keen desire to develop oral dosage forms for biologics, sponsor companies seek innovative CDMO partners with proprietary technologies that also have the flexibility to respond quickly to constantly changing market conditions and stakeholder expectations.

For that reason, drug manufacturers carefully consider many different characteristics when initially evaluating CDMOs. Approximately 70% of respondents identified a positive regulatory compliance track record, having an understanding of customer requirements, experience (operational, methodological and therapeutic), financial stability, industry reputation, cost, assurance of intellectual property protection, and risk adherence as important attributes that factor into the selection process.

After engaging a CDMO, sponsor companies continue to evaluate the performance of the supplier against a different set of expectations. Top attributes considered at this stage of the relationship include good communication and transparency, on-time delivery, quality compliance, responsiveness when problems arise, performance on safety and compliance audits, meeting project deliverables, customer service, and the willingness of the CDMO to go beyond requirements.

Patients and payers are also looking for **evidence of added value** in new treatments.

Survey participants also identified several areas where CDMOs did not perform to expectations. The top five sources of dissatisfaction were the unavailability of products and services, poor product or service quality (previously the top issue), incomplete and untimely completion of documentation, inadequate maintenance of security or confidentiality, and cost overruns.

Some of these issues are sufficiently serious to drive sponsor companies to switch to another CDMO, which involves significant project delays and additional costs. One-third or more of respondents would change CDMOs to obtain better quality, pricing and timeliness.

Despite the expectation of respondents that their companies will increase the number of CDMOs they work with in the near future, 88% of all survey participants were either very interested or interested in becoming involved in a strategic partnership with a CDMO in the next 12-18 months. In addition, 75% felt it was likely that a preferred provider would become a strategic partner, while 66% agreed that a CDMO that started off as a tactical service provider would likely become a preferred provider. P

ATTRIBUTES THAT FACTOR INTO CDMO ENGAGEMENT (IMPORTANCE)

INITIAL EVALUATIONS

Regulatory Compliance	72%
Understanding of Customer Requirements	72%
Operational, Methodological & Therapeutic Experience	72%
CDMO/CMO Industry Reputation	71%
Cost	71%
Contractual Approach – Assured IP Protection	70%
Risk Adherence	70%

POST-ENGAGEMENT

75%	Good Communication & Transparency
74%	On-Time Delivery
74%	Quality Compliance
74%	Responsiveness in Case of Troubleshooting
74%	Safety Audits
73%	Willingness to Go Above & Beyond the Requirements
73%	Meeting Project Deliverable(s)

TOP THREE SOURCES OF DISSATISFACTION

1. **Products / Services Availability**
2. Product / Service Quality
3. Documentation Completion & Timeliness

OF CDMO PARTNERSHIP

38% Less than 10

39% 10 to 20

23% 21 to 30

FUTURE OF CDMO PARTNERSHIPS

55% Increase

40% Remain the same

2% Decrease

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3. *Global Pharmaceutical Contract Manufacturing Market – Trends & Forecasts (2016–2021).* Rep. Mordor Intelligence. Aug. 2016. Web.
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CRO SURVEY RESPONDENTS PROFILE

# of Survey Respondents: **608**

# of Companies in the Study: **73**

By Region

45% Europe

North America **37%**

Asia **18%**

By Company Size

40% Big Pharma/Biotech

Midsized Pharma/Biotech **34%**

Small Pharma/Biotech **20%**

Emerging Pharma/Biotech **6%**

By Department

The Majority of Respondents Surveyed Were Key Decision Makers.

31% Corporate Management

16% R&D/Formulation/Analytical

Clinical Trials Operations/Management	12%
Quality Assurance/Quality Control	15%
Regulatory Affairs	4%
Preclinical Operations	6%
Contracting/Sourcing/Purchasing	8%
Other	8%

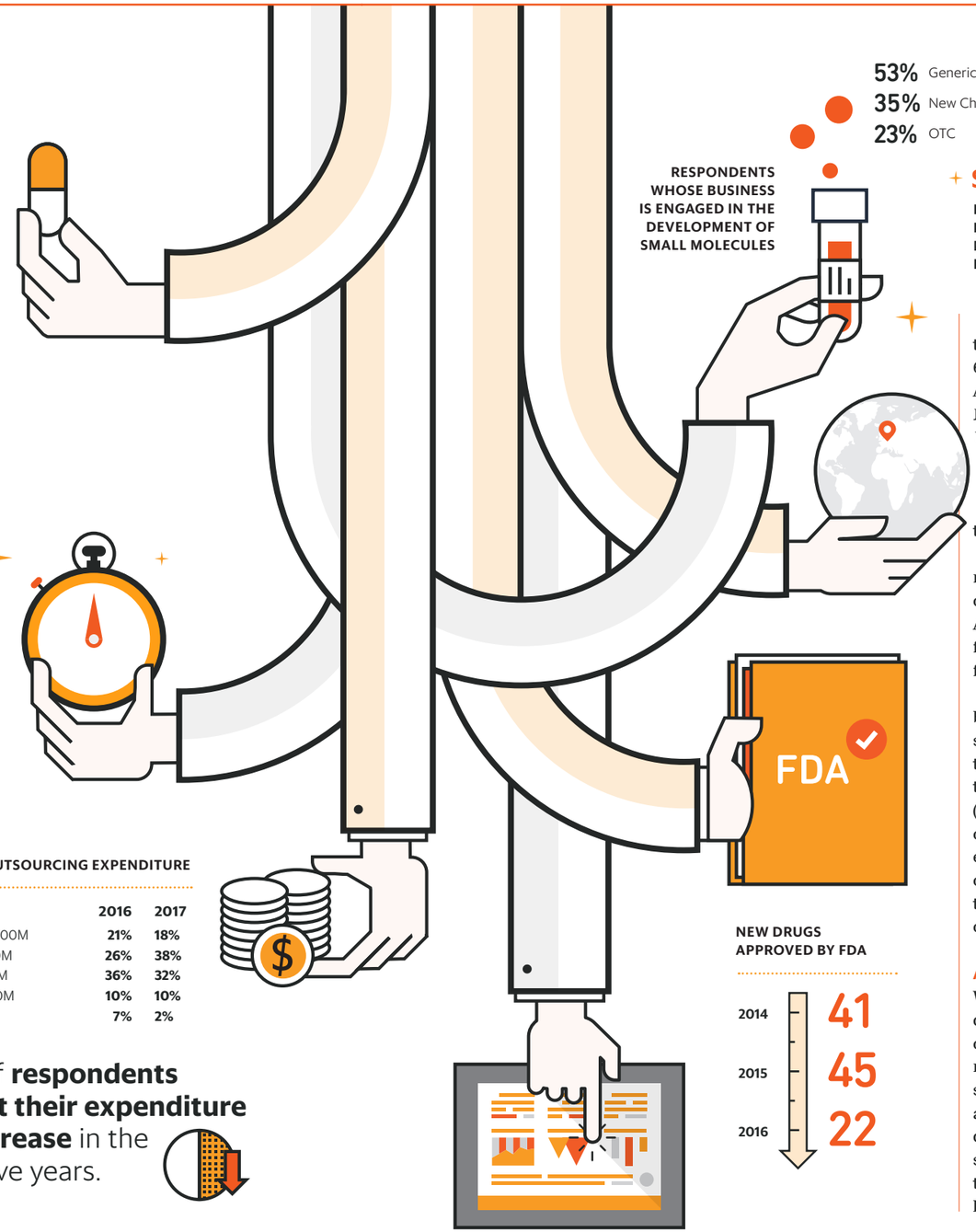
SPENDING ON CONTRACT RESEARCH SERVICES SLOWING DOWN

The results for the 2017 Nice Insight CRO survey are in. This year is different from others as there is a dramatic downward shift in spending by survey participants, with reductions in spending expected to continue over the next five years.

The 2017 Nice Insight Clinical Research Organization (CRO) Outsourcing Survey[1] includes input from 608 outsourcing-facing pharmaceutical and biotechnology executives. The majority of the respondents are key decision makers; nearly one-third (31%) hold corporate or management positions, with an additional 12% responsible for clinical trials operations and management.

R&D and formulation/analytical departments, as well as quality assurance and quality control departments, are well represented (16% and 15%, respectively). Other respondents hold positions in contracting, sourcing and purchasing; preclinical operations; and regulatory affairs (8%, 6% and 4%, respectively).

Respondents come from around the world (Europe 45%, North America 37%, Asia 18%) and work for all sizes of pharmaceutical companies. While the majority of survey participants work for large pharma and biotech firms (40% are working for firms with over $5 billion/year in sales), midsized ($500 million to $5 billion), small ($100-$500 million) and emerging (<$100 million) pharma and biotech organizations are well represented, with 34%, 20% and 6% of respondents, respectively.



ANNUAL OUTSOURCING EXPENDITURE

	2016	2017
More than $100M	21%	18%
$51M to $100M	26%	38%
$10M to $50M	36%	32%
Less than $10M	10%	10%
Don't Know	7%	2%

50% of **respondents expect their expenditure to decrease** in the next five years.

NEW DRUGS APPROVED BY FDA

2014	41
2015	45
2016	22

RESPONDENTS WHOSE BUSINESS IS ENGAGED IN THE DEVELOPMENT OF SMALL MOLECULES

53% Generics

35% New Chemical Entities (NCE)

23% OTC

Small-Molecule Generics

DESPITE THE CONTINUED GROWTH IN THE NUMBER OF BIOLOGIC COMPOUNDS IN THE CANDIDATE PIPELINE, MORE SURVEY RESPONDENTS WORK FOR COMPANIES INVOLVED IN THE DEVELOPMENT OF SMALL MOLECULES

Furthermore, outsourcing takes place all around the globe. At least 20% of survey participants have 6%-10% of their outsourcing projects in Brazil and Argentina, China, Eastern Europe and Turkey, India, Japan, the Middle East, Singapore, Southeast Asia, the U.S. and Canada. In addition, 19% of respondents also have 6%-10% of their projects in Western Europe. These statistics indicate that the survey data should well reflect the current trends and issues occurring in the global pharmaceutical contract research market.

Over one-third of respondents represent companies pursuing the development of new drugs to treat cardiovascular, infectious and respiratory diseases. An additional third work for pharmaceutical manufacturers focused on metabolic disorders and various forms of cancer.

Despite the continued growth in the number of biologic compounds in the candidate pipeline, more survey respondents work for companies involved in the development of small-molecule generics (53%) than large molecules, including new biologic entities (NBEs, 43%) and biosimilars (32%). Meanwhile, 35% of survey participants work for drug manufacturers engaged in the development of new medicines based on small-molecule new chemical entities (NCEs), with the remaining 23% involved in the development of over-the-counter products.

ACCESS TO TECHNOLOGY DRIVING CRO USE

While initially many companies outsourced research, development and manufacturing activities to reduce costs, this is no longer a top driver. Nearly one-third of respondents to the 2017 Nice Insight CRO Outsourcing survey (32%) listed access to specialized technologies as the main reason they partner with CROs. They also desire to improve quality (12%), have incorporated outsourcing in their strategic plans (11%), look for operational and subject matter expertise (9%) and seek to leverage the regulatory expertise of CROs (7%).

The Most Popular Methods Used to Select an Outsourcing Partner

47% Industry Research

Consultants	39%
Referrals/Colleagues	38%
Periodicals/Publications	33%
Web Searches	33%
Trade Shows/Events	30%
Online Directories	28%
Others	1%

Average Number of Methods Used to Select an Outsourcing Partner

2.5

Rank of Industry Drivers

1. Reliability
2. Quality
3. Productivity
4. Innovation
5. Affordability

Use of Outsourcing Partners by Phase

47% Phase II

Preclinical	37%
Phase I	42%
Phase III	32%
Phase IV/Postlaunch	22%

Therapeutic Areas of Focus

40% Cardiovascular Diseases

Infectious Diseases	38%
Respiratory Diseases	36%
Metabolic Disorders	33%
Oncology Diseases	33%
Endocrine Diseases	29%
CNS Disorders	28%

CROs can have a **significant impact on the overall timeliness and cost** of a development project; it is essential to find a CRO that not only has the desired technical capabilities, but can act as a true partner and serve as an extension of the sponsor company.

RESPONDENTS WHOSE BUSINESS IS ENGAGED IN THE DEVELOPMENT OF BIOLOGICS

43% New Biological Entities (NBE)

32% Biosimilars

OUTSOURCING PRACTICES BASED ON MOLECULE TYPE

25% New Chemical Entities (NCE)

- Generics **22%**
- New Biological Entities (NBE) **21%**
- Biosimilars **16%**
- Over-the-Counter Medications (OTC) **16%**

Interestingly, although more respondents work for companies involved in the development of biopharmaceuticals, more of the sponsor firms represented by survey participants outsource small-molecule than large-molecule projects: 25% and 22%, respectively, outsource NCEs and generics, while 21% and 16% look for research assistance for NBEs and biosimilars. These numbers are consistent with past outsourcing behavior: drug manufacturers have historically been less likely to use contract service organizations for biopharmaceuticals.

With respect to different phases of the development cycle, survey respondents most frequently outsource to CROs during phase II (47%), phase I (42%) and the preclinical stage (37%). Reduced outsourcing at later stages likely reflects the attrition of projects; far fewer candidates enter phase III and IV trials. Based on these results, it is not surprising that clinical trial services are most often outsourced by survey respondents (64%), followed by preclinical trial services (58%) and specialized services (29%), including process development and scale-up, research (animal) models, *in vitro* assays and regulatory services.

CAREFUL SELECTION OF PARTNERS

Choosing a CRO is not a trivial exercise. CROs can have a significant impact on the overall timeliness and cost of a development project; it is essential to find a CRO that not only has the desired technical capabilities, but can act as a true partner and serve as an extension of the sponsor company. According to the 2017 Nice Insight CRO survey, industry research, consultants and referrals from colleagues are most often used to identify potential CRO partners. To ensure quality, sponsors are using more methods to identify new partners.

The top industry drivers for respondents when selecting a CRO on a weighted-mean basis are reliability, quality, productivity, innovation, affordability and regulatory track record. It is worth noting, however, that quality was the most frequently cited driver, with 43% of survey participants listing it as an important selection criterion.

Attributes identified most often by respondents as very important factors during initial CRO evaluations include operational, methodological and therapeutic experience (38%), regulatory compliance (34%), having an understanding of customer requirements (34%) and cost (30%).

Once a sponsor company has engaged a CEO, other attributes become important. Those most frequently indicated by survey participants to be very important include quality compliance and on-time delivery. These two factors, along with communication and transparency and meeting project deliverables, were noted as somewhat or very important by 74% of respondents.

The top sources of dissatisfaction with CROs are product and service availability, quality and documentation completion, and timeliness. CROs should take performance in these areas seriously, as they are also factors that will prompt sponsor companies to switch to another provider. Top reasons for doing so as identified by survey participants include better quality (41%), price (37%) and promised timeliness (30%), improved logistics (29%) and lower error rates (29%).

There is good news for those CROs that perform well: 68% of respondents felt it was highly likely that a preferred provider would become a strategic partner, while 62% of survey participants agreed that a CRO that started off as a tactical service provider would become a preferred provider. In addition, 86% of respondents were either very interested or interested in becoming a strategic partner with a CRO in the next 12-18 months.

DECLINE IN SPENDING UNDERWAY

Survey participants currently use a large number of service providers – 45% work with up to 10, 33% with 10 to 20 and 22% with 21 to 30. Notably, 48% of respondents expect the number of CROs they work with to increase, while 44% expect to continue with the same level of outsourcing.

On the other hand, the number of drug manufacturers spending more than $50 million/year on contract research services dropped noticeably from 56% in 2016 – which was itself more than double the proportion of previous years – to 47%. More importantly, while 40% expect their spending on outsourcing to CROs to increase, 50% predict it will decline in the next five years.

These numbers are quite different from those obtained for the 2016 Nice Insight CRO survey, in which nearly 75% of respondents expected spending to increase.[2] The reduced spending matches the significant drop in the number of new drugs approved by FDA in 2016 – down from 41 in 2014[3] and 45 in 2015[4] to just 22 in 2016[5] as of the end of the year.

Competition in the CRO marketplace appears to be tightening, making it increasingly important for CROs to meet the quality, reliability, timeliness and other expectations of sponsor firms looking to outsource discovery, preclinical and clinical research activities. P

MAIN REASONS TO PARTNER WITH CROs

Access to Specialized Technologies **32%**

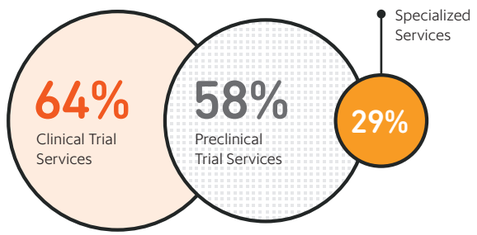
Improve Quality	12%
Incorporated Outsourcing in Strategic Plans	11%
Operational & Subject Matter Expertise	9%
Leverage Regulatory Expertise of CROs	7%

MAIN REASONS FOR SWITCHING CROs

Better Quality at Competing CRO **41%**

Better Price Offered by Competing CRO	37%
Better Timelines Promised by Competing CRO	30%
Improved Logistics	29%
Low Error Rate Compared to Current CRO	29%

% OF RESPONDENTS THAT OUTSOURCED EACH SERVICE CATEGORY



% OF RESPONDENTS THAT OUTSOURCED THE FOLLOWING SERVICES

CLINICAL TRIAL SERVICES

Clinical Trial Design	39%
Clinical Trial Phase I/IIa	39%
Clinical Trial Phase II/III	39%

PRECLINICAL TRIAL SERVICES

Bio-analytical Testing	49%
Analytical Testing	45%
General Toxicology	38%

SPECIALIZED SERVICES

Process Chemistry/Scale-up	44%
Research Models (animal models)	41%
Invitro Assays	40%

ATTRIBUTES THAT FACTOR INTO CRO ENGAGEMENT

INITIAL EVALUATIONS

- **38%** Operational, Methodological & Therapeutic Experience
- **34%** Regulatory Compliance
- **34%** Understanding of Customer Requirements
- **30%** Cost

POST-ENGAGEMENT

- **41%** Quality Compliance
- **40%** On-Time Delivery
- **35%** Communication & Transparency
- **35%** CRO Staff Knowledge
- **34%** Meeting Project Deliverable(s)

% OF PROJECTS CONTRACTED TO EACH TYPE OF OUTSOURCING RELATIONSHIP

25% Tactical Service Provider

50% Preferred Provider

25% Strategic Partnership

 # OF CRO PARTNERSHIPS

45% Less than 10

33% 10 to 20

22% 21 to 30

68% of respondents felt it was highly likely that a preferred provider would become a strategic partner, while 62% of respondents agreed that a CRO that started off as a tactical service provider would become a preferred provider.

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3. "Novel Drug Approvals for 2014." *U.S. Food and Drug Administration.* Web.
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5. "Novel Drug Approvals for 2016." *U.S. Food and Drug Administration.* Web.

EXCIPIENTS SURVEY RESPONDENTS PROFILE

# of Survey Respondents: **541**

# of Companies in the Study: **31**

By Region

38% Asia

North America	33%
Europe	29%

By Company Size

39% Midsized Pharma/Biotech

Big Pharma/Biotech	35%
Small Pharma/Biotech	19%
Emerging Pharma/Biotech	6%
CDMO	1%

By Department

Analytical	29%
Manufacturing	24%
Corporate Management	23%
Formulation	15%
Contracting/Sourcing/Purchasing	9%

By Job Title

Manager/Sr. Manager	26%
Analyst/Associate	15%
Director/Sr. Director	16%
Vice President/Sr. Vice President	6%
C-Level Executive	10%

27% Scientist/ Chemist

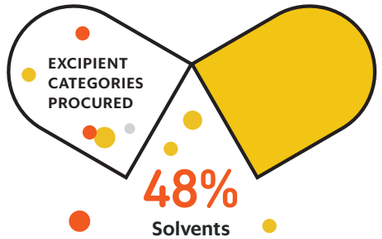
Purchase Authority

For Renewing Existent Supplier Contracts	87%
For Selecting and Approving New Supplier Contracts	87%

SPENDING ON EXCIPIENTS GROWS & DIVERSIFIES

The 2017 Nice Insight Pharmaceutical Excipients Survey demonstrates spending is expected to increase in all regions and across all categories.

Most excipient users expect their consumption to increase in the coming three years, both overall and in every major category of excipient. They also expect to broaden their supplier bases.



Coatings	38%
Solubilizers	38%
Thickeners	38%
Flavoring Agents	38%
Buffering Agents	36%
Preservatives	36%
Emulsifiers	36%
Diluents/Fillers	36%
Binders	36%
Coloring Agents	35%
Lubricants	34%
Disintegrants	30%
Antiadherent	24%
Humectants	24%
Combination of Excipients	20%
Glidants	20%

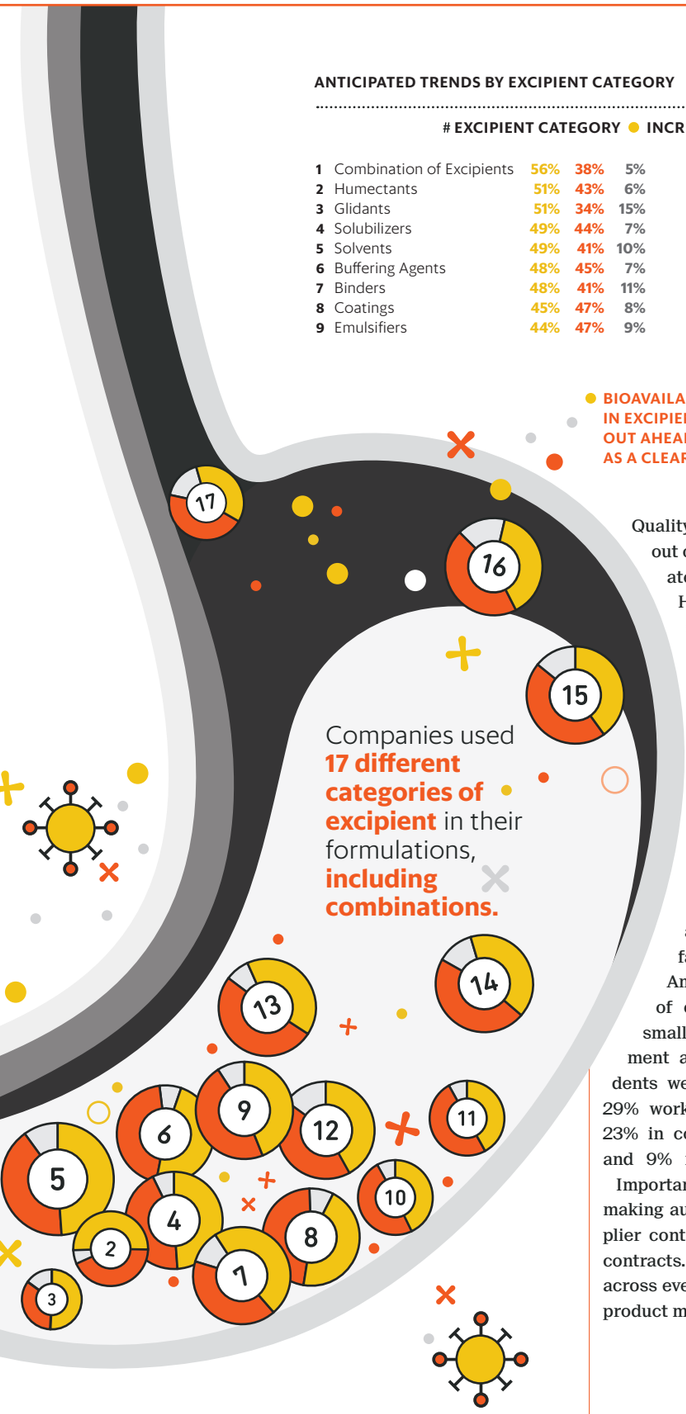
Pharmaceutical excipients are used in combination with APIs in multiple medicinal products, including tablets, capsules, oral liquids, transdermal patches, implants and inhalers. Traditionally, these excipients were used to add bulk to formulations. However, they are increasingly used for functional reasons, such as improving the wetting and organoleptic properties of a drug or providing stability.

According to Mordor Intelligence, the global pharmaceutical excipients market is expected to reach $9.9 billion by the end of 2021, increasing at a compound annual growth rate of around 7.2% from 2016. This will be driven by increasing demand for the drugs themselves, but also by innovation in the excipients and the techniques used to manufacture them.[1]

The 2017 Nice Insight Pharmaceutical Excipients Survey finds that companies across the pharmaceutical and biotechnology sectors worldwide use an extraordinary variety of excipients in their formulations, with no single category either dominant or insignificant in consumption terms.[2] Most excipient users expect their consumption to increase in the coming three years, both overall and in every major category of excipient. They also expect to broaden their supplier bases.

ANTICIPATED TRENDS BY EXCIPIENT CATEGORY

#	EXCIPIENT CATEGORY	INCREASE	SAME	DECREASE
1	Combination of Excipients	56%	38%	5%
2	Humectants	51%	43%	6%
3	Glidants	51%	34%	15%
4	Solubilizers	49%	44%	7%
5	Solvents	49%	41%	10%
6	Buffering Agents	48%	45%	7%
7	Binders	48%	41%	11%
8	Coatings	45%	47%	8%
9	Emulsifiers	44%	47%	9%
10	Disintegrants	43%	49%	8%
11	Antiadherent	42%	50%	8%
12	Lubricants	42%	43%	15%
13	Flavoring Agents	41%	51%	8%
14	Diluents/Fillers	41%	47%	12%
15	Thickeners	40%	46%	14%
16	Preservatives	39%	45%	16%
17	Coloring Agents	38%	45%	17%



BIOAVAILABLITY IS AN INTEGRAL FEATURE IN EXCIPIENTS; THE MANUFACTURER WHO COMES OUT AHEAD IN THIS GAME IS LIKELY TO EMERGE AS A CLEAR CHOICE FOR BUYERS.

Quality, in the broadest sense of the word, comes out on top when users are asked how they evaluate potential suppliers and rank existing ones. However, there is no single most important selection criterion. Naturally, cost matters, but it does not drive decisions very often, except when all other things are equal.

This industry segment includes some of the biggest general chemicals companies as well as small specialists. Name recognition does not harm the former, but it does not necessarily get them picked as suppliers either.

BROAD BASE

The survey was based on responses from a grand total of 541 respondents, spread fairly evenly by geography (33% in North America, 29% Europe, 38% Asia) and size of company (35% large, 39% midsized, 19% small, 6% emerging and 1% contract development and manufacturing organizations). Respondents were split in terms of their job titles, with 29% working in analytical, 24% in manufacturing, 23% in corporate management, 15% in formulation and 9% in contracting, sourcing and purchasing. Importantly, 87% of those polled had decision-making authority on renewing existing excipient supplier contracts and on selecting and approving new contracts. That proportion was consistently high across every region, type and size of company, type of product manufactured, and department worked in.

By Types of Product Manufactured

48% **Small Molecule Generics**

Large Molecule – New Biological Entities	39%
Small Molecule – New Chemical Entities	37%
Large Molecule – Biosimilars	34%
Over-the-Counter Medications (OTC)	28%

By Types of Dosage Form

65% **Oral Solid Dosage Form**

Non-Oral Solid Dosage Form	42%
Semisolid Dosage Form	49%
Liquid Dosage Form	46%

By Annual Outsourcing Expenditure

64% of respondents expect this number to increase in the next three years.

More than $100M	14%
$50M to $100M	19%
$10M to $50M	30%
$1M up to $10M	24%
Under $1M	8%

Therapeutic Areas of Focus

38% **Infectious Diseases**

Metabolic Disorders	37%
Cardiovascular Diseases	36%
Respiratory Diseases	36%
Oncology Diseases	35%
Endocrine Diseases	31%
CNS Disorders	27%

RESPONDENTS WHOSE BUSINESS IS ENGAGED IN THE DEVELOPMENT OF BIOLOGICS

42% New Biological Entities (NBE)

35% Biosimilars

RESPONDENTS WHOSE BUSINESS IS ENGAGED IN THE DEVELOPMENT OF SMALL MOLECULES

52% Generics

38% New Chemical Entities (NCE)

29% OTC Drugs

At least 29% and up to 52% of the companies where respondents work are involved in manufacturing one or more of five main product categories, i.e., branded and generic small molecules, branded large molecules, biosimilars and over-the-counter drugs. Likewise, at least 42% and up to 65% were active in the four main types of dosage form, i.e., oral and non-oral, solid, semisolid and liquid.

There was also a good spread in company size, with 23% and 12% respectively considered large pharma and biotechs (>2,500 employees), 25% and 14% respectively midsized pharma and biotechs (501-2,500) and 10% and 9% respectively small pharma and biotechs (<500). U.S. players in both fields were relatively more likely to be "big." On the other hand, Asian firms skewed more on the smaller side.

The companies in the survey are active across a wide and even spread of therapies, with drugs for infectious, metabolic, cardiovascular, respiratory, oncological, endocrine and central nervous system diseases in their pipelines.

These companies used 16 different categories of excipient in their formulations, plus combinations. The most important were solvents (used by 48%), coatings, solubilizers and thickeners (all about 38%). Even the least common were used by over one-fifth, i.e., glidants and combinations (both about 20%) and humectants (24%). This shows an extraordinary diversity in product consumption, even at the most basic level.

SPENDING MORE

The companies vary hugely in their purchasing budgets, though nearly half spend between $10 million and $100 million/year on excipients. In all, 64% expect this expenditure to increase in the next year and 30% say that it will stay the same, while only 2% expect a decrease and 4% are unsure. This trend is particularly marked in Asia, where 82% expect an increase, 16% say it will say the same, none expect a decrease and 2% are unsure.

Every single product category is expected to see growing expenditure in that time frame. This also holds true for the three categories that are currently used the least: over 50% of participants expect combinations, glidants and humectants to increase.

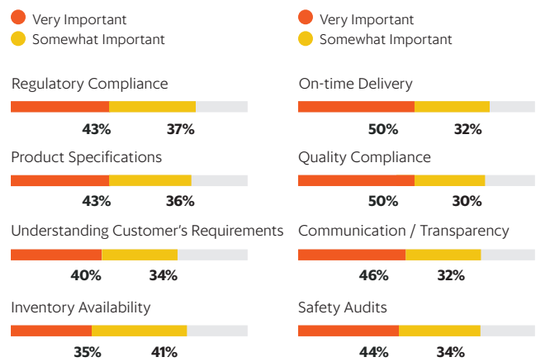
Coloring agents are perceived to be the least promising category, with the lowest proportion projecting an increase in purchasing (38%) and the highest projecting a decrease (17%). Other traditional products – preservatives, thickeners and lubricants – also show relatively low growth projections. Even so, demand is expected to grow far more often than it is to fall, in every case.

The mean number of excipient suppliers used by companies is 8, though this is somewhat lower in North America (7) and somewhat higher in Asia (9). Most respondents – 61% globally, but 84% in Asia – think that this number will grow in the next three years.

PURCHASING CRITERIA

SELECTION OF NEW EXCIPIENT SUPPLIERS

EVALUATION OF EXISTING EXCIPIENT SUPPLIER



SWITCHING FROM THEIR CURRENT EXCIPIENT SUPPLIER

Better quality products promised by competitor **56%**

Better price offered by competitor **56%**

Better time lines promised by competitor	41%
Improved logistics	38%
Poor regulatory compliance of current supplier	33%
Geographic convenience of competitor	29%

Chemical stability and **bioavailability** were the most important of nine major characteristics ranked for designing drug product formulations.

SOURCES TO SEEK EXCIPIENTS SUPPLIERS

Approved Supplier List **53%**

Supplier Databases	45%
Referrals/Colleagues	39%
Industry Events	37%
Internet Searches	35%

QUALITY THE DRIVER

In order of importance, the key criteria customers use when ranking suppliers is quality assurance, reliability, minimizing risks, regulatory track record and affordability. There is no single main selection criterion when deciding to work with an excipient supplier, however.

References from colleagues and coworkers, personal relationships with suppliers, a global presence, and supplier size and structure all scored between 61% and 65%, though the latter two were significantly more important for Asian customers than North Americans or Europeans. There were fewer differences when the criteria were collated against product type and company size.

When evaluating an excipient supplier, quality compliance is tied in importance with on-time delivery, both at 50%. Communication and transparency (46%), safety audits (44%) and regulatory compliance audits (43%) round out the top five criteria. As the difference between these selectors is just a few percentage points, it is easy to assume that a strong service provider can successfully demonstrate a track record with each.

When deciding to work with an excipient supplier, 80% rank regulatory compliance as important, ahead of product specifications (79%) and inventory availability (76%). A global presence, while still important at 61%, ranks last of the 14 specified attributes. In other words, being a big player may get you considered, but will not swing the final decision.

Once actually working with a supplier, companies value on-time delivery (82%), quality compliance (80%) and communication and transparency (78%); there are some subtle changes in priorities for customers at this stage of the process. Similarly, the most common sources of dissatisfaction when working with a supplier are product or service quality, ahead of product or service delivery.

COST MATTERS, BUT...

Users are more likely to select suppliers from an already approved supplier list than any other source: 53% do this, ahead of databases (45%), referrals and colleagues (39%) and industry events (37%). At every stage of the pharmaceutical manufacturing process – bench, kilo, pilot plant and commercial – they are most likely to buy direct from the manufacturer in a list of approved suppliers. Other sources vary considerably in popularity at different stages.

Although 'better price offered by competitor' is the most common reason (mentioned by 56%) to change supplier, companies of all sizes in all regions agreed that cost is less important than quality and reliability when selecting an excipient.

Asked about their pricing tolerance, 'We select a mid-priced option when other performance metrics prove similar' was the choice of 41% of the global total, followed by 'We select an excipient based on other factors when there is a small price differential between them' at 38%. Chemical stability and bioavailability were the most important of nine major characteristics ranked for designing drug product formulations. Likewise, bioavailability and solubility were cited as the technically most challenging aspects when designing oral solid dose formulations. This indicates that bioavailablity is an integral feature in excipients; the manufacturer who comes out ahead in this game is likely to emerge as a clear choice for buyers. P

REFERENCES

1. *Global Pharmaceutical Excipients Market Growth, Trends & Forecasts (2016-2021).* Rep. Mordor Intelligence. Nov. 2016. Web.
2. The 2017 Nice Insight Pharmaceutical Excipients Survey.

ATTRIBUTES THAT FACTOR INTO DESIGNING DRUG PRODUCT FORMULATIONS

1. **Chemical Stability**
2. Bioavailability
3. Product shelf life
4. Physical stability
5. Solubility

FORMULATION DESIGN CHALLENGES FOR ORAL SOLID DOSE FORMULATIONS

1. **Bioavailability**
2. Solubility
3. Compactibility
4. Uniformity
5. Dissolution

SOURCES FOR ORDERING EXCIPIENTS

1. **Manufacturer Direct from a List of Approved Suppliers**

PHARMACEUTICAL INTERMEDIATES SURVEY RESPONDENTS PROFILE

# of Survey Respondents: **545**

# of Companies in the Study: **62**

By Region

38% Asia

North America	25%
Europe	37%

By Company Size

36% Big Pharma

Midsized Pharma	31%
Small Pharma	28%
Emerging Pharma	5%

30% Corporate Management

By Department

R&D/Formulation/Analytical	24%
Quality Assurance/Quality Control	21%
Drug Development/Production/ Manufacturing	17%
Contracting/Sourcing/Purchasing	8%

76% of respondents expect this expenditure to increase in the next five years.

By Annual Outsourcing Expenditure

More than $10M	14%
$5M to $10M	25%
$2M to $5M	39%
$1M to $2M	17%
Less than $1M	3%

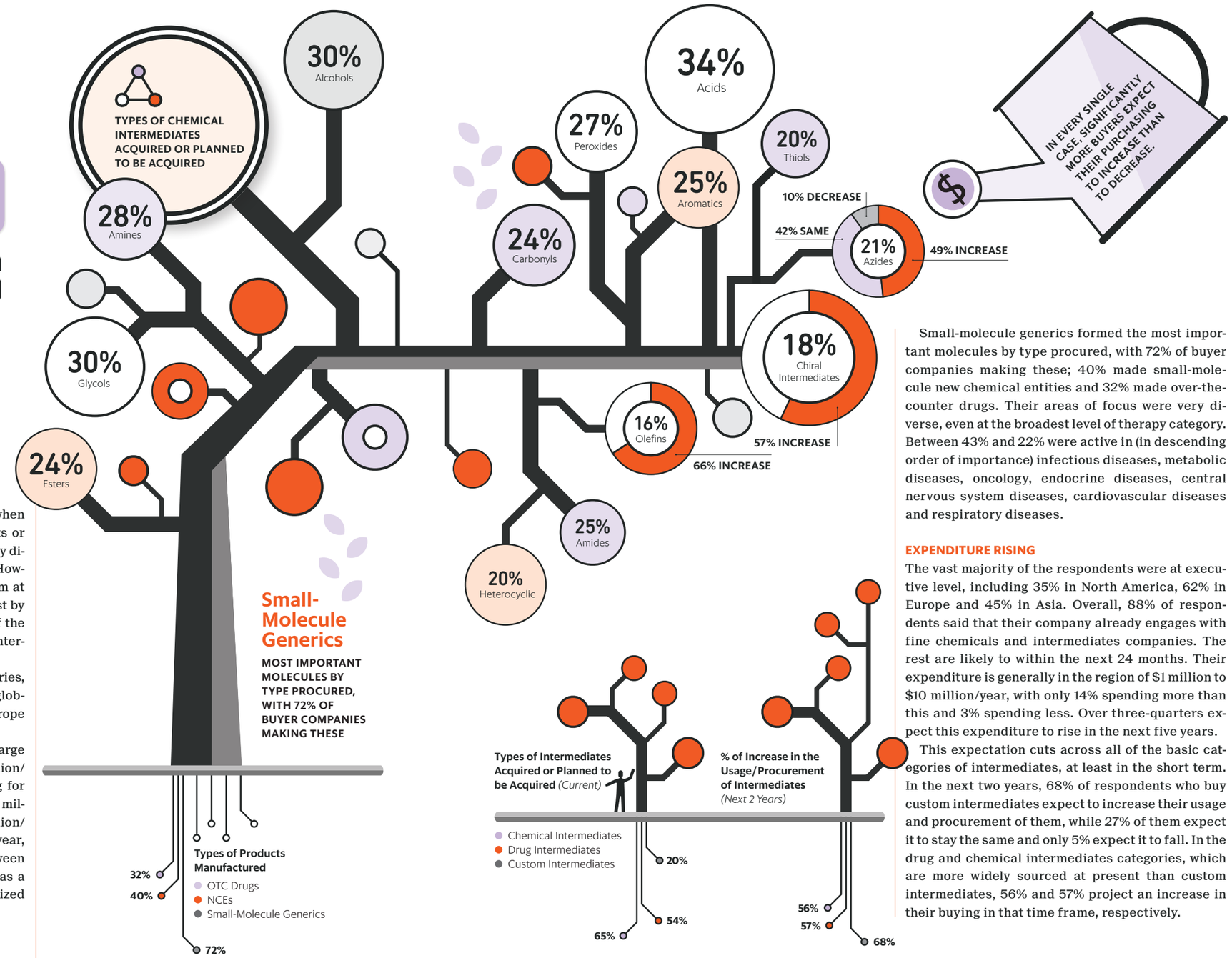
GROWTH ANTICIPATED FOR INTERMEDIATES

Pharma buyers not only expect to spend more on intermediates in the coming years, they are driven as much by quality as in the traditionally service-based segments.

Pharmaceutical buyers have much lower budgets when it comes to buying intermediates than excipients or outsourced services, but their needs remain highly diverse in terms of type of product and chemistry. However basic this segment of the industry may seem at first glance, buyers' needs are driven first and last by quality. These were some of the main insights of the 2017 Nice Insight Pharmaceutical & Chemical Intermediates Survey.[1]

As with the other Nice Insight surveys in this series, the respondents, who totalled 545, had a strong global geographic spread with 38% in Asia, 37% in Europe and 25% in North America.

They also came from companies of all sizes. Large pharma companies – those with sales of >$5 billion/year – were the largest single group, accounting for 36% of the total, followed by medium-sized ($500 million-$5 billion/year, 31%), small ($100-500 million/year, 28%) and emerging pharma (<$100 million/year, 5%). However, there were large differences between the sizes of the companies on a regional basis, as a much higher proportion were small or medium-sized in Asia than in North America or Europe.



Small-molecule generics formed the most important molecules by type procured, with 72% of buyer companies making these; 40% made small-molecule new chemical entities and 32% made over-the-counter drugs. Their areas of focus were very diverse, even at the broadest level of therapy category. Between 43% and 22% were active in (in descending order of importance) infectious diseases, metabolic diseases, oncology, endocrine diseases, central nervous system diseases, cardiovascular diseases and respiratory diseases.

EXPENDITURE RISING

The vast majority of the respondents were at executive level, including 35% in North America, 62% in Europe and 45% in Asia. Overall, 88% of respondents said that their company already engages with fine chemicals and intermediates companies. The rest are likely to within the next 24 months. Their expenditure is generally in the region of $1 million to $10 million/year, with only 14% spending more than this and 3% spending less. Over three-quarters expect this expenditure to rise in the next five years.

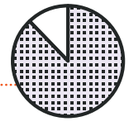
This expectation cuts across all of the basic categories of intermediates, at least in the short term. In the next two years, 68% of respondents who buy custom intermediates expect to increase their usage and procurement of them, while 27% of them expect it to stay the same and only 5% expect it to fall. In the drug and chemical intermediates categories, which are more widely sourced at present than custom intermediates, 56% and 57% project an increase in their buying in that time frame, respectively.

The Most Popular Methods Used to Select an Outsourcing Partner

53%
Industry Research

Previous Experience	48%
Referrals/Colleagues	40%
Trade Shows/Events	40%
Consultants	38%
Periodicals/Publications	32%
Online Directories	27%
Web Searches	15%

Respondents with Respect to Engaging with Fine Chemicals/ Intermediate Companies



88% **Yes,** we procure or outsource synthesis services

12% **No,** but likely to need within the next 24 months

Rank Of Industry Drivers

1
1. Quality Standards
2. Reliability
3. Minimizing Risks
4. Regulatory Track Record
5. Affordability

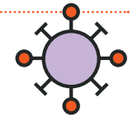
By Types of Product Manufactured

72% **Small-Molecule Generics**

NCEs	40%
OTC Drugs	32%

By Therapeutic Areas of Focus

43% **Infectious Diseases**



Metabolic Disorders	41%
Oncology Diseases	36%
Endocrine Diseases	34%
CNS Disorders	33%
Cardiovascular Diseases	24%
Respiratory Diseases	22%

Companies' need for intermediates are typically highest in the earliest stages of development, though the tapering-off effect in the later stages is not even. About half of those surveyed need them at clinical and bench scale and again at pilot scale, while the proportion falls to nearer one-quarter at kilo lab scale and again at commercial scale.

The types of chemicals that intermediate buyers acquire or plan to acquire for their immediate needs are extremely diverse. Acids (cited by 34% of respondents) head the list, ahead of alcohols and glycols (both 30%), amines (28%) and peroxides (27%), though nine other broad categories are being acquired by at least 16% of those surveyed. Geographically, the rankings varied little, though North American companies are more frequent and heavy buyers of the top categories of product.

MULTIPLE REACTIONS

In every single case, significantly more buyers expect their purchasing to increase than to decrease. This was most marked in the case of olefins and chiral intermediates, where 66% and 57% said that they would increase their purchasing over the next two years. The gulf was smallest with azides, but here too 49% expect an increase, 42% expect this to stay the same and only 10% anticipate a decrease.

Not surprisingly, there was also considerable diversity when it comes to the reactions used to transform intermediates into final API states. Protection/deprotection was the most widely used, but only by 37%. Other widely used reactions were led by hydrogenation (30%), nitration (29%), coupling, methylation/demethylation and enzymatic reactions (all 27%). The main technologies used to this end were crystallization (used by 57%), high temperature (250°C+, 51%), high pressure (37%) and cryogenic chemistry (-80°C, 34%).

There was a more clear-cut answer when it came to the types of specialized service respondents have acquired or plan to acquire. Protein chemistry is in the sights of 54%, ahead of green chemistry (48%), which is a looser term that could be taken to refer to many different techniques.

Most strikingly, perhaps, combinatorial chemistry – which has earned a poor reputation for discovering vastly more molecules without this having much of an effect on the number of final products emerging from the pipeline – is still in the plans of 40% of respondents, ahead of the 'sexier' areas of fluorine, chiral and hazardous chemistry.

While companies' methods of finding outsourcing partners are diverse, it is striking that Internet methods were the least common, with web searches and online directories being used by only 15% and 27%, respectively. Personal contact of one sort or another was considerably more common, with industry research being used by 53% and previous experience by 48%. Referrals/colleagues and trade shows/events each scored 40%: ChemOutsourcing was the single most popular event in this respect, with 48% of those surveyed attending it, though over 30% of respondents attended each of seven others, all in North America or Europe.

QUALITY COMES FIRST

Survey respondents were clear on their top priorities as buyers. Quality standards came first, with reliability, minimizing risks, regulatory track records, and affordability rounding out the top five. This fits well with the results of similar questions in other 2017 Nice Insight surveys of buyers' attitudes to working with contract research organizations and contract development and manufacturing organizations.[2,3]

Product or service quality is similarly the single factor likely to cause pharma companies dissatisfaction when working with fine chemicals and intermediates companies. Cost overruns came second, suggesting that cost becomes more of a factor only when there is a 'sting in the tail.' The other major sources of problems are, in descending order of importance, security and confidentiality, product or service availability, and communication and transparency.

Conceivably, pharma companies are seeing suppliers of fine chemicals and intermediates increasingly as partners rather than simple suppliers of products. The main reason cited for partnering includes being part of a strategic plan. The others, in descending order, are to find a shorter synthetic route to an API, reducing costs, a lack of in-house capabilities, and access to specialized technologies.

No single attribute stood out for pharma companies when evaluating fine chemicals and intermediates companies. In fact, the proportion of respondents rating 17 of 18 listed factors as important only varied between 61% and 66%, with the ability to resolve technical hurdles, quality compliance, experience (operational, methodological or therapeutic) and compliance audits in the top four. This shows that each trait is important; intermediate companies are expected to demonstrate strength across a host of service sectors to be considered.

The only factor that did stand out from the trend did so in a negative sense, albeit only slightly: 55% saw geographic convenience as important. In other words, being in the same region or country as the customer is a definite bonus, but only if all the other factors are right first. This is an increasingly sophisticated industry sector, as well as a thoroughly globalized one, and the rewards will go to those who offer high-quality products and services. P

Small-molecule generics formed the most important molecules by type procured.

Pharma companies are seeing suppliers of fine chemicals and intermediates increasingly **as partners rather than simple suppliers of products.**

REACTION USED FOR TRANSFORMATION OF AN INTERMEDIATE INTO FINAL API STATE

37% Protection/De-Protection

Hydrogenation	30%
Nitration	29%
Coupling	27%
Methylation/Demethylation	27%
Enzymatic	27%
Oxidation/Reduction	25%
Acylation/Alkylation	24%
Isomerization	22%
Cycloaddition	19%
Halogenation	17%
Sulphonation	15%
Condensation	14%

SPECIALIZED SERVICE ACQUIRED OR PLANNED TO BE ACQUIRED

54% Protein Chemistry

Green Chemistry	48%
Combinatorial Chemistry	40%
Fluorine Chemistry	37%
Chiral Chemistry	27%
Hazardous Chemistry	27%

SCALE OF INTERMEDIATES REQUIRED WHILE OUTSOURCING

Clinical Scale 51%

Bench Scale	49%
Pilot Scale	47%
Kilo Lab Scale	28%
Commercial Scale	24%

TECHNOLOGY USED FOR TRANSFORMATION OF AN INTERMEDIATE INTO FINAL API STATE

Crystallization/Recrystallization	57%
High Temperature (250OC +)	51%
High-Pressure Reactions	37%
Cryogenic Chemistry (-80OC)	34%

ATTRIBUTES THAT FACTOR INTO EVALUATING THE FINE CHEMICAL/INTERMEDIATE COMPANY

Ability to Resolve Technical Hurdles	66%
Quality Compliance	66%
Operational, Methodological & Therapeutic Experience	65%
Compliance Audits	65%

TOP FIVE REASONS FOR PARTNERING

1 **Part of Strategic Plan**
2. Shorter Synthetic Route to API
3. Reduce Costs
4. Lack of In-House Capabilities
5. Access to Specialized Technologies

TOP FIVE SOURCES OF DISSATISFACTION

1 **Product/ Service Quality**
2. Cost Overruns
3. Security/Confidentiality
4. Product/Service Availability
5. Communication/ Transparency

REFERENCES

1. The 2017 Nice Insight Pharmaceutical and Chemical Intermediates Survey.
2. The 2017 Nice Insight Preclinical and Clinical Contract Research Survey.
3. The 2017 Nice Insight Contract Development and Manufacturing Survey.

OEM SURVEY RESPONDENTS PROFILE

# of Survey Respondents: **597**

# of Companies in the Study: **90**

By Region

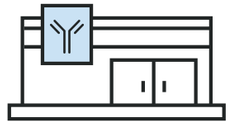
41% **Asia**

North America	27%
Europe	32%

By Company Size

44% **Small Emerging Pharmaceuticals**

Big Pharma	25%
Midsized Pharma	31%



By Type of Product

54% **Big Pharma/ Biotech**

Branded Pharmaceuticals	19%
Generic Pharmaceuticals	17%
OTC Pharmaceuticals	4%
CMO	3%
Nutraceuticals	3%

Majority of the respondents had a sound technical/commercial understanding of their respective pharmaceutical equipment categories.

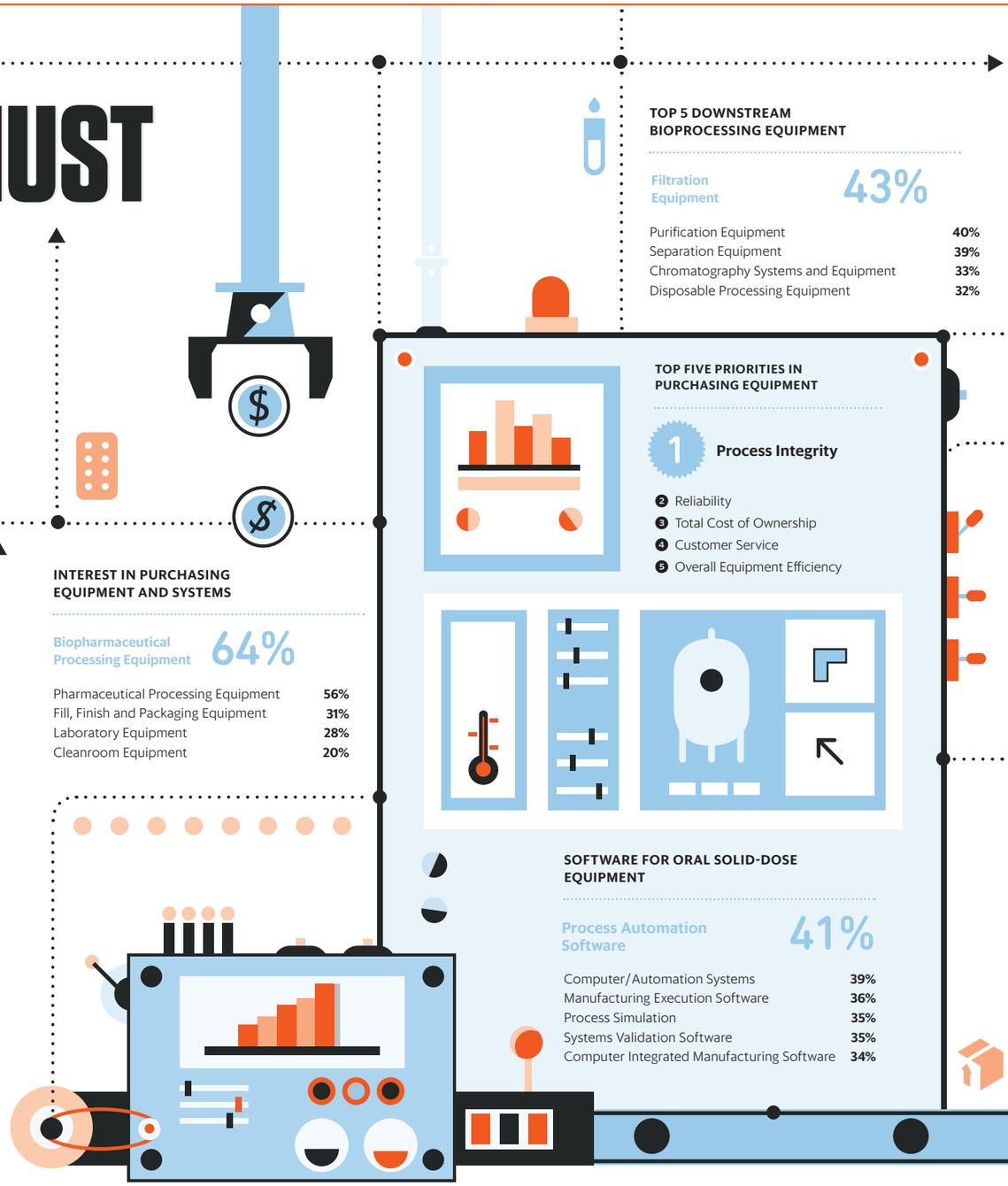
By Department

38% **Technical/Research**

Corporate/Management	25%
Operations/Engineering	37%

EQUIPMENT MUST INTEGRATE

Budgets for pharmaceutical equipment continue to increase as manufacturers seek to boost their in-house capabilities while moving towards more integrated and streamlined processes.



20% of respondents ranked Process Integrity first when asked to rank top drivers for purchasing equipment

Modern pharmaceutical manufacturing equipment and associated analytical instrumentation is the fundamental 'hardware' required to produce safe, effective, high-quality medicinal products. To meet the challenges from increasingly downward price pressure, stringent regulation, shifting markets and outcome-based insurance reimbursement, modern manufacturing processes rely heavily on innovative, integral, flexible equipment to achieve quality, efficiency and cost-effectiveness.

The trend to invest in pharmaceutical equipment continues, as observed in the 2017 Nice Insight Pharmaceutical Equipment Survey.[1] Other prominent trends revealed in this survey include strong interest in purchasing biopharmaceutical processing equipment, and in purchasing software systems for process automation, simulation, validation and integration. Equipment contributing to manufacturing process integrity plays an increasingly important role in making equipment-purchasing decisions. Equipment providers with the ability to provide GMP-compliant equipment that improves process integrity have a strong competitive advantage.

MORE RESPONDENTS

For the 2017 survey, Nice Insight polled over 100 more respondents in comparison to the 2016 survey (597 vs. 489) from pharmaceutical and biotechnology companies worldwide. Additionally, there were several key differences in respondents' backgrounds, including location, company type and size.

Geographically, the new survey recruited more respondents from Europe (32% vs. 19%), while respondents from North America decreased to 27% from 41% in 2016. Respondents from small and emerging pharmaceutical companies represent the largest portion of the buyer group (44%), up by 28% from 2016, while representation from large and midsized pharmaceutical companies was down.

Measured by type of product, the percentage of respondents from biopharmaceutical and biotechnology companies was even more dominant than before, rising from 45% to 54%, while the proportion from branded pharmaceutical companies decreased from 27% to 19%. The percentage for the rest of the buyer groups was close to last year's level, including generic (17%) and over-the-counter (OTC) pharmaceutical companies (4%), contract manufacturing organizations (CMOs) and nutraceutical companies (3% each).

With respect to respondents' job title, the 2017 survey included feedback from two new groups of professionals – engineers (14%) and technicians (9%) – so that a more comprehensive industry perspective on equipment purchasing can be explored.[1,2] To some extent, these differences in respondents' profiles may contribute to the data variations observed in the 2017 survey, since companies of different types and/or sizes have different equipment needs.

Despite the differences, however, the vast majority of those surveyed in both 2016 and 2017 possess a sound knowledge of the technical and financial aspects of the categories of pharmaceutical equipment being analyzed. Additionally, 88% play a supporting role in the internal processes for specification and purchase of process and production technologies; 78% of them are authorized to approve capital equipment spending.

By Job Title

Director/Sr. Director	17%
Engineers	14%
Technicians	9%
C-Level Executive	7%
Vice President/Sr. Vice President	4%

25% Manager/ Sr. Manager

24% Analyst/ Associate

Annual Equipment Purchasing Budget

38% More than $100M

Less than $10M	7%
$10M to $50M	25%
$50M to $100M	27%
Don't Know	3%

Changes in Equipment Budget 2014 to 2016

73% Increase

Remain the Same	22%
Decrease	3%
Unsure	2%

Purchase Authority

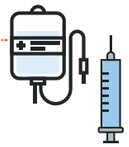
78% Yes

No	19%
Unsure	3%

Types of Dosage Forms Manufactured

61% Liquid Dosage

Oral Solid Dosage	55%
Semisolid Dosage	50%
Specialty Dosage	27%



With respect to respondents' intention to purchase a specific type of bioprocessing equipment, **the interest level is relatively higher for downstream equipment than upstream equipment.**

INCREASES IN BUDGET

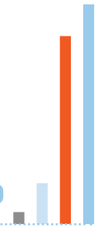
The trend of budget increase for equipment purchasing continues into 2017. As many as 38% of respondents reported an annual budget for equipment purchasing exceeding $100 million, a remarkable increase from 2016. The second leading budget category is between $50 million to $100 million (27%), followed by $10 million to $50 million (25%). The outlook for equipment budget in the near future also looks quite positive, with 73% of respondents projecting a budget increase.

Investing in equipment has been a strategy for the pharmaceutical and biotechnology industry to increase productivity, lower cost and shorten the development timeline, as well as to access specialized technologies and capabilities. In the case of the 2017 survey, the significant budget increase may indicate a strong intention on the part of these companies, particularly those that are small and emerging, to improve or expand their in-house manufacturing capability.

In the 2017 survey, 98% of the respondents' companies indicated in-house manufacturing capability: 48% with both clinical and commercial scale in-house, 41% with clinical scale in-house and 9% with clinical scale in-house manufacturing capability but no scale-up capability. The remaining 2% outsource their manufacturing needs completely. The large percentage of small and emerging companies in the survey may partially contribute to this pattern of in-house manufacturing capability.

IN-HOUSE MANUFACTURING CAPABILITIES

Clinical and Commercial Scale 48%



Clinical-Scale In-House Manufacturing	41%
Clinical-Scale but No Commercial Scale-Up Capability	9%
No In-House Manufacturing Line	2%

HIGH INTEREST IN BIOPHARMACEUTICAL EQUIPMENT

To gain a full picture of respondents' equipment purchasing needs, the 2017 Nice Insight Pharmaceutical Equipment Survey breaks down pharmaceutical equipment into five categories: oral solid-dose processing equipment, oral solid-dose packaging equipment, bioprocessing equipment, sterile process equipment and sterile packaging equipment. Each is further divided into sub-categories, such as primary and secondary equipment for packaging equipment; and upstream, downstream and accessory equipment for bioprocessing equipment.

A deep drop in the interest level in purchasing equipment and systems was observed in all of the five categories surveyed, in comparison with 2016. Despite this, however, 64% of respondents expressed interest in purchasing biopharmaceutical processing equipment, followed by pharmaceutical processing equipment (56%). This observation reflects the shifting focus of R&D to biologicals, as well as the rapid market growth of this sector.

The interest in purchasing the remaining three categories (fill, finish and packaging equipment, laboratory equipment and cleanroom equipment) is moderate (31%, 28% and 20%, respectively).

With respect to respondents' intention to purchase a specific type of bioprocessing equipment, the interest level is relatively higher for downstream equipment than upstream equipment. The top three highly demanded downstream equipment includes filtration (43%), purification (40%) and separation (39%) equipment, while the top three items of upstream equipment are mixers, blenders and millers (37%), incubators (34%) and fermenters (29%). The greater demand in downstream equipment is largely due to the shift of the biomanufacturing bottleneck to downstream, mainly because the productivity in upstream bioreactors has increased dramatically.

TOP FIVE PRIMARY STERILE PACKAGING EQUIPMENT

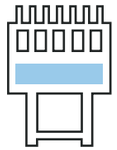
Terminal Sterilization Equipment 38%

Aseptic Filling And Sealing	36%
Inspection Systems	35%
Leak Detection Machines	34%
Aseptic Blow-Fill-Seal Equipment	29%

STRONG INTEREST IN SOFTWARE

Oral solid dosage forms accounts for the largest formulation category on the market. However, due to increasing development efforts in novel biopharmaceuticals and biosimilars, parenteral dosage forms are gaining a higher market share. The 2017 survey results reflect this trend: 61% of respondents reported that their companies manufacture liquid dosage forms (parenteral, injectable and vials) while 55% reported manufacture of oral solid dosage forms (capsules, tablets, etc.).

TOP FIVE STERILE PROCESSING EQUIPMENT



Filtration Equipment 33%

Clean Room Equipment	29%
Cleaning Systems	28%
Liquid Filling Machines	28%
Autoclave/Oven	28%

One prominent trend in the demand for a variety of oral solid-dose processing equipment is the strong interest in purchasing software for solid-dose equipment, especially for process automation software (41%) and computer and automation systems (39%). Over one-third of the respondents are also interested in purchasing software for manufacturing execution, process simulation, system validation and computer-integrated manufacturing.

The application of this technology goes beyond oral drug manufacturing. Automation and robotic technology has been steadily incorporated into every aspect of modern pharmaceutical manufacturing processes to replace manual labor, reduce human error and improve line efficiency.

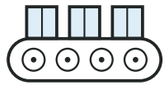
These technologies also have been used in process optimization, real-time monitoring and quality control. For highly potent drug manufacturing, they can be especially useful in decreasing human contact while creating a safer working environment and addressing regulatory concerns. The demand in this area is more likely to increase in the future.

PROCESS INTEGRITY COMES FIRST

Making pharmaceutical equipment purchasing decisions is a complex process that is affected by a myriad of influencing factors and evaluating attributes. Variations are evident regarding the ranking of these factors from 2016 to 2017.

In the 2017 survey, process integrity replaces reliability as the number one priority for purchasing equipment, followed by reliability, total cost of ownership and customer service. Additionally, when evaluating equipment providers, manufacturing and process integrity and certified or GMP equipment are the leading attributes as 'very important.' Other highly ranked, very important attributes include the ability to support

TOP FIVE ORAL SOLID DOSE – PRIMARY PACKAGING EQUIPMENT



Product Assembly Lines 43%

Blister Packaging	39%
Unit Dose Form-Fill-Seal	37%
Inspection Systems	35%
Non-Aseptic Filling & Capping	33%

equipment troubleshooting, customer service, providing good product life-cycle management, the ability to inspect and test equipment, and communication and transparency.

The top five influencers of equipment purchase are an increase in capacity to meet increased demand for existing product, to improve equipment effectiveness, market demand and needs, to upgrade to newer equipment, and quality and sterility imperatives. The top five sources of dissatisfaction include product durability or reliability, cost overruns, poor equipment design, equipment specification not being met, and product and system quality.

Based on this survey, it is unquestionable that modern pharmaceutical manufacturing is moving towards a more integrated and streamlined process from raw materials to the final products. As an integral and indispensable part of this process, pharmaceutical equipment plays an increasingly important role in enabling the manufacturing process to achieve efficiency, robustness and cost-saving with built-in quality and safety.

Equipment that can be adapted and/or upgraded to meet changing manufacturing needs and/or to improve process integrity, productivity and quality is highly desired. Equipment providers who understand the changing demands for pharmaceutical equipment and are capable of developing equipment that addresses a client's desired specifications, notably in terms of quality, reliability, regulatory compliance and cost, will have a strong competitive advantage. P

TOP FIVE PRIORITIES IN PURCHASING EQUIPMENT

1. **Increase in Capacity**
2. Improve Equipment Effectiveness
3. Market Demand & Needs
4. Upgrade to Newer Equipment
5. Quality & Sterility Imperative

TOP FIVE SOURCES OF DISSATISFACTION

1. **Product Durability/ Reliability**
2. Cost Overruns
3. Poor Equipment Design
4. Equipment Specification Not Being Met
5. Product/System Quality

REFERENCES

1. The 2017 Nice Insight Pharmaceutical Equipment Survey.
2. The 2016 Nice Insight Pharmaceutical Equipment Survey.

CLINICAL SUPPLY CHAIN LOGISTICS SURVEY RESPONDENTS PROFILE

# of Survey Respondents: **320**

# of Companies in the Study: **22**

By Region

37% Asia

North America	**30%**
Europe	**33%**

By Customer Type

Big Pharma/Biotech	**52%**	Central/Diagnostic/ Preclinical Lab	**3%**
Midsized Pharma/Biotech	**18%**	CRO	**2%**
Small Pharma/Biotech	**21%**	CDMO	**1%**
Emerging Pharma/Biotech	**3%**		

By Type of Biopharmaceutical Firm

Branded Pharmaceuticals	**19%**
OTC	**7%**
Generic Pharmaceuticals	**4%**

70% Biopharmaceuticals/ Biotechnology

By Department

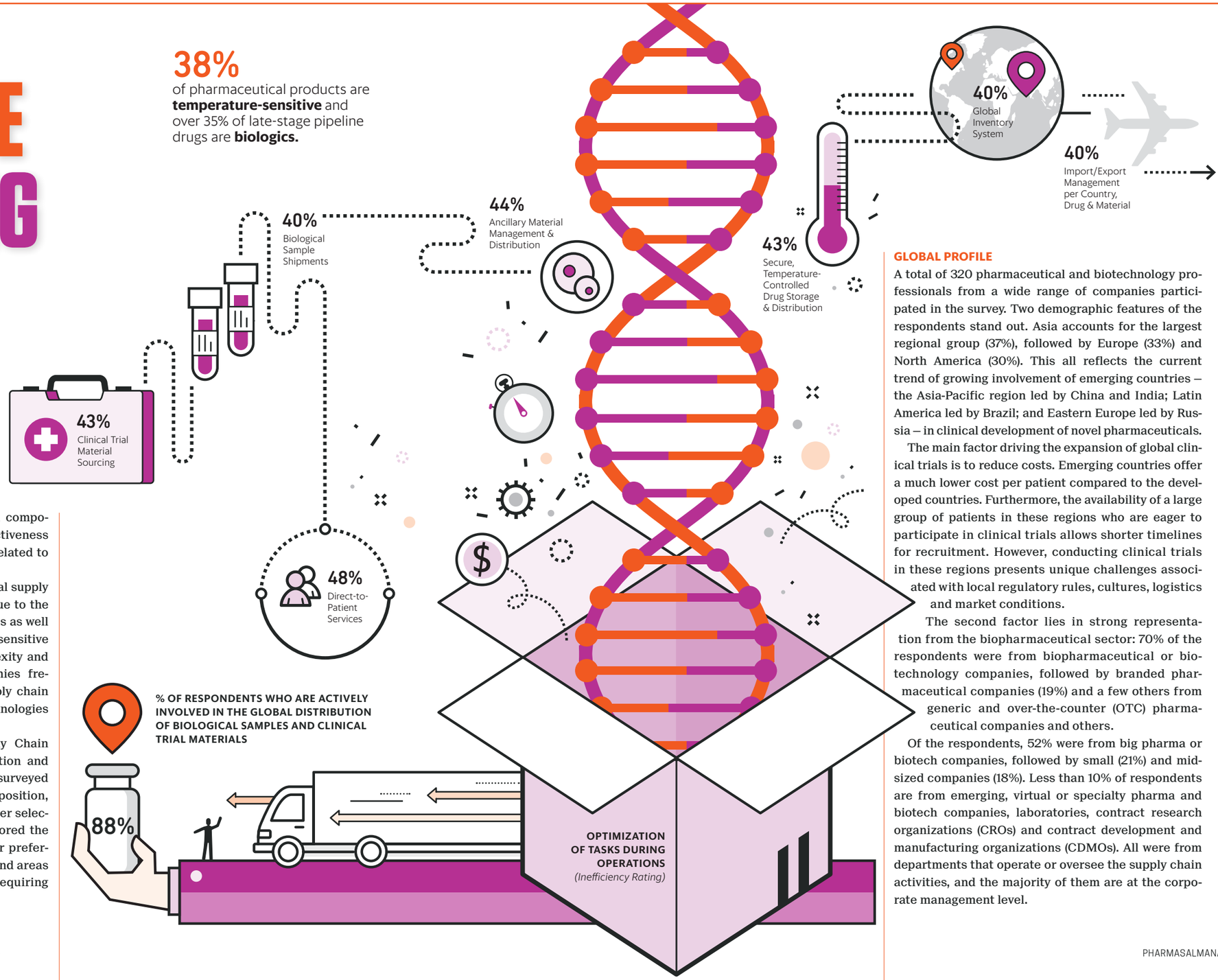
The majority of respondents surveyed were at the corpoate management level.

Corporate Management	**41%**
Clinical Supply Chain	**19%**
Business Supply Chain	**14%**
Drug Supply Management	**12%**
Purchasing/Sourcing/Procurement	**9%**
Packaging	**5%**

KEEPING THE CHAIN GOING

Cold chain needs and globalization are driving the clinical supply chain logistics sector as the pharmaceutical industry increasingly looks towards biologics.

38% of pharmaceutical products are **temperature-sensitive** and over 35% of late-stage pipeline drugs are **biologics.**



Clinical supply chain logistics form a crucial component of clinical trial infrastructure. The effectiveness and efficiency of a supply chain is directly related to the outcome of clinical trials.

In the last decade, the complexity of clinical supply chain logistics has increased dramatically due to the growing number of multinational clinical trials as well as the requirements to handle temperature-sensitive therapeutics. In order to manage the complexity and related challenges, pharmaceutical companies frequently turn to outsourcing to improve supply chain efficiency, reduce costs and access new technologies and new markets.

In the 2017 Nice Insight Clinical Supply Chain Logistics Survey, the influence of globalization and cold chain logistics can be observed in every surveyed category, including survey respondents' composition, outsourcing service needs and service provider selection. In addition, Nice Insight has also explored the patterns of buyer outsourcing practice, their preferences in forming outsourcing partnerships, and areas in the clinical supply chain and logistics requiring improvement.[1]

GLOBAL PROFILE

A total of 320 pharmaceutical and biotechnology professionals from a wide range of companies participated in the survey. Two demographic features of the respondents stand out. Asia accounts for the largest regional group (37%), followed by Europe (33%) and North America (30%). This all reflects the current trend of growing involvement of emerging countries – the Asia-Pacific region led by China and India; Latin America led by Brazil; and Eastern Europe led by Russia – in clinical development of novel pharmaceuticals.

The main factor driving the expansion of global clinical trials is to reduce costs. Emerging countries offer a much lower cost per patient compared to the developed countries. Furthermore, the availability of a large group of patients in these regions who are eager to participate in clinical trials allows shorter timelines for recruitment. However, conducting clinical trials in these regions presents unique challenges associated with local regulatory rules, cultures, logistics and market conditions.

The second factor lies in strong representation from the biopharmaceutical sector: 70% of the respondents were from biopharmaceutical or biotechnology companies, followed by branded pharmaceutical companies (19%) and a few others from generic and over-the-counter (OTC) pharmaceutical companies and others.

Of the respondents, 52% were from big pharma or biotech companies, followed by small (21%) and midsized companies (18%). Less than 10% of respondents are from emerging, virtual or specialty pharma and biotech companies, laboratories, contract research organizations (CROs) and contract development and manufacturing organizations (CDMOs). All were from departments that operate or oversee the supply chain activities, and the majority of them are at the corporate management level.

The Most Popular Methods Used to Select an Outsourcing Partner

52% Industry Research

Trade Shows/Events	42%
Referrals/Colleagues	40%
Periodicals/Publications	36%
Consultants	32%
Online Directories	25%
Web Searches	13%
Other	1%

Top 5 Industry Drivers

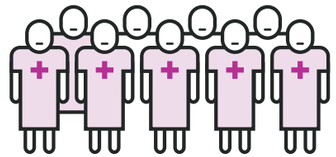
1. Management
2. Reliability
3. Cost
4. Regulatory Compliance
5. Global Reach

Buyers are increasingly seeking **strategic partnership** rather than a transactional vendor-sponsor relationship.

Use of Outsourcing Partners by Phase

60% Phase II

Preclinical	29%
Phase I	54%
Phase III	35%
Phase IV/Postlaunch	21%



By Therapeutic Areas of Focus

41% Metabolic Disorders

Infectious Diseases	34%
Endocrine Diseases	31%
CNS Disorders	29%
Cardiovascular Diseases	29%
Oncology Diseases	25%
Respiratory Diseases	18%

By 2020, it is projected that **eight of the top ten** global pharmaceutical products will require cold chain handling.

COLD CHAIN

The strong presence of the biopharmaceutical sector in the survey is a reflection on increasing R&D efforts on biologicals. Today, 38% of pharmaceutical products are temperature-sensitive and over 35% of late-stage pipeline drugs are biologics.[2]

Biological materials often require cold chain logistics to ensure that they are stored, transported and distributed within their required temperature range. The demand in this area is mounting: by 2020, it is projected that eight of the top ten global pharmaceutical products will require cold chain handling.[2]

Managing cold chain logistics at the global scale is extremely complex and challenging. As shown in the 2017 survey, establishing secure temperature-controlled drug storage and distribution is ranked as one of the most complex tasks during clinical supply chain logistics operations. It is also an area that needs a great deal of efficiency improvement.

One important component in managing a temperature-controlled supply chain is temperature-monitoring. The demand for new equipment and technologies to monitor temperature conditions throughout the investigational drug life cycle is growing: 30% of survey respondents plan to acquire temperature data collection and management services. Aside from regulatory compliance, using temperature-monitoring technologies to reduce the likelihood of temperature deviation offers an effective cost-containment strategy.

CURRENT OUTSOURCING PRACTICE

The engagement of buyers with clinical supply chain logistics providers – for assistance in the global distribution of biological samples and clinical trial materials – is fairly high: 88% of the respondents are actively involved and the remainder are likely to require this type of service in the next 24 months.

Outsourcing occurs at every development phase, with the highest level of outsourcing partnership engagement reported in phase II (60%), followed by phase I (54%), phase III (35%), preclinical (29%) and phase IV/postlaunch (21%). As investigational drugs advance to the next stage of clinical development, more outsourcing activities are likely to be seen in the late phase (II and III) development in the future.

The respondents work for companies that are focused on a variety of therapeutic areas. Metabolic disorders (41%), infectious diseases (34%) and endocrine diseases (31%) are the most common target areas. The interest in oncology seems to have decreased within this survey group (25%). However, cancer therapeutics still account for about 25% of the global late-stage pipeline.[2] This observation may indicate that drug innovators are shifting away from cancer in the search for new agents.

To meet their clinical supply chain and logistics needs, pharmaceutical and biotechnology companies demand a wide range of services – from services related to global trials to cold chain logistics to controlled drugs. The top five most frequently demanded services are drug/material import and export requirements and management (39%), supply chain strategy development (34%), regional import/export requirements and management (33%), schedule I to IV controlled drug storage and distribution (33%) and depot services for clinical trial materials (32%).

The least frequently sought services include direct-to-patient services (13%), secure, temperature-controlled drug storage and distribution (17%), ancillary material management and distribution (18%), retest labeling of clinical trial materials at depots (18%) and global project management point-of-contact person (19%). It is likely that companies tend to conduct these types of services in-house.

TOP FIVE ATTRIBUTES IN SUPPLIER SELECTION

Regulatory Compliance **59%**

Innovation	58%
Operational and Methodological Experience	58%
Import/Export and Customs Expertise	57%
Supplier Industry Reputation	57%

PARTNER SELECTION DRIVERS

For pharmaceutical companies, selecting clinical supply chain logistics partners is a complex and strategic decision. The capability and quality of service providers have a direct impact on the quality and outcome of the clinical development.

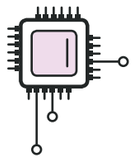
During the initial selection, service providers are evaluated based on an array of attributes. The most important attributes include regulatory compliance (59%), innovation (leading the industry with new logistics solutions) (58%), experience (operational, methodological) (58%), import/export and customs expertise (57%) and supplier industry reputation (57%). Structure of supplier receives the lowest ranking (43%), though the gulf from top to bottom was not vast.

It is interesting to note that industry research is ranked as the most popular method used to select an outsourcing partner (52%), followed by trade shows/events (42%) and referrals and colleagues (40%). Online directories and web searches are much less popular. In practice, a combination of these methods is often used in service provider selection.

Several industry drivers also play significant roles in this selection, with management ranked the most important industry driver by 49% of respondents, followed by reliability, cost, regulatory compliance, global reach and customer service. The importance of management from service providers in establishing an outsourcing partnership is prominent. Their commitment is fundamental for a long-term strategic partnership.

Interestingly, reducing costs ranks only fifth among the top reasons for partnering with clinical supply chain logistics providers. Access to specialized technologies, supply planning, process improvement and packaging design are all seen as more important. As in other sectors, it appears that cost is likelier to become an issue further down the road and only if all other things are equal.

MAIN REASON TO PARTNER WITH CLINICAL SUPPLY CHAIN LOGISTICS PROVIDERS



Access to Specialized Technologies **1**

Supply Planning	2
Process Improvement	3
Packaging Design	4
Reducing Costs	5

STRATEGIC PARTNERSHIP

In the field of clinical supply chain logistics, buyers are increasingly seeking strategic partnerships rather than a transactional vendor-sponsor relationship.

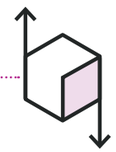
Although the ranking of costs is low in developing outsourcing partnerships, better price offered by competing suppliers accounts for the most popular factor that would prompt respondents to switch from their current supplier(s) (51%). Other highly ranked triggering factors include improved logistics (40%), low error rate compared to the current supplier (35%) and poor regulatory compliance of the current supplier (33%).

FACTORS THAT WOULD PROMPT RESPONDENTS TO SWITCH FROM THEIR CURRENT SUPPLIERS

Better Price Offered by Competing Supplier **51%**

Improved Logistics	40%
Low Error Rate Compared to Current Supplier	35%
Poor Regulatory Compliance of Current Supplier	33%
Better Timelines Promised by Competing Supplier	29%
Geographic Convenience of the Competing Supplier	23%
Innovative Solutions Proposed by Competing Supplier	16%

TOP FIVE CLINICAL SUPPLY CHAIN LOGISTICS SERVICES TO BE ACQUIRED FROM SUPPLIERS



Drug Material Import/Export Requirements & Management **39%**

Supply Chain Strategy Development	34%
Regional Import/Export Requirements & Management	33%
Schedule I-IV Controlled Drug Storage & Distribution	33%
Depot Services for Clinical Trial Materials	32%

With respect to respondents' satisfaction level in working with clinical supply chain logistics service providers, 23% are satisfied and 28% somewhat satisfied, against 1% unsatisfied and 12% somewhat unsatisfied. The rest are neither satisfied nor dissatisfied.

The top five sources of dissatisfaction listed from greatest to least are lack of contingency planning, enrollment delay, service quality, returns and destruction, and quality control. Undoubtedly, there is much that can be done to improve outsourcing partnerships in these areas.

Service providers may also find their niche by helping buyers address tasks that received high inefficiency ratings in clinical supply chain logistics operations. These include direct-to-patient services (48%), ancillary material management and distribution (44%), clinical trial material sourcing (43%), secure, temperature-controlled drug storage and distribution (43%), global inventory system, import/export management per country, drug and material (40%) and biological sample shipments (40%). P

SATISFACTION LEVEL FOR WORKING WITH CURRENT SERVICE PROVIDERS

35%

Satisfied **23%**
Somewhat Satisfied **28%**
Neutral **35%**
Somewhat Unsatisfied **12%**
Unsatisfied **1%**

TOP FIVE SOURCES OF DISSATISFACTION

1. **Lack of Contingency Planning**
2. Enrollment Delay
3. Service Quality
4. Returns & Destruction
5. Quality Control

REFERENCES

1. The 2017 Nice Insight Clinical Supply Chain Logistics Survey.
2. "Expertise." *Global Trends in Clinical Trial Logistics: 2020 Perspective – Corex*. Web.

PE/VC SURVEY RESPONDENTS PROFILE

# of Survey Respondents: **69**

# of Companies Profiled: **135**

By Region

99%
North America

By Type of Investor

Combination	32%
Private Equity Investor	13%
Angel Investor	3%
Venture Capital Investor	1%

51%
Broker/ Investment Banker

By Average Range of Acquisition

29%
Less than $50 million

$500 Million to $1 Billion	15%
$250 to $500 Million	20%
$100 to $250 Million	7%
$50 to $100 Million	16%
More than $1 Billion	13%

By Type of Industries

100%
Healthcare/ Life Sciences

Technology	93%
Energy	88%
Consumer & Retail	87%
Real Estate	84%
Financials	81%
Media and Telecommunication	75%

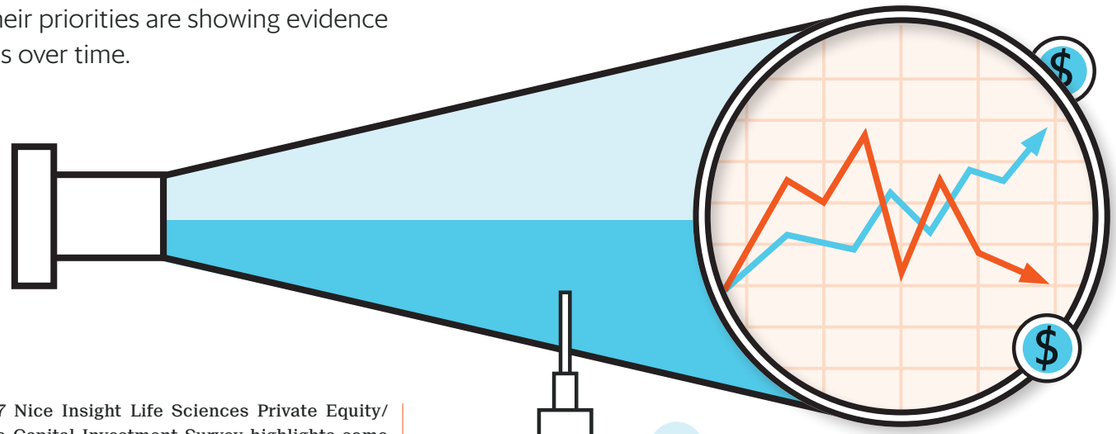
INVESTORS MAY LOOK SMALLER

Private equity and other investors still see many opportunities in the life science and healthcare sectors — and their priorities are showing evidence of subtle changes over time.

11 Investments

65% OF RESPONDENTS SAID THAT THEY MADE MORE THAN 11 INVESTMENTS IN THE LIFE SCIENCE INDUSTRY FOR THE YEAR 2015, DESPITE HIGH RISK BEING A MAJOR CHALLENGE

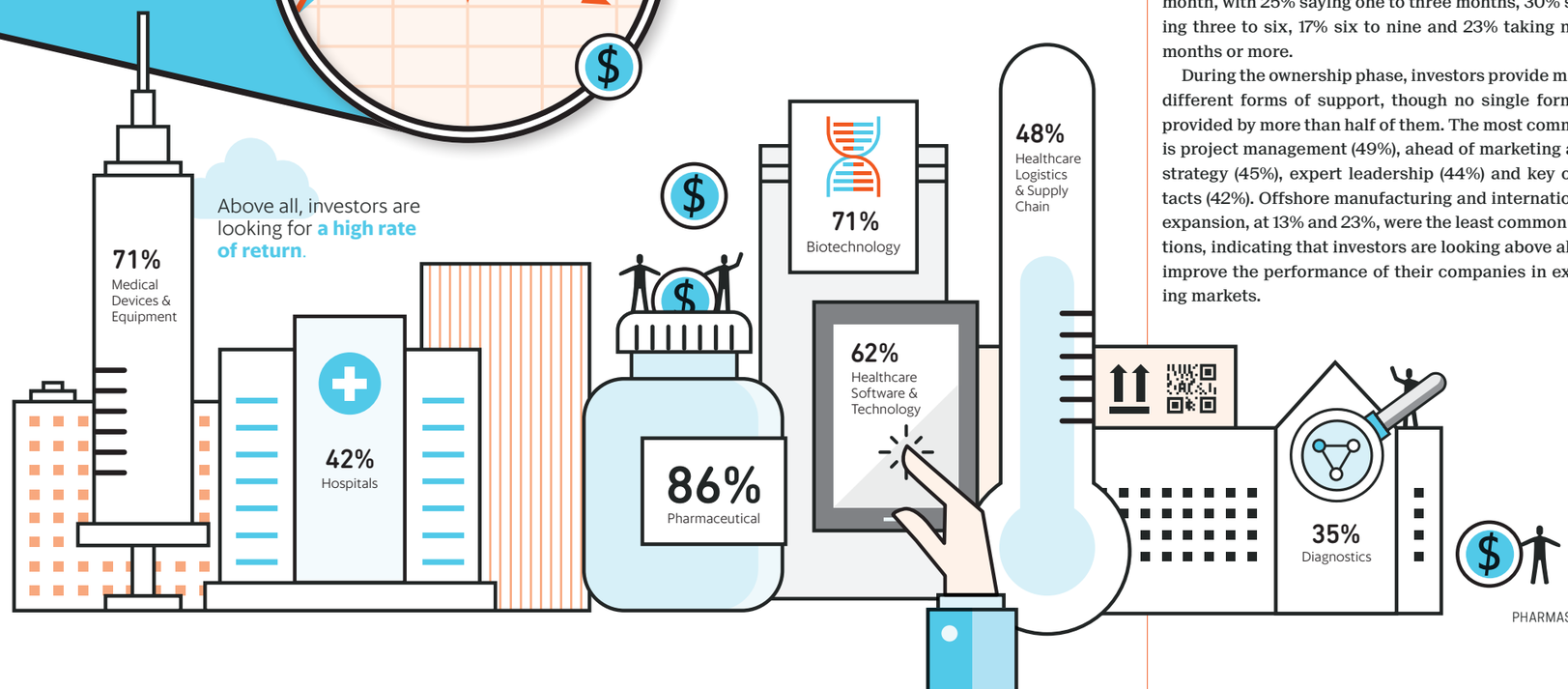
OVER THE NEXT 3 YEARS, 39% OF RESPONDENTS INDICATED THAT THEIR FIRM IS LOOKING TO INVEST IN SMALLER COMPANIES RELATIVE TO PAST TRANSACTIONS



49%
of Respondents Prefer Investing in a Company at the **Growth Capital Stage.**

DECREASE	CURRENT	NEXT 3 YEARS	
Pharmaceutical	86%	74%	-12
Discovery Lab	59%	55%	-4
Healthcare Logistics & Supply Chain	48%	46%	-2
Hospitals	42%	39%	-3
Managed Care	41%	38%	-3

INCREASE	CURRENT	NEXT 3 YEARS	
Biotechnology	71%	73%	+2
Medical Devices & Equipment	71%	73%	+2
Healthcare Software & Technology	62%	68%	+6
Specialty Pharmaceutical	54%	57%	+3
CRO	36%	41%	+5
Diagnostics	35%	55%	+20
CDMO	35%	42%	+7



The 2017 Nice Insight Life Sciences Private Equity/ Venture Capital Investment Survey highlights some interesting trends in the way investors of all kinds currently look at opportunities in the life science and healthcare sectors.[1]

Despite the high and acknowledged risks, investors – who are typically active in multiple other areas – continue to make substantial investments in this field, mostly in pharmaceuticals, biotechnology and medical devices, although there are indications that this will change to some degree in the next three years.

Above all, investors are looking for a high rate of return, driven by strong demand for the products or services offered by the companies they own, and seek opportunities more in improving performance than from expansion. They are still focused above all on North America. However, they are also looking at smaller companies more than they did in the past.

WIDE INVESTOR BASE

The respondents to the survey, who all invest in healthcare and the life sciences, were based in North America. They comprise mainly brokers and investment bankers (51%), plus private equity investors (13%), angel investors (3%) and venture capitalists (1%), the remaining 32% being combinations of categories. As well as healthcare and the life sciences, at least 75% and up to 93% are active in other major areas, like technology, energy, consumer and retail, real estate, financials and media/telecommunications.

These companies make investments over a wide range of acquisitions, with 29% saying that their average investment was below $50 million, 16% in the $50 million to $100 million range, 7% at $100 million to $250 million, 23% in the $250 million to $500 million range, 15% at $500 million to $1 billion and the remaining 10% reaching over $1 billion. Over the next three years, 39% said that they will be looking to invest more in smaller companies relative to past transactions.

Of the respondents, 49% prefer to invest at the growth capital stage, as opposed to 22% at the early or start-up stage and 26% at the later or initial public offer (IPO) stage. Only 3% are focused on the seed stage at the very start. The time they typically take to close a deal also varies considerably: 4% take less than one month, with 25% saying one to three months, 30% saying three to six, 17% six to nine and 23% taking nine months or more.

During the ownership phase, investors provide many different forms of support, though no single form is provided by more than half of them. The most common is project management (49%), ahead of marketing and strategy (45%), expert leadership (44%) and key contacts (42%). Offshore manufacturing and international expansion, at 13% and 23%, were the least common options, indicating that investors are looking above all to improve the performance of their companies in existing markets.

Typically, **three to five years is seen as the ideal time frame** for holding a company.

Preferred Exit Strategy

36% **Acquisition by Financial Buyer**

Acquisition by Strategic Buyer	**29%**
IPO	**17%**
Merger	**7%**
Employee Stock Ownership Plan	**4%**
N/A	**6%**

Average Timeline to Close a Deal

Less than 1 Month	**4%**
1 to 3 Months	**25%**
3 to 6 Months	**30%**
6 to 9 Months	**17%**
9 Months or more	**23%**

TOP 5 MARKET SCENARIO

Decision Drivers

1 Demand for Product/Service
is regarded as the main market scenario decision driver for a new healthcare/life science investment opportunity by respondents.

2. Stage of Product/Service at Time of Investment
3. Market Size
4. Ability to Patent Product/Service or Make It Exclusive
5. Competitive Landscape

TOP CHALLENGES FACED WHEN INVESTING

58% **High Risks**

Insufficient Data for Evaluation	**48%**
Tighter & Complex Regulations	**46%**
Complex Exit Strategy	**36%**
High Investments Needed	**36%**
Lack of Industry Experts to Evaluate Companies	**30%**
Lack of Feedback Loop	**15%**

DRAWBACKS OF COMPANIES SEEKING INVESTMENT OPPORTUNITY

67% Unrealistic Projections

65% Inaccurate Estimates of Capital & Resources

55% Weak Management

Flawed Go-To-Market Strategies	**45%**
Inaccurate Competitor Analysis	**39%**
Accounting Issues	**29%**

PHARMA TOPS THE RANKINGS – FOR NOW

These companies invest in many parts of the healthcare and life science industry. The most common in the survey was pharmaceuticals (86%), followed by biotechnology and medical devices and equipment (both 71%), healthcare software and technology (62%) and discovery laboratories (59%). Suppliers of all kinds were usually among the least common of the 12 categories, with contract development and manufacturing (35%), diagnostics (also 35%) and pre-clinical and clinical contract research (36%) at the bottom.

Conversely, when asked about their plans for the next three years, pharmaceuticals remain at the top but fall from 86% to 74% of investors, while biotechnology and medical devices and equipment are almost static at 73%. Suppliers are expected to creep up the rankings slightly, with managed care and hospitals falling away slightly. Diagnostics could rocket in importance, from being a target for 35% of investors to one for 55%.

Typically, three to five years is seen as the ideal time frame for holding a company; 45% of respondents said this. The most popular exit strategies at the end of that are sale to a financial or strategic buyer (the options of 36% and 29%, respectively) or an IPO (17%). Exit generally means either exactly that, or retaining a minority: 49% take a 0%-25% stake afterwards, while 28% hang on to up to 50%. Only one-fifth retain a majority stake.

Not surprisingly, North America comfortably ranks the highest for ease of investment among a community largely based there and familiar with it. Next comes Western Europe, with Japan and Korea ranking equally alongside Australia, then Singapore and Southeast Asia fractionally above China. Turkey and the Middle East were a long way last.

RISKS AND BENEFITS

High risks were cited as the biggest challenge investors faced, with 58% of them mentioning this, ahead of insufficient data for evaluation (48%), tighter and complex regulations (46%), a complex exit strategy (36%), high investments being needed (also 36%), lack of industry experts to evaluate companies (30%) and the lack of a feedback loop (15%). For all that, 65% of respondents had made over 11 investments in the life science field in 2015.

Asked what were the key drawbacks of companies seeking investment, a very high 67% and 65%, respectively, cited unrealistic projections and inaccurate estimates of capital and resources required for product development as issues. Weak management (55%) and flawed go-to-market strategies (45%) were also common, with accounting issues (29%) far less so. It is thus largely the intangibles that make investors hold back.

Demand for the relevant products and services is regarded as the main market-scenario decision driver for a new healthcare or life science investment opportunity, ahead of the stage of the product or service at the time of investment, market size, the ability to patent the product or service or otherwise make it exclusive, and the competitive landscape as a whole. Established distribution and marketing channels were the least important of the ten named criteria.

A high projected or realized internal rate of return was seen as the top ranking financial driver when considering a new investment opportunity, ahead of a high profit margin, low relative capital investment or early exit potential. When it came to the management team at the acquired company, what mattered above all was their knowledge of the business or industry, their team record and their risk management experience. Being familiar to the investor and educational qualifications counted for much less. P

REFERENCES

1. 2017 Nice Insight Life Sciences Private Equity/Venture Capital Investment Survey.

2017 Industry **Leaders**

Nice Insight conducted seven annual studies to survey the pharma landscape and measure what buyers in the market want. These surveys were deployed to respondents in the diverse and dynamic sectors of CDMO, CRO, Equipment, Intermediate, Excipient, Private Equity Venture Capital and Supply Chain. That being said, each space has winners and losers. Respondents to the study ranked companies on key drivers, including Quality, Reliability, Affordability, Productivity, Innovation and Regulatory. The best of the best in a wide range of categories are honored here, with commentary from key players on what it means to be in the Top 5 for 2017.

Pfizer CentreOne

CATEGORY LEADER

Clinical-Scale Manufacturing
Solid-Dose Drug Product
Small-Molecule Drug Substance

Commercial-Scale Manufacturing
Solid-Dose Drug Product
Small- & Large-Molecule Drug Substance

Drug Product Fill-Finish

Pete Stevenson
Vice President and General Manager,
Pfizer CentreOne

This really is a great honor for our people at Pfizer CentreOne and for the relationships we've built with our biopharma partners over the years. We're proud of the quality and technology we can offer on a global scale. On a personal level, trust is just as important: genuine trust on both sides. Drug development can be a rough road with lots of twists and turns. Trusting relationships make that journey possible.

CDMO INDUSTRY LEADERS

CLINICAL-SCALE MANUFACTURING SOLID-DOSE DRUG PRODUCT

1	**Pfizer CentreOne**	**82.33%**
2	Famar	81.17%
2	GSK Contract Manufacturing	81.17%
4	Metrics Contract Services, Inc. (Mayne Pharma)	80.33%
5	Catalent	80.00%

COMMERCIAL-SCALE MANUFACTURING SOLID-DOSE DRUG PRODUCT

1	**Pfizer CentreOne**	**84.83%**
2	Sanofi CEPiA	81.50%
3	GSK Contract Manufacturing	81.17%
4	Albany Molecular Research Inc. (AMRI)	80.67%
4	Patheon	80.67%

CLINICAL-SCALE MANUFACTURING SMALL-MOLECULE DRUG SUBSTANCE

1	**Pfizer CentreOne**	**82.33%**
2	Bayer Pharma Chemicals	81.00%
2	Minakem	81.00%
4	GSK Contract Manufacturing	80.33%
5	Albany Molecular Research Inc. (AMRI)	79.33%

COMMERCIAL-SCALE MANUFACTURING SMALL-MOLECULE DRUG SUBSTANCE

1	**Pfizer CentreOne**	**85.00%**
2	GSK Contract Manufacturing	84.00%
3	Dr. Reddy's CPS	82.50%
4	Patheon	82.17%
5	Albany Molecular Research Inc. (AMRI)	82.00%

CLINICAL-SCALE MANUFACTURING LARGE-MOLECULE DRUG SUBSTANCE

1	**Sandoz**	**83.17%**
2	Pfizer CentreOne	81.17%
3	GSK Contract Manufacturing	80.50%
4	Patheon	79.83%
5	SAFC Life Sciences	79.67%

COMMERCIAL-SCALE MANUFACTURING LARGE-MOLECULE DRUG SUBSTANCE

1	**Pfizer CentreOne**	**84.00%**
2	Sandoz	83.67%
3	Novasep	83.50%
4	GSK Contract Manufacturing	81.50%
5	Sanofi CEPiA	81.00%

DRUG PRODUCT FILL-FINISH

1	**Pfizer CentreOne**	**84.50%**
2	GSK Contract Manufacturing	83.17%
3	Fresenius Kabi Product Partnering	83.00%
3	Patheon	83.00%
5	Baxter BioPharma Solutions	82.50%

GSK Contract Manufacturing

CATEGORY LEADER

Clinical-Scale Manufacturing
Solid-Dose Drug Product
Small- & Large-Molecule Drug Substance

Commercial Scale Manufacturing
Solid-Dose Drug Product
Small- & Large-Molecule Drug Substance

GSK Contract Manufacturing is delighted that our extensive expertise helps our clients deliver products for their patients and customers. We offer the Pharma/Biopharma industry a fully integrated supply chain solution with FDA- and EMA-approved multiproduct facilities. We also provide multiple services for Consumer/OTC products. GSK works with both small-molecule APIs and large molecules, offering development services and site capacity that is suitable for finishing in multiple formats.

By evaluating our customers' specific needs — from development through commercial production — and matching them with our capabilities and facilities, we ensure successful tech transfer at any stage. We look forward to more successful collaborations in the future.

Janice L. Graff
Director of Finished Product Sales & Business Development, Americas, GSK

www.gsk.com/contractmanufacturing

CRO INDUSTRY LEADERS

Peter Benton
President and COO,
Worldwide Clinical Trials

Worldwide Clinical Trials

CATEGORY LEADER

Research

For many years, Worldwide Clinical Trials and our depth of clinical expertise and breadth of global capabilities has been one of the industry's best kept secrets. With this 2017 survey ranking, it looks like that secret is getting out and customers who are demanding a better experience and looking for more — proactive insight, dogged determination, rigorous processes and a commitment to getting it right — are taking notice, choosing Worldwide and recognizing what we can do. I'm very proud of this recognition, on behalf of the entire Worldwide Clinical Trials team.

RESEARCH

1	**Worldwide Clinical Trials**	**84.83%**
2	Exova Group	84.50%
3	Eurofins Lancaster Laboratories	84.00%
4	Nelson Laboratories	83.50%
5	Microconstants	83.17%

PRECLINICAL

1	**Nelson Laboratories**	**79.17%**
1	SRI International	79.17%
3	Quintiles	79.00%
4	AMRI	78.83%
4	INNOPHARMA S.r.L.	78.83%
4	Parexel	78.83%

CLINICAL

1	**Fisher Clinical Services Inc.**	**80.00%**
2	Novotech	79.50%
2	Piramal Clinical Research	79.50%
2	Worldwide Clinical Trials	79.50%
5	Quintiles	78.67%

ORIGINAL EQUIPMENT MANUFACTURERS (OEM) INDUSTRY LEADERS

Bosch Systems

CATEGORY LEADER

Biopharma Processing Equipment

BIOPHARMA PROCESSING EQUIPMENT

1	**Bosch Systems**	**78.33%**
2	GE Healthcare	77.50%
3	Thermofisher Scientific	76.50%
4	EMD Millipore	74.83%
5	Pall Corporation	74.50%

Uwe Harbauer
Member of the Board of Management at Bosch Packaging Technology and Head of the Product Division Pharma, Bosch Systems

For Bosch, of course, it is an honor to be recognized as one of the leading suppliers of process and pharmaceutical packaging technology worldwide. The U.S. is one of our most important markets and is expected to grow even further in the future. The study validates our commitment to develop and deliver complete packaging and production lines for the pharmaceutical industry and provide corresponding services. Rather than resting on this success, we continue to develop future-proof solutions and create value for our customers: Bosch Packaging Technology is investing significant resources to understand and to solve pharma-specific tasks and challenges.

BASF Pharma Solutions

CATEGORY LEADER

Solubilizers

EXCIPIENTS INDUSTRY LEADERS

SOLUBILIZERS

1	**BASF**	**85.20%**
2	Dow Chemical Company	84.60%
3	Millipore Sigma	84.40%
4	Ashland	82.00%
5	SPI Pharma	81.60%

Kai Sievert
Director Global Marketing & Innovation, BASF Pharma Solutions

We are honored our industry partners ranked BASF Pharma Solutions a leading solubilizer supplier. Low-solubilization properties have created significant challenges for the pharmaceutical industry, and we are gratified to be recognized for our expertise and products that have helped overcome them. Moving forward, we will continue to work closely with our customers to gain a thorough understanding of their changing needs, and address them by leveraging our unique solubilization platform in combination with insights from our academic and industry partners across the globe.

CLINICAL SUPPLY CHAIN LOGISTICS INDUSTRY LEADERS

UPS/Marken

CATEGORY LEADER

Temperature Data Collection and Management

Geoff Light
President of Healthcare Logistics Strategy, UPS

UPS is honored to be recognized by survey respondents for its best-in-class service offerings for clinical trials. Improved health outcomes through sophisticated drugs and vaccines start with successful trials, and optimized logistics is an integral component of medical research and development. UPS will continue to make key investments in technology, temperature-control capabilities and customer service to meet the complex demands of healthcare and life-science organizations. And with our recent acquisition of Marken, a patient-centric supply chain innovator in clinical trial logistics, we are working hard toward becoming the global leader in biological specimen transportation.

TEMPERATURE DATA COLLECTION AND MANAGEMENT

1	**UPS/Marken**	**78.50%**
2	Fisher Bioservices	74.67%
3	World Courier	73.33%
4	Almac	72.83%
5	Durbin	71.00%

PHARMACEUTICAL INTERMEDIATES INDUSTRY LEADERS

DRUG INTERMEDIATES

1	**Bayer**	**78.40%**
2	GSK	76.00%
3	Pfizer CentreOne	75.60%
4	Bachem	74.80%
5	Piramal Pharma Solutions	74.60%
5	Sandoz	74.60%

NICE INSIGHT

Company Tracking in 2017
856 Outsourcing Providers

Benchmarking with Nice Insight Annual Studies: Company profiles with Deep Dive Customer Awareness and Perception Ratings

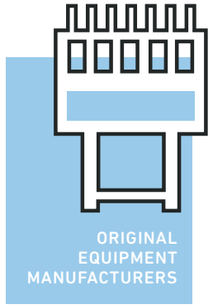
DEEP DIVE
3M Drug Delivery Systems
Aarti Drugs Ltd.
AbbVie Contract Manufacturing
Abiogen Pharma S.p.A.
Accucaps Industries Ltd.
Accupac, Inc.
Acino
Adcock Ingram
Aenova Group
Aesica
Ajinomoto Althea, Inc.
Akorn, Inc.
AkzoNobel Polymer Chemistry
Albany Molecular Research, Inc. (AMRI)
Albemarle
Alcami
Alkermes plc
Almac Group
AMPAC Fine Chemicals
Aptuit
Arch Pharmalabs Ltd.
Arevipharma GmbH
Aspen Pharmacare Holdings Ltd.
Avara Pharmaceutical Services
Avid Bioservices, Inc.
Bachem
BASF
Baxter BioPharma Solutions
Bayer HealthCare Pharmaceuticals, Inc.
Biocon Ltd.
BioDuro LLC
BioVectra, Inc.
Boehringer Ingelheim
Brammer Bio
Cambrex Corporation
Capsugel
Catalent Pharma Solutions
Celltrion Healthcare
Cenexi
Centaur Pharmaceuticals
Charles River Laboratories, Inc.
Chartwell Pharmaceuticals
CIMA Labs, Inc.
CMC Biologics
CMIC, Inc.
Cobra Biologics
Codexis, Inc.
Confab
Contract Pharmacal Corp.
Contract Pharmaceuticals Ltd.
Cook Pharmica
Corden Pharma
CoreRx, Inc.
Cytovance Biologics
Delpharm
Dishman Pharmaceuticals and Chemicals Ltd.
Divis Laboratories, Ltd.
Dottikon Exclusive Synthesis
DPT Laboratories Ltd.
Dr. Reddy's CPS
EI
Emcure Pharmaceuticals Ltd.
Emergent BioSolutions
Evonik Industries
Evotec
F.I.S. Fabbrica Italiana Sintetici
Famar
Fareva
Fermion Oy
Formulated Solutions LLC
Fresenius Kabi Product Partnering
Frontage Laboratories, Inc.
Fujifilm Diosynth Biotechnologies
G&W Laboratories, Inc.
Gedeon Richter Plc
Glenmark Pharmaceuticals
Grifols
GSK Contract Manufacturing
Halo Pharmaceutical, Inc.
Helsinn Group
Hermes Pharma
Hetero Drugs Ltd.
Hovione
IDT Biologika
Indoco Remedies Ltd.
Ipca Laboratories
Ipsen S.A.
Irvine Pharmaceutical Services
Isochem
Johnson Matthey Fine Chemicals
JRS Pharma
Jubilant HollisterStier
KBI Biopharma
LGC
Lonza Group
Lyophilization Services of New England, Inc.
Metrics Contract Services, Inc.
Minakem
Neuland Laboratories Ltd.
NextPharma
Norwich Pharma Services
Novacap Group
Novasep
Olon S.p.A.
Par Pharmaceutical
Paragon Bioservices, Inc.
Patheon, Inc.
PCAS
PCI Pharma Services
PCI Synthesis
Perrigo Company plc
Pfizer CentreOne
Pharmaceutics International, Inc. (Pii)
PharmaCore
Pharmascience, Inc.
Pharmasol Corporation
Pharmatek Laboratories, Inc.
Pharmatis
PharmaZell
Pierre Fabre
Piramal Pharma Solutions
Polpharma
Porton Fine Chemicals Ltd.
Qualicaps
Recipharm AB
Recordati S.p.A.
Regis Technologies, Inc.
Reig Jofre
Rentschler
Richter-Helm
Ropack Pharma Solutions
Rottendorf Pharma
ROVI CM
SACHEM, Inc.
SAFC
Sai Life Sciences Ltd.
Saltigo-LANXESS
Samsung BioLogics
Sandoz
Sanofi CEPiA
Senn Chemicals
Servier
Siegfried
Solvay Chemicals
Solvias
SRI International
Stason Pharmaceuticals
Sumitomo chemical
Synerlab
Takeda Pharmaceutical Company Ltd.
Teva Active Pharmaceutical Ingredients (TAPI)
Theon Pharmaceuticals
Therapure Biopharma, Inc.
Unither Pharmaceuticals
UPM Pharmaceuticals, Inc.
Valeant Pharmaceuticals International
Vectura Group
Vetter Pharma
WellSpring Pharmaceutical
West Pharmaceutical Services, Inc.
Wockhardt Ltd.
Wuxi AppTec
ZaCh System S.p.A.

PROFILE ONLY
2Y-Chem Ltd.
ABCO Laboratories, Inc.
Abzena plc
ACIC Fine Chemicals, Inc.
ACS Dobfar
Adeka Pharmaceuticals
Advanced BioScience Laboratories, Inc. (ABL)
Advanced ChemTech
Afton Scientific Corporation
Allergy Laboratories, Inc.
Alphora Research, Inc.
AmbioPharm, Inc.
AMCAPHARM Pharmaceutical
American International Chemical, Inc. (AIC)
Amerigen Pharmaceuticals
Ameya Laboratories
Amsyn, Inc.
Anteco Pharma, LLC
APAC Pharmaceutical, LLC
Apicore US, LLC
Apotex Fermentation, Inc.
Applied Laboratories, Inc.
AstaTech, Inc.
Asymchem Laboratories, Inc.
Atlantic Analytical Laboratory
Avanti Polar Lipids, Inc.
Aveva Drug Delivery Systems
Bell-More Labs, Inc.
Bertin Pharma
Bilcare Global Clinical Supplies
Bio Basic, Inc.
BioBlocks, Inc.
BioConvergence LLC
Bio-Synthesis, Inc.
Bio-Technical Resources
BioTechnique LLC
Biotest Laboratories, Inc.
BioVest International, Inc.
BioZone Laboratories, Inc.
Bluepharma
Borregaard Synthesis
BSP Pharmaceuticals S.p.A.
Canadian Custom Packaging & The Color Group
Cayman Chemical Company
CBL Biopharma (CBL Patras)
Chanelle Medical
Chemic Laboratories
Chemicals Incorporated
Chempacific Corporation
ChemWerth, Inc.
CiVentiChem
Coating Place, Inc.
COREALIS Pharma, Inc.
Cryopak
Dalton Pharma Services
Deepwater Chemicals, Inc.
Deseret Laboratories, Inc.
Digital Specialty Chemicals Ltd.
Elite Pharmaceuticals, Inc.
Emerson Resources, Inc.
Enzon Pharmaceuticals, Inc.
ExxPharma Therapeutics LLC
FAR Chemical, Inc.
Flamma S.p.A.
Galenix
Galenova, Inc.
GFS Chemicals, Inc.
Goodwin Biotechnology, Inc.
Grand River Aseptic Manufacturing
Groupe Parima, Inc.
Guardian Drug Company
GVK Biosciences
Hameln Pharmaceuticals Ltd.
Hanford Pharmaceuticals
Hisun Pharmaceuticals USA
IDT Australia Ltd.
InnoPharmax, Inc.
Integrity Bio
IriSys LLC
Irvine Scientific
Isogen Life Science
Kingchem
Labiana Pharmaceuticals
Laboratorios Alcala Farma
Lacamas Laboratories, Inc.
Legacy Pharmaceuticals International
Ligand Pharmaceuticals
List Biological Laboratories, Inc.
Lupin Pharmaceuticals, Inc.
Lyne Laboratories, Inc.
Lyophilization Technology, Inc.
Maine Biotechnology Services, Inc.
Meridian Life Science, Inc.
Mikart, Inc.
Monument Chemical
Morre-Tec Industries, Inc.
Murty Pharmaceuticals, Inc.
Nexgen Pharma
Niels Clauson-Kaas A/S
Norquay Technology, Inc.
Nova Laboratories Ltd.
Oakwood Laboratories, LLC
OmegaChem, Inc.
Organic Technologies
OYC Americas, Inc.
Pharma Tech Industries (PTI)
Pharmaceutical Manufacturing Research Services, Inc. (PMRS)
Pharmetics, Inc.
Phoenix Pharmaceuticals, Inc.
Phyton Biotech, LLC
Pierrel S.p.A.
Pillar5 Pharma, Inc
Pisgah Labs, Inc.
PolyPeptide Group
Pressure Chemical Company
ProMed Pharma
PYRAMID Laboratories, Inc.
QED Bioscience, Inc.
Quality Chemical Laboratories
Quay Pharmaceuticals
R.S.A. Corporation
Recro Gainesville LLC
Reliable Biopharmaceutical LLC
Rhodes Technologies, Inc.
RMC Pharmaceutical Solutions
Roche Custom Biotech
RohnerChem
Scripps Laboratories, Inc.
ScyTek Laboratories, Inc.
SeraCare Life Sciences, Inc.
Sheffield Pharmaceuticals
SiGNa Chemistry, Inc.
Sovereign Pharmaceuticals LLC
Strem Chemicals, Inc.
SynCo Bio Partners
Synergetica, Inc.
Tapemark
Tedor Pharma, Inc.
Teligent, Inc.
Tergus Pharma
The Ritedose Corporation (TRC)
Therapex
Tower Laboratories Ltd.
Tris Pharma, Inc.
Tyger Scientific, Inc.
Unicep Packaging, Inc.
Ursatec Verpackung GmbH
Varsal
Vistin Pharma
Zyleris Pharmatech

NICE INSIGHT

DEEP DIVE
Accelevance
Albany Molecular Research, Inc. (AMRI)
Altasciences Clinical Research
American Preclinical Services LLC
Battelle
Bertin Pharma
Bioanalytical Systems, Inc. (BASi)
bioskin GmbH
Celerion
Charles River Laboratories
Chiltern
CiToxLAB
Clinipace Worldwide
ClinTec International
CNS Network
Covance
CROMSOURCE
EAG Laboratories
Envigo
Eurofins Lancaster Laboratories
Eurotrials
Evotec
Exova Group
Fisher Clinical Services, Inc.
Frontage Laboratories
GenScript
Icagen
ICON plc
Inamed GmbH
INC Research
InnoPharma S.r.L.
Intertek
InVentiv Health
JAI Research Foundation (JRF)
JANIX LLC
Jubilant Life Sciences Ltd.
Lambda Therapeutic Research
Medpace
Microbac Laboratories, Inc.
MicroConstants
MMS Holdings, Inc.
MPI Research
Nelson Laboratories
Norwich Clinical Services
Novotech
Novum Pharmaceutical Research Services
Parexel
Piramal Clinical Research
PPD
PRA Health Sciences
Premier Research
Product Safety Labs
ProTrials Research, Inc.
QPS
Quanticate
Quest Diagnostics Clinical Trials
Quintiles
Rho
Ricera Biosciences
SanaClis
Sannova Analytical, Inc.
Seventh Wave Laboratories LLC
SGS Life Science Services
Shin Nippon Biomedical Laboratories, Ltd. (SNBL)
Spaulding Clinical Research
SRI International
Surpass, Inc.
SynteractHCR
TKL Research, Inc.
Toxikon
United BioSource Corporation (UBC)
WCCT
Worldwide Clinical Trials

PROFILE ONLY
Acceleration Laboratory Services, Inc.
Accell Clinical Research
Adpen Laboratories, Inc.
Agilux Laboratories, Inc.
Alturas Analytics, Inc.
Analytical Research Laboratories (ARL)
Archer Pharmaceuticals, Inc.
Bio Research Laboratories, Inc.
Biorasi
Biotrial
Boston Analytical, Inc.
BRI Biopharmaceutical Research, Inc.
Calbiotech, Inc.
Cirion Clinical Trial Services
Clinlogix
Clintex Research Group
Critical Path Services LLC
Diteba
Dokumeds
Ecron Acunova
Encompass Pharmaceutical Services
Galbraith Laboratories, Inc.
Granlen LLC
Impact Analytical
KCAS
KGK Synergize
LakePharma, Inc.
Laxai Avanti Life Sciences Pvt. Ltd.
Mapi
McCrone Associates, Inc.
MedSource
Merieux NutriSciences
Molecular Epidemiology, Inc.
NSF Health Sciences
Optivia Biotechnology, Inc.
Pace Analytical Services LLC
Pacific BioLabs, Inc.
Particle Sciences
Particle Technology Labs
Perritt Laboratories, Inc.
Pion, Inc.
Proveris Scientific Corporation
Pyxant Labs, Inc.
Quality Assistance S.A.
Quantex Laboratories, Inc.
SafeBridge Consultants, Inc.
SIRO Clinpharm Pvt. Ltd.
Smithers Avanza
Southern Star Research
Wolfe Laboratories, Inc.
Zaycor Biotech



DEEP DIVE
3C! Packaging
ACG Worldwide
ACIC Pharmaceutical Machinery
AdvantaPure
AES Clean Technology
Alexanderwerk
Alfa Laval
Applikon Biotechnology
Bausch + Stroebel
Bosch Systems
Brevetti CEA
Burkert Fluid Control Systems
Capmatic Ltd.
Chase-Logeman Corporation
Commissioning Agents, Inc. (CAI)
Coperion
Cozzoli Machine Company
CRB USA
CVC Technologies, Inc.
Dara Pharmaceutical Packaging
Driam USA, Inc.
Dynamic Air, Inc.
EMD Millipore
Eppendorf
Fette Compacting
Finesse Solutions, Inc.
Fitzpatrick Company
Fluid Metering, Inc.
Fluor Life Sciences
Freund-Vector Corporation
GE Healthcare
GEA Pharma Systems
GEMU Valves, Inc.
Getinge Group
Glatt Air Techniques
Groninger
Harro Hofliger Systems
Honeywell
Hosokawa Micron Powder Systems
IKA Works, Inc.
IMA Life North America, Inc.
INFORS HT
Integrated Project Services (IPS)
Key International, Inc.
Klockner Pentaplast
Körber Medipak Systems NA, Inc.
KORSCH America, Inc.
Kuhner Shaker, Inc.
L.B. Bohle
M+W Group
Marchesini Group
Matcon
Mettler Toledo
MG America
Microfluidics International Corporation
Modular Packaging Systems, Inc.
Natoli Engineering Company, Inc.
Nicos Group, Inc.
NJM Packaging
OCS Checkweighers
O'Hara Technologies, Inc.
OPTIMA Pharma
Pall Corporation
Paul Mueller Company
Quadro Engineering Corp.
Rockwell Automation
Romaco Group
Rommelag
Saint-Gobain
Sartorius Stedim Biotech
Schenck AccuRate
Schott Pharmaceutical Packaging
Seidenader Maschinenbau
SERVOLiFT LLC
Siemens Healthineers
SKAN
SP Scientific
STERIS
Stilmas
Telstar Life Science
The Elizabeth Companies, Inc.
Thermo Fisher Scientific, Inc.
Thomas Engineering, Inc.
Top Line Process Equipment Company
Uhlmann Packaging Systems
Veltek Associates, Inc. (VAI)
Watson-Marlow Fluid Technology Group
Weiler Engineering, Inc.
WILCO AG
Zeta Instruments

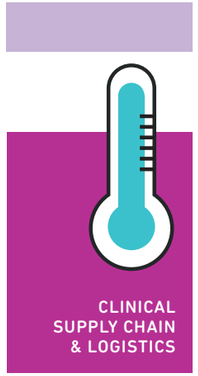
PROFILE ONLY
AC Compacting
Astro Pak
Atlantic Scale Company, Inc.
AZO
B&P Process Equipment and Systems
BEE International
Brooks Equipment
Buflovak LLC
Charles Ross & Son Company
Colder Products Company
Custom Powder Systems LLC
DCI
Dwyer
Feldmeier Equipment, Inc.
Flexicon Corporation
Fluid Air
Fluke Corporation
Fristam Pumps
GlobePharma, Inc.
Harsco Industrial Patterson-Kelley
HealthStar, Inc.
HEMCO
Integrated Packaging Systems
Kaeser Compressors, Inc.
Kemutec Group, Inc.
Keystone Process Equipment
Komeline-Sanderson
Lee Industries
M.O. Industries
MECO
MicroThermics, Inc.
MKS Instruments, Inc.
National Bulk Equipment, Inc. (NBE)
NETZSCH
New England Machinery, Inc.
Paul O. Abbe
Rice Lake Weighing Systems
Sharpe Mixers
Silverson Machines, Inc.
Spraying Systems
Stainless Motors, Inc.
Steri Technologies, Inc.
Steriflow Valve
SteriValves
Sturtevant, Inc.
SWECO
Tuthill

DEEP DIVE
Archer Daniels Midland (ADM)
Asahi Kasei
Ashland
Avantor
Azelis
BASF
Blanver
Cargill
Colorcon
Croda
DFE Pharma
Dow Chemical Company
DuPont
Eastman Chemical Company
EMD Millipore – Millipore Sigma
Evonik Industries
FMC Corporation
Gattefosse
JRS Pharma
Kerry / Sheffield
Lubrizol
Meggle
Mutchler
Nisso HPC
Pfanstiehl, Inc.
Roquette
SEPPIC
Shin-Etsu Chemical
Spectrum Chemical
SPI Pharma
Univar

PROFILE ONLY
ABITEC Corporation
BENEO GalenIQ
Brenntag
Fuji Chemical Industries Co., Ltd.
Peter Greven
Sensient Technologies
Sigachi Industries Pvt. Ltd.
Wacker Group

DEEP DIVE
A.R. Life Sciences
Aarti Healthcare
Aceto Chem Pvt. Ltd.
Advanced Chemical Intermediates
Agno Pharma
AkzoNobel
Albany Molecular Research, Inc. (AMRI)
American Pacific
AMPAC Fine Chemicals
Arkema
Bachem
BASF
Bayer Pharma Chemicals
BioSpectra, Inc.
Centaur Pharmaceuticals
Cepia — Sanofi
Chemcon Specialty Chemicals Pvt. Ltd
Chiral Quest
Corden Pharma
CTX Lifesciences Pvt. Ltd.
Cureworth Drugs & Intermediates Pvt. Ltd.
Dishman Pharmaceuticals and Chemicals Ltd.
Dottikon Exclusive Synthesis
Dow Chemical Company
Eastar Chemical Corporation
Evonik Industries
Ganesh Group
GSK Contract Manufacturing
Halo Pharmaceutical, Inc.
Hangzhou FST Pharmaceutical
Hovione
INEOS Group Ltd.
Interchem Corporation
Isochem
Jiangyin Kangda Chemical Company
Johnson Matthey Fine Chemicals
Lacamas Laboratories
Lanxess-Saltigo
Lianhe Tech
Midas Pharma
Minakem
Navin Fluorine International Ltd.
Novasep
Parchem Fine & Specialty Chemicals
Patheon
Paushak Ltd.
PCAS
Pfizer CentreOne
PharmaCore-Cambrex
Piramal Pharma Solutions
SAI Life Sciences
Sandoz
Saudi Basic Industries Corporation
SI Group
Siegfried
Sigma Aldrich
Solvias
Valtris Specialty Chemicals
Vertellus Specialties
W.R. Grace
WeylChem
Zylexa Pharma

PROFILE ONLY
ABR Organics Ltd.
Acanthus Research, Inc.
Ambuja Intermediates Ltd.
Amines & Plasticizers Ltd. (APL)
Amsyn, Inc.
Apollo Scientific Ltd.
Bodal Chemicals Ltd.
Ceres Chemical Company, Inc.
Chempacific Corp.
Dr. Reddy's Laboratories
Farmak, A.S.
Hetero Drugs Ltd.
Infinium Pharmachem Pvt. Ltd.
Insight Finechem Company Ltd. (IFC)
INVISTA
MP Biomedicals
Northernchem Inc.
Novacap
Stepan Company
Sumitomo Chemical
Wintersun Chemical
WuXi AppTec
Yashica Pharmaceuticals Pvt. Ltd.
ZaCh System S.p.A.



DEEP DIVE
Almac Group
Biocair
Catalent
COREX Clinical Logistics
Cryoport
DB Schenker
DHL
DSV Air & Sea, Inc.
Durbin
FedEx
Fisher BioServices
International Bonded Couriers, Inc. (IBC)
Marken
MNX Global Logistics
OCASA
PCI Pharma Services
PDP Couriers
Pharmaserv Logistics
QuickSTAT
UPS
World Courier
Yourway Transport

PROFILE ONLY
21 Partners S.p.A.
5AM Ventures
Abingworth
Advent International
Aisling Capital
Alta Partners
Altaris Capital Partners LLC
American Capital Ltd.
Apax Partners
Apple Tree Partners
Archer Capital
Arsenal Capital Partners
Astorg Partners
Audax Group
Bain Capital
BC Partners
Beecken Petty O'Keefe & Company (BPOC)
Blackstone Group
Bourne Partners
Boyne Capital Partners
Bridgepoint
Caltius Capital Management
Canaan Partners
Carlyle Group
Castle Crow & Company
Cerberus Capital Management
Clarus Ventures
Credit Suisse
Cressey & Company
Crestview Partners
Deerfield Management
Delphi Ventures
Domain Associates LLC
DW Healthcare Partners
EDG Partners
Elm Creek Partners
Enhanced Equity Funds (EEF)
EQT
Essex Woodlands
Flagship Pioneering
Flexpoint Ford LLC
Frazier Healthcare Partners
Friedman Fleischer & Lowe LLC (FFL)
Frontenac Company
Gemini Investors
General Atlantic
Geneva Glen Capital
Genstar Capital
GI Partners
Goldman Sachs Group, Inc.
GTCR
H.I.G. Capital
Harbour Point Capital
Harren Equity Partners
Harvest Partners
HCP & Company
Health Enterprise Partners (HEP)
HealthEdge Investment Partners
Hellman & Friedman LLC
Heritage Group
High Road Capital Partners
High Street Capital
Horizon Ventures
IK Investment Partners
InterWest Partners
J.H. Whitney & Company
J.W. Childs Associates
JLL Partners
Johnson & Johnson Innovation, Inc.
Kaiser Permanente Ventures
Kleiner Perkins Caufield & Byers (KPCB)
Kohlberg Kravis Roberts (KKR)
LaSalle Capital
Lee Equity Partners LLC
Life Science Partners (LSP)
Linden Capital Partners
LLR Partners
Madison Dearborn Partners LLC
Metalmark Capital
Montagu Private Equity
Morgenthaler Ventures
Morningside Group
MPM Capital
MTS Health Investors
Navigator Healthcare Partners
NEMO Capital Partners LLC
New Leaf Venture Partners
NewSpring Capital
Nova Bright Capital
Novartis Venture Funds
Novo Ventures
OrbiMed Advisors
ORIX
Pamlico Capital
Pamplona Capital Management
Persistence Capital Partners
Pharos Capital Group LLC
Pritzker Group
Provident Healthcare Partners
Riata Capital Group LLC
Ridgemont Equity Partners
Riverside Partners
RoundTable Healthcare Partners
Sentinel Capital Partners
Sheridan Capital Partners
Shore Capital Partners
Silver Oak Services Partners LLC
Spanos Barber Jesse & Company (SBJ)
Spindletop Capital
Split Rock Partners
STAR Capital Partners
Sterling Partners
Summit Partners
SV Life Sciences
Sverica Capital Management LLC
TA Associates
Texas Pacific Group (TPG)
The Gores Group
The Jordan Company (TJC)
The Riverside Company
The Vistria Group
Third Rock Ventures
Third Security LLC
Thomas H. Lee Partners (THL)
Thompson Street Capital Partners
Triton Pacific Capital Partners LLC
Tullis Health Investors
Tyree & D'Angelo Partners
Venture Investors
Versant Ventures
Vesey Street Capital Partners LLC
Vestar Capital Partners
Water Street Healthcare Partners
Waud Capital Partners
Welsh, Carson, Anderson & Stowe (WCAS)

Nice Insight **Annual Market Surveys**

Benchmarking
That's Nice/Nice Insight can provide insights to your marketing presence and known service offering based on industry buyer responses to one of our annual market surveys.

CDMO
+ Annual Study Year 6
+ 702 Respondents
+ 313 Profiles
+ 163 Deep Dive
www.NiceInsightCDMO.com

CRO
+ Annual Study Year 6
+ 608 Respondents
+ 124 Profiles
+ 73 Deep Dive
www.NiceInsightCRO.com

Original Equipment Manufacturers (OEM)
+ Annual Study Year 3
+ 597 Respondents
+ 137 Profiles
+ 90 Deep Dive
www.NiceInsightPharmaEquipment.com

Excipients
+ Annual Study Year 2
+ 541 Respondents
+ 39 Profiles
+ 31 Deep Dive
www.NiceInsightExcipients.com

Clinical Supply Chain Logistics
+ Annual Study Year 1
+ 320 Respondents
+ 22 Profiles
+ 22 Deep Dive
www.NiceInsightLogistics.com

Pharmaceutical Intermediates
+ Annual Study Year 1
+ 545 Respondents
+ 86 Profiles
+ 62 Deep Dive
www.NiceInsightIntermediates.com

Private Equity/Venture Capital
+ Annual Study Year 1
+ 69 Respondents
+ 135 Profiles
www.NiceInsightPEVC.com

SUPPORTING THE PHARMA INDUSTRY SMALL BUSINESS GROWTH ENGINE

→ BY **SYED T. HUSAIN** AND **CATHERINE HANLEY**, ALCAMI

Small and medium-sized companies generate greater than two-thirds of the clinical candidates in the pharma and biotech industry drug pipeline. They often, however, lack the knowledge and resources required to take a new medicine from the lab to the market and need support from CDMOs that offer integrated, tailored, customized solutions and personalized technical support.

NEW GROWTH ENGINE FOR A CHANGING MARKET

The pharmaceutical industry looks very little as it did even a decade ago. Not only has the focus shifted from the development of blockbusters to drugs aimed at indications for smaller patient populations, the majority of new clinical candidates now come from medium-sized and smaller companies, including those that consist of two employees and a patent.

Notable is the increased interest in the development of drugs for the treatment of rare diseases. In 2014 and 2015 respectively, approximately 47%[1] and 41%[2] of the novel new drugs approved each year by FDA were destined to treat rare or orphan diseases. In 2016 (through November 10), 32.5% of the 19 FDA-approved drugs received orphan drug designations.[3]

One driver for this growing interest is the lower phase III development costs for orphan drugs, which according to market research firm EvaluatePharma, are generally half those for non-orphan drugs.[4] In addition, according to a recent study of nearly 10,000 clinical and regulatory phase transitions by the Biotechnology Industry Association, Biomedtracker and Amplion, rare disease programs have higher success rates at each phase of development than the average for all programs.[5]

It has been reported by the Tufts Center for the Study of Drug Development that smaller firms developing small-molecule drugs have higher clinical approval success rates than large companies.[6] However, it was also noted that "this advantage was offset to some degree by lower returns on approved drugs, suggesting different strategic objectives with regard to risk and reward by firm size."[7]

To complicate matters, a growing percentage of drugs are being developed under accelerated timelines through the use of four FDA programs designed to reduce drug approval times: Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review.[6] In 2014[1] and 2015,[2] respectively, 60% and 66% of the new FDA-approved drugs fell into one or more of these expedited categories. As of November 10, just over 50% of the new drugs approved in 2016 received special designations from the FDA.[3]

Alcami has identified approximately 2,800 pharmaceutical companies and universities in the U.S. alone with revenues up to $500 million. Of those, approximately 50% are located in "neglected" states, or states that have little or no outsourcing options. These companies often have limited knowledge of the drug development and approval process and in many cases are unsure what their next steps should be. As a result, they need extensive support and require more than just contract service providers – they need partners.

NEW OUTSOURCING PARADIGM

The historical outsourcing paradigm involving RFP processes managed by procurement personnel at pharmaceutical companies is not relevant for these small and medium-sized firms. They have limited resources and time; the longer a project takes, the more their minimal capital is consumed. A new approach for rapidly selecting service partners and implementing projects is essential. These companies also need solutions that are tailored and customized for their specific circumstances and include personalized technical support.

Alcami has elected to take an educational approach, showing small and medium-sized pharmaceutical companies what they need to know when they are still potential customers. Rather than these firms needing to seek and find an outsourcing partner, Alcami is actively providing information about the entire drug development process, including regulatory compliance requirements.

In addition to a playbook on drug development and commercialization, Alcami is creating educational events designed specifically for different regions of the country where there are high concentrations of biotech startups and university-based companies. This "create your own forum" approach will serve as a way to connect companies in need of information with experts on all aspects of the pharmaceutical development process – both Alcami scientists and external specialists, such as university professors actively involved in joint programs with the industry.

A second component to Alcami's approach involves a departure from commission-based sales. This conventional system encourages short-term thinking, which is inappropriate for small and medium-sized businesses that require on-going support. Indeed, our sales approach is tailored to educating customers, and our salespeople are intimately involved in the establishment of educational relationships. They have technical knowledge and can understand all aspects of drug development and manufacturing, and thus are able to help customers identify the technical and operational support they need to progress to the next stage.

OPERATIONAL FLEXIBILITY IS PARAMOUNT

Such an educational approach has, as a prerequisite, operational flexibility. Often small and medium-sized companies do not know what they need until shortly before they need it – and many times only after receiving information from our technical sales staff. As a CDMO, Alcami must be extremely flexible and responsive in order to rapidly accommodate these changing requirements.

Continued growth of the company (expectations of portfolio expansion by 3-4 times) with increasing emphasis on the support of small and medium-sized customers translates to the simultaneous pursuit of numerous clinical programs. In order to remain flexible and responsive under these conditions, Alcami is implementing work cells.

Every company has its own set of unique requirements for development and manufacturing projects. Consistent among our clients, however, is the need for project certainty. In response, Alcami is implementing teams of dedicated resources, referred to as work cells, that are fully accountable for the end-to-end lifecycle of management of client projects.

ANTICIPATING CUSTOMER NEEDS AND MEETING THEM WILL ULTIMATELY DRIVE BUSINESS GROWTH – AND IT IS THIS BELIEF THAT IS **DRIVING ALCAMI TO IMPLEMENT THE "CUSTOMER COMES FIRST" CONCEPT IN A NUMBER OF DIFFERENT WAYS.**

Alcami's work cells are designed such that the cell either already has or will develop specialized knowledge of client product(s) and processes. The work cell will remain with the project in all phases for the entirety of its duration, as well as with a particular client over multiple projects and years. This level of specialization creates strategic advantage for our clients in the form of change readiness, complexity reduction and elimination of waste.

Close collaboration with our clients along the way take lessons learned and transform them into best practices to ensure future projects benefit from the experiences and knowledge already gained. With Alcami's global team executing under the same standards and best practices, our clients will experience unrivaled levels of project performance, quality and certainty.

INTEGRATION IS CRUCIAL TOO

Customers of all sizes, from "two employees and a patent" to small to mid-sized also benefit strongly from partnerships with CDMOs that can provide end-to-end solutions from development to commercialization. Alcami addresses this need by incorporating three components in all of its offerings to support projects at different stages: concept-to-clinic, approval and post-approval. Technical governance, including well laid-out plans from the bench to the pilot and plant scales, is another important aspect of the support offered to smaller sponsor firms. A single program manager

also oversees each project – acting as a mentor – listening to and providing the customer with valuable guidance.

PUTTING THE CUSTOMER FIRST

The key concept behind Alcami's proactive, educational approach is that the needs of the customer come before those of the CDMO. This concept isn't new in many industry sectors, but is a novel approach in pharmaceutical outsourcing. Anticipating customer needs and meeting them will ultimately drive business growth – and it is this belief that is driving Alcami to implement the "customer comes first" concept in a number of different ways.

Our Protect Your Brand™ offering is one example. This innovative solution supports pharma and biotech companies looking to implement a dual sourcing strategy but that lack the resources to secure a permanent second sourcing option. It enables customers to quickly bridge unexpected gaps in a given supply chain without any requirement for a long-term commitment. Customers can secure their supply chains by being proactively prepared on an annual basis for potential future needs.

Under the program, Alcami will validate a product (API or formulated product) in advance of potential manufacturing needs (for clinical or commercial supply) without any long-term commitment and no minimum volume – just validation. We will maintain the required capacity for our partners at an agreed-upon level and be ready on quick notice to accommodate the start of production in accordance with U.S. and international regulatory compliance requirements. As with other offerings, the Protect Your Brand service comprises three distinct supply chain solutions to prevent disruptions from occurring at the earliest concept through to post-approval commercial supply. Customers can also choose their desired state of readiness via our propriety Alcami State of Readiness Ranking system. By responding quickly, Alcami can minimize the effects of a supply disruption, helping to prevent shortages and delays. We do this by using our proprietary state of Alcami Readiness™ scoring system and cover it in our annual state of readiness meeting.

Meanwhile, the ProForm Select™ integrated offering, by addressing both API process and formulation development in parallel, ensures that customers avoid process instabilities and missed clinical milestones. Under the guidance of a single project manager, solid-state chemistry and formulation development occur together, allowing seamless technical and quality alignment and a focus on proactive solutions. As a result, projects move more quickly with improved process stability, mitigated risk and no need for tech transfer.

CONCLUSION

Small and medium-sized drug companies are the growth engine of the pharmaceutical industry but lack easy access to service providers with the knowledge and capabilities they need to take their promising candidates from the clinic to the market. These innovative firms desire to partner with fully integrated science and technology CDMOs like Alcami that are easy to work with and committed to helping them move rapidly through the drug development process.

At Alcami, we continue to invest in our capabilities to ensure that we can meet the needs of this important customer base, including the development of educational initiatives specifically tailored to meet their needs. Simultaneously, we are working to achieve operational and commercial excellence in all aspects of our business (people, processes and systems) and implementing programs that redefine the role of a CDMO by considering the customer first. P

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ADVANCING SOLID DOSE PROCESSING EFFICIENCY AND EFFECTIVENESS

→ BY **ED GODEK** AND **STEPHEN SIRABIAN**, GLATT AIR TECHNIQUES, INC.

Pharma is approaching continuous manufacturing with caution. However, equipped with fresh technical experience, plus decades of process design and control science across chemical synthesis and manufacture, pharma's confidence is growing in continuous manufacturing's cost, quality and risk-controlling benefits and its potential application to a broader range of oral solid dose processing environments.

Because oral solid dose (OSD) pharmaceuticals will remain the dominant dose form, the pharmaceutical industry will continue to be responsible for the high-quality manufacture of hundreds of millions of individual doses every day, every year for the foreseeable future. But as the world's uptake of solid-dosage pharmaceuticals continues to grow, so does the perception that drugs are too expensive and increasingly unaffordable, and even though there is evidence to the contrary, there has never been more pressure on pharma to produce its products at the lowest cost possible.

It's well established that the safety, effectiveness and value of a given OSD pharmaceutical is reliant on the quality and reliability of its manufacture. At a certain point the FDA – and, subsequently, the world's regulators – recognized that fact and ushered in a regulatory era focused on (among other things) how pharma manufactures its drugs. In its effort to promote, rather than hinder, the safe, reliable supply of drugs to patients and consumers, regulators began to collaborate more closely with the industry and its suppliers to forward an operational excellence agenda and work to implement technologies and systems like continuous manufacturing (CM).

The emphasis by regulators and the industry's technology suppliers on institutionalizing CM and similar technical innovation across drug manufacturing comes from a good place, one based on solid experience and empirical data gathered from real-world industrial manufacturing experience outside of pharma. Including chemical and petrochemical processors, electronics and steel manufacturers and food and beverage processors, most prominent industrial sectors have employed continuous and semicontinuous processing for decades. According to *BioProcess International*, there's one thing they all have in common: "Most of these industries are capital intensive and switched to flow manufacturing to increase productivity and flexibility; reduce cycle times, inventory, waste and costs; and achieve enhanced product quality."[1]

WARMING TREND

The FDA's drive to introduce continuous manufacturing innovation to pharma gained steam with Center for Drug Evaluation and Research (CDER) director Janet Woodcock's public advocacy of the processing technique. To assist industry in evaluating the technology and its implementation, FDA released its draft guidance in December 2015, "Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base." Intended to help manufacturers implement a variety of technological advancements, the guidance was developed by FDA's Emerging Technology Team and published to help further establish CM's viability and regulatory frame to support the transition from batch to CM and its ability to approve CM lines in step with drug development.[2] In hearings before Congress in January 2016, director Woodcock reminded lawmakers of the agency's desire to convince more manufacturers to consider switching to CM methods.

Within a year of FDA's guidance (April 2016), the agency approved a first-ever manufacturing change for Janssen's HIV-1 treatment Prezista from batch to continuous. According to CDER's FDA deputy director Lawrence Yu, Ph.D., from the Office of Pharmaceutical Quality, the event marked another significant step towards integrating CM into pharmaceutical production. FDA approved, for the first time, a manufacturer's change in their production method from "batch" to CM.[3] The change approved the manufacturing of tablets on its CM production platform installed at its manufacturing facility in Puerto Rico. According to Dr. Yu, continuous "enables much faster production and more reliable products through an uninterrupted process." How much faster is CM? In some cases, said Dr. Yu, "manufacturing that takes a month by batch technology might only take a day using continuous manufacturing techniques." He noted, though, that such speed alone would not matter if CM compromised quality. "But by eliminating breaks between steps and reducing opportunities for human errors during the stops and starts in the batch process, continuous manufacturing is more reliable – and safer. That's a powerful combination."

About that same time, Hovione announced its plans in a press release to "host and operate a commercial-scale continuous manufacturing facility as part of an agreement with Vertex Pharmaceuticals," another continuous innovator deploying CM.[4] In June 2016, Hovione announced the groundbreaking for a significant expansion of their New Jersey facility to more than double drug substance manufacturing capacity at the site.[5] Hovione explained that the "site will be unique in offering a single location for drug substance, spray drying, hot-melt extrusion and drug product manufacturing services using innovative continuous manufacturing technology." The company said the investment was part of the company's strategy to increase its global development and commercial capacity to meet the increasing demands of Hovione's customers.

Industry and academia have formed alliances to help bring the benefits of advanced CM process to pharma – for example, the Center for Structured Organic Particulate Systems (C-SOPS), a National Science Foundation engineering research center led by Rutgers University. Prominent engineering schools, including Purdue and the University of Puerto Rico, also participate, along with Glatt, which has contributed equipment, engineering and material support to the R&D collaboration. The Novartis-MIT Center for Continuous Manufacturing is another similar collaboration. According to the group, the 10-year research alliance is aimed at transforming pharmaceutical production by combining the industrial expertise of Novartis with MIT's scientific and technological leadership.[6]

CONTINUOUS BENEFITS

According to C-SOPS, "Continuous manufacturing represents an innovative shift from the traditional multistep, multilocation batch production process, which can take up to four weeks or more to make commercial-ready medicines." C-SOPS finds that "Continuous manufacturing is well suited for the production of precision

medicines and those with breakthrough therapy designations where development time lines may be short and there are patients in urgent need of transformative new treatments."

CM can also be deployed in a smaller footprint than conventional batch process and is proving to be an efficient solution, regardless of proposed product volume. Producing product at commercial volumes becomes a time exercise rather than a capacity/scale issue because making more product means running the process longer as opposed to making it bigger. Suddenly the capital outlay to support a high-demand product becomes a more affordable and sustainable exercise.

QBD-FORWARD

Among the many things regulators and process engineers point out about continuous processing is that a transition from batch to continuous processing enables the development of processes within the cGMP principle Quality by Design framework. To achieve equipment coordination and predictive capabilities that CM promises, process analytical technologies (PAT) are required if the relationships between critical quality attributes, critical material properties and critical process parameters are to be correlated sequentially between the multiple unit operations in product manufacturing.

GAIN CONFIDENCE HERE

In spite of its successes, the industry is understandably recalcitrant to more fully accept and integrate CM, largely because of fears regarding additional capital investment required beyond existing batch processes, as well as the prospect of new equipment and staff training that would be required.

To help drug innovators gain the confidence it's going to take to make the necessary capital and operational investments behind a transition to CM, not to mention instituting CM more comprehensively, Glatt opened a multimillion-dollar innovation center in Binzen, Germany, in 2016. Within the center, Glatt has configured two stand-alone CM process lines to support drug innovators and manufacturers and provide a chance to evaluate the performance of specific compounds and formulations in a CM scheme. Anyone considering a move to CM can bring their molecule and formulation to Glatt for a comprehensive real-time trial within the CM processing environment.

These lines feature Glatt's CM solution called MODCOS (Modular Continuous System). MODCOS offers flexible configuration and consists of dosing feeders and a dry mixer for powder or microgranulates, followed by granulate production using a twin-screw extruder or single shaft granulator, drying in a fluidized bed processor (including a new rotary chamber), followed by a tablet press, which can be supplemented with an extra dry mixer or sizing mill, if required. Both lines are similar in scope, with one sized for R&D and the other for manufacturing. A supervisory control system is employed for each system integrating PAT for monitor and control of (critical) quality attributes and process parameters, such as particle size and moisture. Regardless, drug manufacturers now have a great opportunity to evaluate and pilot the CM process without an intensive financial or operational commitment.

Evidence is mounting that the pharma industry has reached the technical limits of batch processing when it comes to quality control and production efficiency. Any new gains in reliability, cost control or flow optimization from this point are increasingly incremental and expensive to implement. In the coming decades, and as pharma moves well past the blockbuster era, the incentives supporting CM's efficiencies, quality optimization and cost control will continue to mount and prompt the industry to more universally embrace CM as the common standard. P

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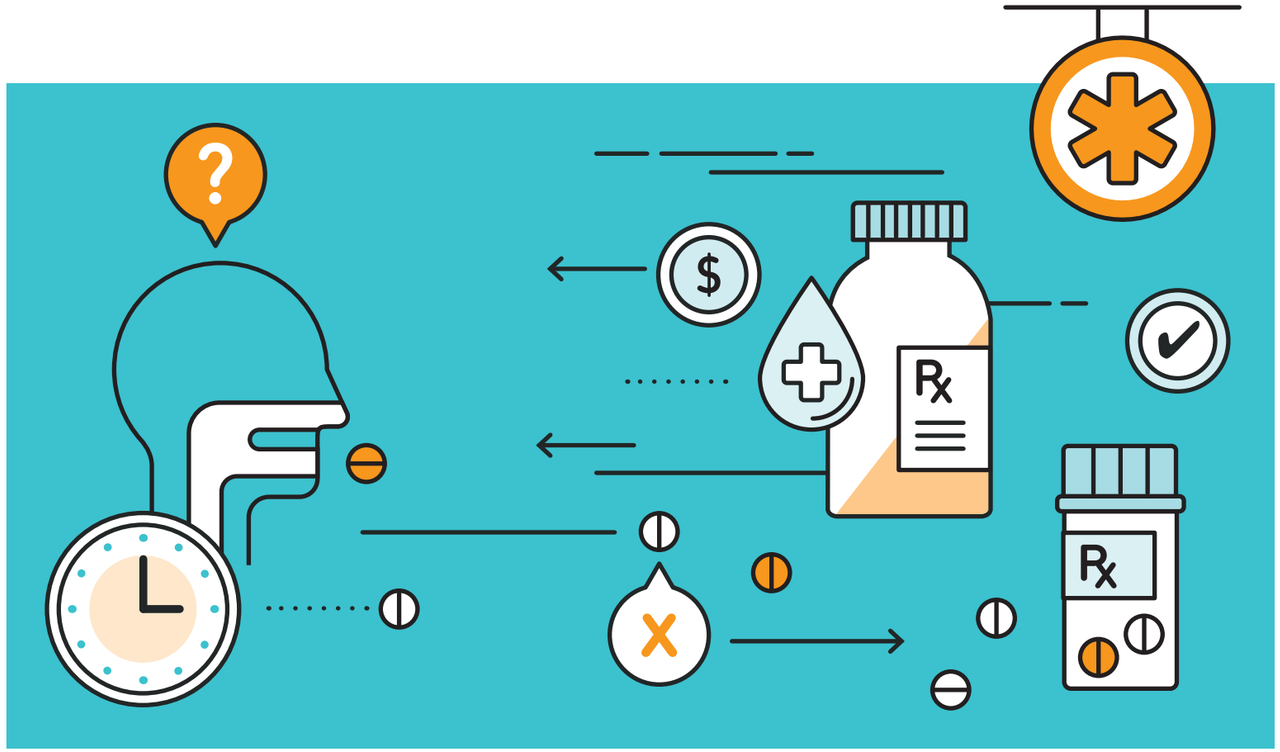
PHARMA'S REPUTATION GAP: CONSUMER BUSINESS INNOVATION

BY **KEVIN HAEHL**, UNITHER PHARMACEUTICALS



Pharma has an image problem; innovation is the answer. From pricing and value to safety and quality, there are few elements of the pharmaceutical industry that haven't been subject to harsh criticism by society — it's a long-term trend.

Headlines on exploitive pricing practices are just the most recent examples of pharma's corporate social "irresponsibility" presented for public vilification. Right or wrong, pharma remains a perennial target and a popular bogeyman among politicians, the media and a broad range of interest groups.

Let's face it, Americans have a terrible view of the pharmaceutical industry, which is "now rated one of the worst industries" according to Gallup analyst Jim Norman. In Gallup's annual measure of 25 major U.S. business sectors, the percentage of Americans with a positive view of the pharmaceutical industry dropped from 40% in 2014 to 35% in 2015.[1] Gallup's polling data revealed only the oil and gas industry (ranking last 10 times) and the federal government (which took the bottom spot itself for three years) have consistently scored lower.

Owning and addressing this reality with tangible action is crucial to our future. Pharma's poor reputation is hurting our business, limiting available investment, and, perhaps most damaging, leading the brightest minds away from the pharmaceutical industry.

BAD PUBLIC OPINION LEADS TO BAD BUSINESS ENVIRONMENTS

Recent headlines notwithstanding, pharma's brand equity and reputation is a critical issue that the entire supply chain must respond to more vigorously. During the recent political cycle, presidential candidates Clinton and Trump offered remarks critical to the industry.[2,3] Citing high-profile price increases, Hillary Clinton's policy brief declared "Between 2008 and 2015, drug makers increased the prices of almost 400 generic drugs by over 1,000 percent."[4] Prior to the election both candidates proposed bills and policy reforms to regulate the industry's assumed excesses and curtail future profiteering.

And the election did not end the rhetoric. Continuing the necessary debate on pharmaceutical pricing, Donald Trump said at his first post-election news conference that pharmaceutical companies are "getting away with murder" and vowed, "We are going to start bidding. We are going to save billions of dollars over time."[5] If not reversed, the poor perception of the pharma industry will inevitably lead to policies damaging to the industry, including price controls and limits on intellectual property protection, discouraging costly research into cures and treatments.

UNCERTAINTY TURNS AWAY INVESTMENT

A poor reputation hits companies where it hurts – in the stock price. Investors shy away from such industries, and reduce investment even more as uncertainty increases. Part of pharma's consumer "brand" has become its alleged exploitive pricing – which continues to prompt remarks like those of the president. According to Forbes January 11, after Donald Trump's remarks targeted high drug prices, billions fled biotech and pharma stocks in a steep selloff.[6] Shares of Pfizer, Endo and BMS were all identified by Forbes as the "biggest losers" in the wake of the Trump press conference. The uncertainty of future drug prices in light of the price controls proposed by Trump had a real negative impact on pharma stock valuation across the sector.

MARKETS VALUE INNOVATION IN PHARMA ABOVE ALL ELSE.

Markets value innovation in pharma above all else. In the same article, Forbes noted Merck managed to beat the trend, ending the day up by 2.6%, the Dow's best performer on the announcement that the FDA accepted its request for an accelerated review of its new drug for patients with advanced lung cancer. With a bad reputation stifling the flow of market capitalization into research, the next generation of cures may be delayed.

POOR REPUTATION REPELS TALENT

Pharma's bad image is creating other losses that may not be seen for decades. "Individuals want to work for organizations with a positive reputation and ethical c-suite leadership," said Jill Schwieters, president of Cielo Healthcare, commenting on a recent Corporate Responsibility magazine survey on reputation and talent acquisition.[7] "The research demonstrates that a bad reputation could cost real money by increasing recruiting costs as organizations perceived as unethical struggle to successfully recruit women and Millennials."

The declining availability of scientific, technology, engineering and math graduates is well documented. Pharma is already challenged to attract top talent and the negative connotation pharma carries is doing nothing to help the situation. It's going to be tough for pharma if the best minds aren't on board to fuel its future.

IF A COMPANY LIKE APPLE DISCOVERED THAT HALF OF CELL PHONE BUYERS COULD NOT PROPERLY USE AN IPHONE, **WOULD THEY NOT TAKE ACTION TO IMPROVE THE USER EXPERIENCE?**

THE ONLY WAY TO FIX THE PERCEPTION IS TO OWN IT

All too often pharma's answer to negative press has been to assume that it is a communication problem. "If only society knew the good that pharma does" or "Drug pricing is too complex for people to understand, we have to explain it better" are common responses, but pharma's poor reputation will never improve unless the industry can reconcile price versus value in the public's eye.

Pharma needs to own its reputation and act to address it by better serving the interests of patients with products that directly meet their needs. We need to start thinking like a consumer business.

THE ANSWER IS INNOVATION — MEETING THE PATIENT'S NEEDS

Research from the New England Healthcare Institute revealed something interesting: drugs that are too expensive to consumers or that are too difficult or too complex for people to take as prescribed generate as much as $290 billion in direct but avoidable health care costs – otherwise a third of all unnecessary health care waste and spending.[8]

A key cause of this waste is the poor pharmionic attributes (the drug's effectiveness in the real world rather than in a controlled clinical study) of highly-consumed drugs – especially those treating chronic age-related disease categories like arthritis and heart disease. When geriatric patients, a major drug-consuming constituency, can't or won't take their medications properly and fail to adhere to their prescriptions, they tend to go to the hospital for long, expensive and unnecessary hospital stays.

The fact is that approximately half of patients are not taking their medicines as prescribed.[9] If a company like Apple discovered that half of cell phone buyers could not properly use an iPhone, would they not take action to improve the user experience?

With medication adherence at the center of unnecessary costs and poor health outcomes, it's an obvious opportunity for the industry to take a leading role in reducing health care's tremendous bill and improving the user experience – just the thing to improve public perception.

THE TECHNOLOGY TO MAKE CONVENIENT, AFFORDABLE AND EASY-TO-USE MEDICINES IS HERE

Combining effective drugs, convenient delivery and personalized analysis of data is one way that we can improve the patient experience. The September 2016 FDA approval of Medtronic's MiniMed 670G hybrid closed looped system, the first FDA-approved device that is intended to automatically monitor glucose (sugar) and provide appropriate basal insulin doses, is a good example.[10] The easier it is for patients to automatically control blood sugar level excursions, the better they will appreciate the industry.

Innovations in packaging, delivery and data sharing are at the forefront of the development and study against drug nonadherence. Contract manufacturers and supply chain partners are leading the effort. Unither Pharmaceuticals, for example, is developing unit dose technology – forms that are proven to enhance adherence – combined with communications technology to monitor the use of pharmaceuticals in real time. Our technologies benefit patients by offering improved safety and compliance with premeasured single doses that are portable and convenient, and reduce the risks of medication errors.

The pharmaceutical industry is at a critical point in its history. Our reputation must improve. If we fail to turn the tide of public opinion, our favorable business environment, available investment and future talent may be lost. Far worse, society will lose out on the potential good that this industry can achieve. It is time we think like a consumer business and innovate in new ways to provide more convenient, affordable and easy-to-use medicines that the public will value. P

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FACILITATING TECH TRANSFER FOR PARENTERAL PRODUCTS

→ BY **MARGA VIÑES**, GRIFOLS PARTNERSHIP

Pharmaceutical outsourcing by definition requires the transfer of technology from the sponsor company to the service provider. Outsourcing of sterile injectable fill-finish projects brings additional complexities and risk. Successful tech transfer in these cases requires a CDMO with extensive process and product understanding, a comprehensive quality culture, and the willingness of both parties to form true collaborations based on trust.

TECHNOLOGY TRANSFER DEFINED

The goal of technology transfer according to ICH Q10 is to "transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization." This knowledge "forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement."[1]

Meanwhile, pharmaceutical technology transfer, according to the Parenteral Drug Association, "consists of planned and controlled actions that are based on well-defined acceptance criteria to convey a manufacturing process, analytical method, packaging component, or any other step or process along the pharmaceutical drug lifecycle from an originator site, known as a sending unit (SU), to a new site, the receiving unit (RU)."[2]

The World Health Organization focuses on controls for transfer of processes along with the necessary documentation and professional expertise: "Technology transfer embodies both the transfer of documentation and the demonstrated ability of the RU to effectively perform the critical elements of the transferred technology to the satisfaction of all parties and any applicable regulatory bodies."[3]

What does all of this actually mean for a sponsor company looking to outsource parenteral drug product fill-finish activities? Strong alignment between the sponsor and CDMO is crucial. The service provider should not only have the physical capabilities – facilities and equipment for manufacturing, sampling and analysis – plus sourcing and technology transfer management systems and various control strategies, but also extensive process and product understanding, a risk-based approach (quality by design) and a culture that both allows for flexibility and is founded on a commitment to quality and trust. In other words, the ideal CDMO must act as an extension of the sponsor and serve as a partner, not simply a supplier.

A FOUNDATION OF TRUST

The more knowledge that a sponsor company shares about the process to be transferred – and the product to be manufactured using that process – the more smoothly tech transfer can be accomplished. Of course, sharing this type of proprietary knowledge carries risks. Sponsor companies should carefully select a CDMO with which they can build an intense, two-way relationship, thus establishing a level of real trust.

Lack of information can have significant, negative consequences for the technology transfer process. Not only does it typically lengthen project time lines, it creates additional work for the CDMO, adds to customer cost, and can potentially have safety consequences for plant personnel and even the patient. Confidentiality agreements between sponsors and CDMOs should help circumvent this issue, as they are designed to protect both parties.

CDMOs with excellent track records of performance, such as Grifols Partnership, have no interest in misusing information or taking any actions that will negatively impact their reputations. Because a large part of our business is in blood derivatives, a market in which success is driven largely by reputation, we are committed to maintaining highly positive perceptions of the Grifols name in all markets that the company participates in.

LEADS TO DEEP COLLABORATION

Establishing a strong foundation of trust not only facilitates technology transfer through greater knowledge sharing, it also leads to the development of much closer relationships between the sponsor and CDMO, which in turn results in deeper collaborations that further enhance the technology transfer process.

Collaboration is also enabled at Grifols by the use of an integrated project management strategy. Cross-functional teams with representatives from all relevant areas – manufacturing, R&D, quality assurance, quality control, regulatory as well as sales and marketing – report to team leaders with expertise in technology transfer and extensive experience within the company. Such a collaborative effort between Grifols and our customer allows for consideration of all potential consequences before implementation of even the smallest changes. The result is the avoidance of unexpected problems and the need to make corrections. Such an effective team also makes it possible to readily resolve any problems that do arise, preventing unwanted delays and keeping projects on schedule.

UNDERSTANDING ON MANY LEVELS

The need for understanding is not limited to the process and product that are being transferred. Knowledge of each party's expectations and limitations is essential. Familiarity with project management and quality systems at both companies can also facilitate rapid completion of tech transfer projects.

Although not often considered during technology transfer, an understanding of the market and the needs and expectations of the ultimate end user can also be highly beneficial to this important process. CDMOs with knowledge of patient preferences and an understanding of how even small changes in process or product design might impact final product acceptance can help guide the tech transfer process towards a more positive outcome. Indeed, bringing patient/physician/caregiver considerations into the development process as early as possible can significantly influence the success of a tech transfer program.

QUALITY MATTERS

A culture of quality and effective quality systems are essential to successful technology transfer, particularly for the production of complex products such as sterile injectables. In order to participate in the plasma-derived proteins market, Grifols has made an extensive commitment to quality. Quality culture is at the roots of our company and it branches out to all of our businesses, including our sterile fill-finish operations.

Perhaps most notably, Grifols has never experienced any quality problems with its blood derivative products due to virus contamination. Also indicative of our robust quality systems is the fact that we received zero 483 complaints following our most recent (June 2015) FDA audit. It is also worth noting that Grifols was one of the first companies in Europe to obtain approval for the parametric release of parenteral solutions in glass and flexible containers from its manufacturing plants in Spain. Parametric release is authorized

for companies that have shown a sterility assurance release program that has demonstrated a control of the sterilization process and high consistency in their overall quality system.

The company has also invested heavily in automation technologies to reduce the risk of error and contamination for increased operator and patient safety. For instance, our "Form-Fill-Seal" technology – implemented for the production of polypropylene bags – and our fully automated glass vial filling lines both minimize human interactions with drug products. Artificial vision systems (developed in collaboration with Diagnostic Grifols), which enable the automatic inspection of injectable products for particulates, also eradicate the potential for human error.

DEEP RESOURCES BRING BENEFITS

Technology transfer is a complex, multistep process requiring the input of teams of experts at both the sponsor and CDMO levels. Access to resources that can simplify the process, provide improved process controls and/or facilitate communication and collaboration can be highly beneficial.

As part of a successful, global pharmaceutical manufacturer, Grifols Partnership has access to a depth of resources not available to stand-alone CDMOs. Financial resources can be available for investment in new technologies, capacity and/or capabilities required for technology transfer projects. In addition, the equipment used for contract manufacturing projects is the same equipment used for internal Grifols production, so operators have intimate knowledge of their performance characteristics.

This equipment is designed specifically for Grifols by Grifols Engineering, a Grifols company devoted to the design of pharmaceutical production plants, processes and machinery. This vertical integration allows Grifols to be as independent from suppliers as possible. It extends, as mentioned above, to the Form-Fill-Seal technology for filling PP bags. Most importantly, vertical integration enables Grifols to control the entire process, ensuring achievement of the highest quality.

CONCLUSION

Technology transfer is integral to pharmaceutical manufacturing. Whether a process is being transferred from one site to another within a company or between a sponsor and an outsourcing partner, success requires extensive knowledge sharing and real collaboration between the sending and receiving teams. While transfer to a CDMO can potentially carry additional risk, selection of a service provider with extensive experience in tech transfer, a robust quality culture and a commitment to collaboration can in fact facilitate the tech transfer process.

For companies looking to outsource sterile injectable fill-finish operations, including the development and manufacturing of products that require advanced technologies and complex production processes, Grifols is just such a CDMO. We focus on the sterile fill-finish of small-molecule intravenous solutions. Approximately 70% of incoming projects are direct tech transfers, with the remainder also involving process/formulation development. We work with customers from early stages of development through commercial manufacturing and provide scale-up and tech transfer of processes, including process development and validation, engineering runs and clinical and commercial batches, analytical method development and validation, stability studies, dossier support documentation, and labeling and packaging in glass and plastic vials, glass bottles and flexible PP bags. P

Regarding trust and understanding customer needs, we would like to highlight a recent customer agreement

A certain company is looking for a new CMO for a product because the current CMO has decided not to continue manufacturing an IV solution.

The project faces different challenges:

- The product is the only product in the portfolio of the company.
- Current product stock is insufficient to cover the expected market demand over the next two years.
- Market demand for the product is increasing at a healthy rate.
- Exhibit batches should be submitted to FDA six months after the signing of the agreement.

Moreover, the customer does not have the analytical protocols available or the manufacturing flow chart. This information is not provided by the current CMO. Based on its experience and knowledge of intravenous solutions, Grifols decides to go ahead with the project. In order to accomplish the narrow time line, we need to define alternative actions for any possible setbacks and ensure a thorough control of the technology transfer stages. Grifols decided to prioritize the project prior to handling internal projects and allocated additional human resources to those initially anticipated; this is an example of our commitment towards customers.

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

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DISSOLVING BOUNDARIES IN WORLDWIDE CLINICAL TRIAL LOGISTICS FOR BIOLOGICAL SAMPLES AND NEW THERAPIES

BY **ARIETTE VAN STRIEN** AND **DANIEL BELL**, MARKEN

Marken maximizes efficiency and enhances service offerings while continuing to specialize in the high-touch, personalized services that the company is known for in providing supply chain solutions for clinical trial materials and sensitive drug shipments.

INDUSTRY-LEADING SERVICES

Marken is a leading patient-centric supply chain logistics organization with a complete focus on the pharmaceutical and life-sciences industries. Its state-of-the-art GMP-compliant network includes 10 GMP-compliant depots and 45 worldwide logistic hubs for clinical trial material and investigational medicinal product storage and distribution, in addition to direct-to-patient (DTP) services and 50,000 monthly shipments of time- and temperature-sensitive drug and biological shipments at all temperature ranges in more than 150 countries, Marken also offers biological kit production; ancillary material sourcing, storage and distribution; shipment lane verification and qualification; and GDP, regulatory and compliance consultancy services.

NO BOUNDARIES

Marken operates a global network of clinical supply chain services to meet the increasingly complex demands of its clients, with no geographic boundaries.

The company is poised to explore the possibilities for new offerings to clients, particularly with regard to expanded drug-distribution solutions. Marken is also well positioned to widen its global network as the company continues to expand into regions of interest, such as the Middle East and Africa, as well as achieve further penetration into Asian markets and Eastern Europe.

PATIENT-CENTRIC APPROACH

One clear trend in the clinical trial space is a move away from the investigator site to the patient's home, which requires DTP services. Homecare networks are now responsible for not only patient treatment, but also for drawing, centrifuging and (if necessary) freezing of blood samples – all while the patient is at home. Latest advancements include extracting biopsies through the blood versus tissue samples, which will further increase the viability of adding DTP services to clinical trials. Logistics providers like Marken must have extremely flexible networks of their own with highly trained personnel who can work closely with these global homecare networks and establish appropriate schedules that ensure timely sample pick-up and delivery at a very diverse number of locations.

Marken became aware of this trend early on and began providing DTP services beginning in 2012. Consequently, they are a pioneer in developing DTP expertise. The challenges posed by the growing preference for in-home care became the platform for Marken's focus on patient-centricity. Currently the company offers DTP services associated with over 100 active clinical trials that involve more than 1,200 investigator sites. The primary issue is the patient's privacy, and if the provider is a data processor or data controller, each needs different levels of control.

DEVELOPING FAST-MOVING SOLUTIONS FOR PERSONALIZED MEDICINES

The growing need for patient-specific clinical trial logistic services can also be attributed to the rapidly expanding interest in next-generation therapies, particularly CAR-T and other cell and gene therapies. In particular, autologous, or patient-specific, cell therapies pose challenges with respect to turnaround times and chain of identity to ensure that the advanced therapy medicinal product (ATMP) is returned to the correct patients.

One of the biggest challenges is establishing an effective chain of identity. When ATMP is being shipped from investigator sites, hospitals or apheresis centers to the manufacturing site and back to the patient, there must be a process in place to guarantee that neither the samples or ATMP are at risk at any moment. Each sample and therapy is so unique that it must be tracked down to the tube or vial level.

Marken applies its exclusive GPS tracker technology, Sentry, as a first approach to addressing this issue. The company has also developed a Sentinel solution that will work in conjunction with the original GPS tracker to provide information for each component within a shipment, such as multiple samples from a single patient or multiple vials for a multi-dose treatment for a given patient.

To be most effective, however, technologies like the GPS tracker and the newer

THE GROWING NEED FOR PATIENT-SPECIFIC CLINICAL TRIAL LOGISTIC SERVICES CAN ALSO BE ATTRIBUTED TO THE **RAPIDLY EXPANDING INTEREST IN NEXT-GENERATION THERAPIES,** PARTICULARLY CAR-T AND OTHER CELL AND GENE THERAPIES.

MARKEN OPERATES A GLOBAL NETWORK OF CLINICAL SUPPLY CHAIN SERVICES TO MEET THE INCREASINGLY COMPLEX DEMANDS OF ITS CLIENTS, WITH NO GEOGRAPHIC BOUNDARIES.

version under development requires that Marken be actively involved in the setup of clinical trials with complex, patient-specific logistic requirements in order to allow complete feasibility assessments at the start of each trial.

Requirements such as these promising therapies are moving to commercialization and must also be considered. As these therapies become commercially available, the logistics issues remain unchanged from those faced during clinical trials. Planning, months in advance of the expected launch date, is a must to ensure a successful outcome.

Overall, therefore, interactions between the various points in the supply chain – hospitals, clinics, manufacturing sites, logistics companies, etc. – for next-generation medicines have a significant impact, and effective communication between the supply chain organization and all vendors is essential. A comprehensive network that can support all of those components is also a critical component.

TACKLING THE REUSABLE PACKAGING CHALLENGE

Updated Good Distribution Practice (GDP) regulations have aided in the development of innovative and temperature-controlled solutions, very often related to new packaging solutions. GDP also addresses the issue of maintaining accurate documentation and proof of temperature control, which were formerly one of the weakest links in the supply chain. Today, the industry needs more environmentally friendly solutions while still maintaining rapid turnaround times and temperature control.

The real challenge today is managing the large number of packaging types available in the face of the need to be greener and provide rapid turnaround times. The question is no longer just, "How do you transport drug products and APIs from one site to the other?" but also, "How can you safely and cost-effectively reuse these advanced packaging solutions within a network that includes both centralized and decentralized aspects?" Regarding inventory management, how many boxes is a key factor to a successful logistics strategy. Clearly the provider must monitor expiration dates of different packaging components and ensure compliance.

The new focus on return logistics presents challenges. The packaging must be perfectly clean and appropriately conditioned. Marken made these investments several years ago to build a network with the right capabilities and to identify geographically strategic locations in each region. In order to optimize the return logistics, clear GPS tracking must be in place to ensure the returns to either one client or multiple clients, as per the client agreement and needs. Investments were also made in quality systems to ensure that the procedures and equipment are properly managed and maintained. The company is also further boosting capabilities in the reusable packaging area; it is easier and more cost-effective to move empty cartons and components for special shippers and to do so at a price that makes reusable solutions sensible. Both pharmaceutical and packaging companies are turning to service providers like Marken that have very specific knowledge and network leverage that enables the economic delivery of this type of service. Marken has extensively developed all of this as a resolution to a key pain point for clients.

CONCLUSION

Marken is well positioned to expand its support of complex, global clinical trials. The company's expertise makes it possible to meet the growing needs of patient homecare by delivering drug products just in time. Marken will continue to enhance further patient-centric services for our clients, including DTP management and assistance with logistic solutions for personalized therapies and economical reuse of advanced packaging materials. P

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Ariette van Strien is Marken's voice of the customer, having spent 25 years in the clinical research industry with the last six years developing new services for Marken, spanning sales, marketing, business development, and global operational and project management roles. Having worked on the central lab and clinical side, Ariette brings a unique perspective from this portion of the supply chain. Ariette has a diploma as a National Public Relation Consultant, a Superior French Language degree from the International College of Cannes, and a baccalaureate of modern languages and biological sciences.

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Daniel Bell
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Dan is a licensed U.S. Customs Broker and a certified customs specialist with 25-plus years' experience in the life-science logistics and temperature control field. His current focus is regulatory and trade compliance aspects for global life-science supply chain solutions. Dan's expertise with thermo-regulating packaging solutions and temperature-logging devices has been critical to meeting the requirements of the recently updated Good Distribution Practices for pharmaceutical transport and similar guidelines.

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DESIGNING A BETTER SINGLE-USE FACILITY

→ BY **CARL CARLSON**, M+W U.S., INC.

With the right tool, single-use facility design can benefit from a proactive review of facility, systems, design intent and risk.

Although single-use, disposable technologies (SUTs) have been around for decades, continued development and implementation of this innovative process technology is needed to help accelerate the advancement of biopharmaceutical drug development.

SHARED RISK, SHARED REWARD

Responding to global market demand is increasingly a part of successful manufacturing strategy. SUTs promote capacity and production schedule flexibility, up to the 2,000L bioreactor batch and perfusion production scale. In addition, reliable process replication across global manufacturing networks and effective technology transfers to contract manufacturers are provided. The ability to use disposable and similar equipment configurations, and the same materials for production equipment at the process development and commercial-scale phases, also simplifies process scale-up and can accelerate time to market. The disposable platform greatly reduces time spent in cleaning validation.

In SUT processing trains, a portion of processing risk and quality control is shifted to the disposable systems manufacturer. Single-use technologies are also proving adept at delivering compliant, flexible cGMP manufacturing process platforms with improved production titers at many commercial scales. According to a 2015 BioPlan Associates study of the biopharmaceutical manufacturing space, more than 90% of biopharmaceutical facilities use single-use/disposable technologies. Also, manufacturers and suppliers consider both disposable and stainless-steel options when planning their manufacturing strategies.[1] Although some low-production titers of mAb scales may require stainless steel production at 20,000L batch volumes, many of the platforms work with perfusion and batch scale at multiple 2,000L scale and orphan drugs at the 2,000L and 500L disposable scale.

GETTING IT RIGHT THE FIRST TIME

For companies implementing SUT-based manufacturing strategically, assessing accurately the costs and benefits associated with implementing the technology optimally is critical. Regardless of existing or green-field facility project plans, facility design 'performance' can benefit from a proactive review of facility, systems, design intent and risk.

With years of experience conducting SUT risk assessments, we began to recognize a pattern. There are some engineering design quality approaches that can identify and quantify SUT process-associated risk, suggest mitigation strategy, and thus manage their impact to a minimum. It was recognized that to evaluate operational risk and forecast process performance accurately, an effective repeatable methodology was called for.

A SHARPER TOOL

Framed by a Failure Mode and Effects Analysis (FMEA) analytical structure, our analysis incorporates M+W Group's Single-Use Design (SUD) template to create a high-quality systematic review and risk assessment tool for evaluating SUT biotechnology facilities.

The SUD tool documents key process operations and ties them to specific processing parameters. In our client's experience this has proven to be an invaluable evaluation tool, bringing insight into the full potential of a given SUT process design decision, or when incorporating a new SUT-based process into current operations.

Regardless of what might be motivating the adoption, successful SUT implementation requires a comprehensive understanding of the design space and the quality structure applied to maintain control.

The SUD tool presents a structured approach for evaluating SUTs. Taking a life-cycle approach to product process design and production, the SUD tool rubric sets out a six-part evaluation sequence to structure the analysis:

1. **Establish the quality system**
2. **Define the design space**
3. **Document the design space**
4. **Perform a risk-based FMEA analysis**
5. **Perform sensitivity analysis on risk data**
6. **Finalize and fix the design approach**

There are many quality systems already established, but SUT processing guidelines are less established. Regardless, QbD life-cycle methodology may provide one of the stronger approaches to implementing an SUT quality system regime. Biopharmaceutical manufacturers are outsourcing the design space more and more. Quality attributes have to be met both by the drug manufacturer within the facility and by the SUT manufacturer as well, and both are tasked with characterizing their products and understanding the effect of leachables, leachable byproducts and similar, so as to not affect product quality. Additionally, documenting the reproducible performance of process activities can boost confidence in the manufacturing process.

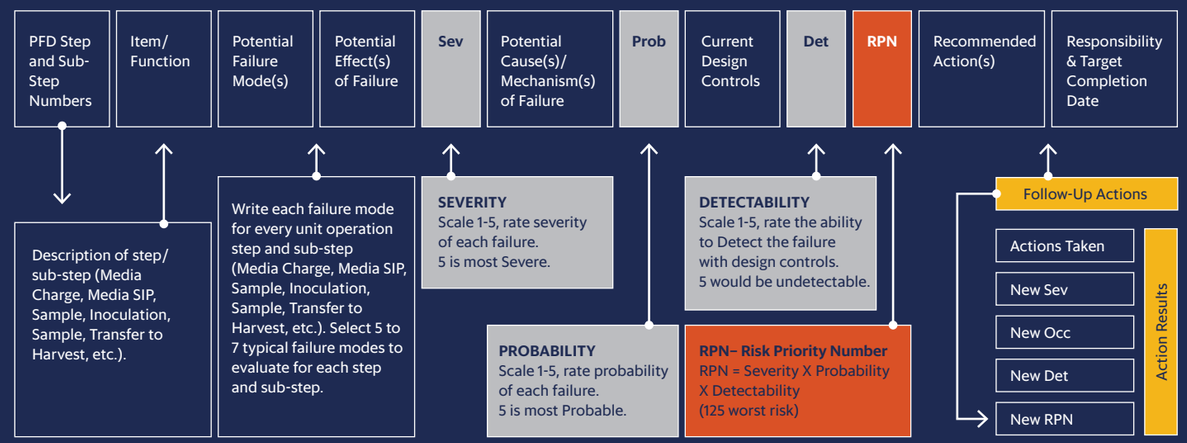
DOCUMENTING THE DESIGN SPACE

A Process Flow Diagram (PFD) is elemental to the process and can facilitate discussion and documentation of the testing studies needed to define the product's design space. Here, it has proven effective to engage SUT suppliers in a discussion involving their production processes and product design space, which are now integral to the biopharmaceutical process design.

To provide the most utility, a PFD (combined with the process description) should portray clearly the process and support functions that affect product quality and identify all process streams to document process and utility flows. The PFD facilitates documenting the steps prescribed by the SUD template and to be evaluated within the FMEA template. Note that this is an expansion of the PFD role. The goal in developing the PFD in this case is to define the process needs

TABLE 1

Potential Failure Mode and Effects Analysis (Design FMEA)



USE OF THE SUD TOOL CAN **DOCUMENT THE KEY PROCESS OPERATIONS** AND TIE THEM TO SPECIFIC PROCESSING PARAMETERS.

and work out those details – the ones that can add significant cost savings to the process design.

The requirement of the PFD in building the SUD template is to capture all the critical steps and operations that pose a risk within the model process to be included in the evaluation. Therefore raw material, heat-up, cool-down, reactions, transfers, changeover, etc., all must be captured in the PFD stream identifications so that the operation can be evaluated within the SUD template and FMEA analysis.

COLLECTING INFORMATION FOR THE SUD TEMPLATE

The SUD template is used to document all critical attributes of the process facility. Here, process steps are walked through while adding details to the steps identified in the PFD. The steps, sub-steps and sub-sub-steps will cover all areas of risk for the inventory, including set-up, run and retirement of the process(es). The process is followed from raw materials through final Vial Fill/Packaging, Bulk Fill/Storage, Freeze-Thaw and Shipment.

FMEA is a tried and true methodology that M+W Group has used successfully for many years. The tool provides an ideal format to compare process parameters identified within the SUD template with the associated risks identified in the FMEA analysis. This numerical evaluation of risk, including thorough cross-references to process details, offers tremendous transparency of all the potential issues SUT implementation may present.

RISK EVALUATION

Selecting failure modes carefully is critical to a successful FMEA, as is consistent, fair evaluation of each of the tasks or functions with potential for risk mitigation. Best practice recommends that the project team evaluating the risk also be involved in brainstorming the failure modes. This will only add to the understanding of the FMEA template prior to filling out the risk evaluation.

Common failure modes familiar to SUT process engineers often considered in M+W Group analysis include:

- **Power Loss**
- **Operator Error**
- **Adverse Leachable**
- **Bag Tear/Leak**
- **Tube or Fitting Wear or Leak**
- **Over Pressure**
- **Material Compatibility**

Although strictly ensuring uniform, consistent ratings is not possible, M+W Group employs a five-point system to help minimize the guessing between hazard ratings. To be effective, we try to keep evaluation simple. For example, address the risk as "it is," "it is not" and "it may be." By starting at this point, using a 5, 3 or 1, then the degrees can be determined (4 or 2 leaning one direction or another). It is best to filter the list to include all of one failure mode so that the evaluator's frame of mind does not wander during the evaluation. Noting carefully what is being considered in the risk ranking can help to make the evaluations more consistent during the evaluation.

It is key that no mitigation is included during the first evaluation, as this would unfairly reduce the perceived risk. The Risk Priority Number (RPN) is established by multiplying the Severity (S) times the Probability (P) times the Detectability (D).

RPN = S × P × D

The max RPN value of 125 can be obtained.

Note that S is the most difficult parameter of RPN to improve. P may be improved, although typically this parameter has already been optimized. Detectability is the most likely parameter to improve through testing or PAT integration.

RISK MITIGATION

Once the FMEA evaluation is completed, the SUD template is expanded with the FMEA failure modes per evaluation step and then updated with the FMEA RPN values. The product of S and P forms a fairly firm value of risk. For executive and operations managers using this methodology, one can provide a distinct line between acceptable risk and unacceptable risk.

Facility design can benefit from a proactive review of facility, systems, design intent and risk. Once accomplished, potential risk-mitigation plans can be put in place to reduce the risk to acceptable limits. Use of the SUD tool can document the key process operations and tie them to specific processing parameters. For M+W Group, this has proven to be a valuable evaluation tool when reviewing the economic suitability and quality potential of integrating SUTs into the existing process or incorporating SUTs into an entirely new process. P

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Mr. Carlson has more than 30 years of industrial process engineering experience. His expertise is in process development and production operations, process and facility design, integration of manufacturing expertise, process engineering, process control and cGMP compliance, providing an ideal background for quality facility and process design. Mr. Carlson's four years of operations experience at DuPont followed by 26 years of design experience with architectural and engineering companies has involved bridging communication across executive, scientific and operations levels of organizations.

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INNOVATION AND PARTNERSHIP THROUGH EXPERIENCE AND ACQUISITION

→ BY **TIM TYSON**, AVARA PHARMACEUTICAL SERVICES

The pharmaceutical marketplace is more global than ever and, as companies fight for market share in this increasingly competitive landscape, contract development and manufacturing organizations (CDMOs) are becoming more important than ever.

However, competition amongst CDMOs is also mounting. Those looking to stand out in this crowded space must remain nimble, customer-focused and, above all else, poised for growth and prepared change. Though niche market partners will continue to remain important in certain areas, pharmaceutical companies are increasingly turning to CDMOs that can demonstrate not only complete competence across the development and manufacturing spectrum, but also an active desire to increase that knowledge and expand their portfolio of service offerings and capabilities with proven expertise based on the customer's business requirements.

Of course, close collaboration and partnership will also become more important as drug complexity continues to grow with biologics remaining strong and biosimilars already beginning to crowd the space. Further, in the face of evolving demands for lower prices, shorter timelines and more effective and patient centric medications, transparency at every stage will become increasingly valuable. However, to turn for a moment to an old yet still applicable adage, knowledge is power. For a CDMO partner to remain truly valuable, it must be able to demonstrate proven market experience throughout the organization and a growth strategy that functions well today and focuses on tomorrow.

WHERE QUALITY AND RELIABILITY INTERSECT!

In every rapidly progressing and scientifically complex industry, experience comes in many forms. In the CDMO space, this is often most apparent though a unique trichotomy that exists between the people within the organization, the time spent in development and manufacturing, and the CDMO's intent to grow and change in response to market and customer demands. When experience in all areas aligns well with the overarching goal of the organization, quality products, productive processes and innovative solutions normally follow, but, as important as these offerings may be, one of the most desirable qualities a CDMO can offer is reliability that, at its core, is a cohesive combination of all these elements.

This claim might seem odd in some ways as, for example, quality is always a critical attribute and innovation is top of mind for nearly every small- and large-molecule drug manufacturer, but reliability covers all of these factors. At its most basic, reliability simply means doing what you say and saying what you will do. For a CDMO to remain valuable in this changing landscape, reliability is demonstrated by first listening to the customers' needs and offering viable solutions and then, most importantly, delivering on those solutions as promised, when promised, at a fair price.

At Avara, reliability is the result of close collaboration with our pharmaceutical customers that allows us to deliver unsurpassed customer service and custom-tailored solutions to our customers' specific needs, from manufacturing to fill-finish operations. Four manufacturing and warehousing facilities offer bulk drug formulation and primary and secondary manufacturing and packaging. Our two primary API manufacturing sites offer experience in large-scale optimization manufacturing as well as smaller, complex chemistry expertise. Our secondary/finished dose form sites have international market experience, including serialization knowledge, with outstanding performance history in manufacturing primary/secondary API manufacturing – including large-scale API manufacturing capabilities – and primary/secondary packaging solutions. Seamless collaboration between sites and scalable capacity allows us to remain agile, effective, committed and, as all of these elements combine, reliable.

However, for this ideal to hold true, partnership must be a systemic part of the organization. Delivering on scope, schedule, quality/regulatory compliance and price commitments requires attention to detail and collaboration not only between the customer and the CDMO, but also within the CDMO itself.

PARTNERSHIP AND EXPERIENCE FROM THE INSIDE OUT

Just as the relationship between the CMDO and its pharmaceutical company customers must remain transparent and honest, relationships within the organization itself should also be similarly marked with a collaborative effort and a mutual respect and understanding for the larger goals of every customer. This ability to communicate and remain cohesive between various departments and global facilities comes with time and experience in the market. It is simple for a CDMO to tout equipment, capabilities and even capacity, but these features carry little weight without a foundation built on years of industry experience in all levels of the organization. Or, more simply put, people must be the emphasis of the foundation for services to offer real value.

PEOPLE MUST BE THE **EMPHASIS OF THE FOUNDATION** FOR SERVICES TO OFFER REAL VALUE.

Though Avara is a relatively young CDMO, our leadership team consists of industry veterans who understand the outsourcing market from both perspectives and strive to apply that understanding to every customer interaction; our commitment to the Avara Promise has been rewarded with repeat business. This experience allows Avara to offer a unique perspective while empathizing with and understanding unique industry challenges; however, as should be the case with any reliable industry partner, this experience extends well beyond leadership and into every position and facility within the company. Through the strategic acquisition of proven facilities that meet the Avara grade, spread across two continents, Avara has worked to maintain experience by retaining personnel with every acquisition. That being said, Avara will not take on sites that have a history of poor performance. In addition to allowing us to show a commitment to our employees, this effort enables us to run smoothly with a lean organization and has produced a diverse team of highly competent, motivated professionals who are dedicated to providing unmatched service in the interest of holding true to promises.

Experience, however, means little in the face of stagnation. True experience comes with time and develops with a desire to do more, and to do better, when faced with challenges new and old. This means that, in the CDMO marketplace of tomorrow, continuous improvement will become increasingly valuable. Processes such as Lean Six Sigma allow organizations to remain effective and comfortable with what they know while also growing with their customers and anticipating what these customers need now and, even more so, may need in the future.

ACQUISITIONS FOR TOMORROW

Last year, Avara acquired three proven facilities (Shannon, Ireland; Norman, Oklahoma; and Avlon, Avonmouth, England) and celebrated the one-year anniversary of our 2015 acquisition in Arecibo, Puerto Rico. Each of these facilities added additional capabilities and/or capacity to Avara's growing service portfolio, with each site offering years of experience, cGMP facilities and a proven track record of success in, among other things, process development, commercialization of NCEs and the production of several blockbuster products. Acquisitions have been instrumental in enabling Avara to provide a world-class experience to its customers – a >99% customer service satisfaction level for five years and counting – while also offering expertise in nearly every position within the organization.

As we look toward the future of the industry and Avara itself, acquisitions remain a critical part of our larger strategy to become the most admired contract manufacturing and technical services company in the pharmaceutical and biopharmaceutical marketplace. Overall, Avara will continue to expand its portfolio with a focus on key regions around the world, including emerging markets, and services that can add or be complementary to our existing offerings. With FDA- and cGMP-compliant operations, we strive to maximize production while minimizing associated issues and serving customers at various stages of development and production, all while meeting rigorous quality expectations and various regulatory requirements.

To ensure that that we continue to meet the growing demands of the industry, Avara is also committed to expanding our global development and manufacturing expertise into the area of biopharmaceutical drug development. We recognize the unique needs associated with the production of these often-sensitive medications and understand that, in order to remain a reliable partner in this competitive market, our solutions must expand to support global growth. However, as Avara plans for the future through developments in internal expertise and acquisitions, the customer experience remains central. We believe additional capabilities will allow Avara to better serve new and existing customers but, as the foundation of our organization is built on the prioritization of customers to optimize the outsourcing experience, every decision will have our customers' and our experienced employees' best interests in mind.

AVARA PHARMACEUTICAL SERVICES — FULL SERVICE, FULL CIRCLE

With Tim Tyson, a global leader in the pharmaceutical industry at the helm, Avara Pharmaceutical Services was created to help revolutionize the CDMO experience in preparation for the changing demands of the pharmaceutical industry. The larger leadership team, in turn, brings over 100 years of combined experience in various areas – including manufacturing, finance and sales – that complement Tyson's direction and the experience of Avara's global staff. When paired with the strength and stability of Avara's parent company, American Industrial Acquisition Corporation, the organization is positioned and prepared to leverage its expertise in an effort to help redefine the meaning of partnership in the outsourcing market. P

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Tim Tyson
Chairman and CEO, Avara Pharmaceutical Services

Tim Tyson, Chairman and CEO of Avara Pharmaceutical Services, is Chairman and previously CEO of Aptuit. Prior to that he was President and CEO of Valeant Pharmaceuticals and served as President of GlaxoSmithKline Global Manufacturing & Supply, where he had responsibility for over 100 manufacturing sites and outsourced manufacturing worldwide. Mr. Tyson holds a bachelor's degree in engineering from the United States Military Academy at West Point and MBA and MPA degrees from Jacksonville State University (USA).

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PARTICLE ENGINEERING FOR IMPROVED BIOAVAILABILITY IN ORAL SOLID DOSE MEDICATIONS

→ BY **RONAK SAVLA, Ph.D.** AND **STEPHEN TINDAL**, CATALENT PHARMA SOLUTIONS

Oral solid dose (OSD) form medications remain the industry juggernaut. Though biopharmaceuticals continue to grow and evolve, offering new and unique treatment options, small-molecule drugs maintain their dominance with OSD medications leading the charge. Considering OSD drugs date back to 1,500 B.C., the industry has had time to perfect the form factor, improve manufacturability and enhance the efficacy of one of the most portable and easily 'packageable' dosage forms.[1]

Despite this long-held dominance, however, challenges in the manufacture of effective OSDs remain – in particular, the gradual decline in aqueous solubility of small molecules coming out of discovery. Hence, there continues to be a strong focus on enhancing the bioavailability of these substances.

Solubility issues are typically the most common hurdles to achieving ideal bioavailability, and these can be divided into molecules that are poorly soluble and those that are just too slow to dissolve. Approximately 80% of the drug candidates in the R&D pipeline exhibit poor solubility in water.[2] Drugs with solubility /dissolution-related issues and those falling into class II and IV of the Biopharmaceutical Classification System (BCS)[2] and class IIa, IIb, and IV of the Developability Classification System (DCS)[3] typically exhibit poor or varying bioavailability, effectively canceling out some of the convenience offered by OSD. For molecules falling in class IIb and IV of the DCS, oral absorption is limited by solubility in the gastrointestinal tract. The molecules will not be completely dissolved in the three-hour transit time of the small intestine (where most drugs are absorbed). For molecules falling into DCS class IIa, complete solubility of the drug is feasible, but the OSD needs to ensure that the drug is freely able to disperse and dissolve. In these cases it may be critical to control particle size, surface area, wettability or all three of these factors.

As manufacturers of OSDs look for ways to successfully provide poorly soluble molecules within the dosage form, there is a growing demand for the application of so-called enabling technologies, i.e., those that can mitigate the poor solubility of the API. Particle engineering approaches, such as micronization and comicronization, remain as simpler, lower-cost options that could be utilized for DCS IIa drugs, and while not likely to solve all the challenges of a DCS IIb drug, could be a cost-effective option for those that are close to being a DCS IIa. Particle-size engineering and analysis require specialized equipment and expertise, leading many pharmaceutical companies to turn to a reliable contract development and manufacturing organization (CDMO) partner.

With more than 25 years of experience handling particle engineering and analysis, Catalent is one such CDMO. After the company made the decision to acquire Micron Technologies in 2014, Catalent has become a leader in particle engineering and analytical services. With a thorough understanding of which approach is needed for each specific API, Catalent can help manufacturers avoid costly trial and error and better direct efforts to produce bioavailability-enhanced products that ultimately offer an improved patient experience.

UNDERSTANDING PARTICLE ENGINEERING

The goal of particle engineering is to first gather quantitative data that can help guide improvement efforts for the drug. More specifically, particle characterization should, at a minimum, not only consider the mean particle size, particle-size distribution and shape of the particles (both API and nonactive ingredients) in the formulation, but may also consider other factors.[4]

Due to the complexities involved in selecting and conducting the best analytical method for this type of research, it is not surprising that the 2017 Nice Insight Contract Development and Manufacturing Survey found access to specialized technologies to be the number one reason for engaging with a CDMO partner.[5] With particle analysis in particular being a costly field, a CDMO partner with experience in characterization can help select the most accurate method(s) while also offering analytical guidance throughout the process. Catalent has over 350 analytical scientists and over 25 years' handling hundreds of APIs, allowing them to provide numerous particle-size testing options for both stand-alone particle analysis and more complete processes

Several different methodologies and technologies may be used for characterization. As with any analysis, it can be helpful to use more than one method, especially when a test is not specific. In addition, more specific, complex methods may provide more information, but a simpler method may be more cost-effective for fast access to data over a large number of samples. For example, while scanning electron microscopy provides more information about particle form, optical microscopy and laser diffraction are still more commonly used for run-of-the-mill samples.

THE PATH TO IMPROVED BIOAVAILABILITY

The solubility and oral absorption of DCS Class IIa drugs is limited by their dissolution rate. Based on the Noyes-Whitney equation, dissolution rate is directly proportional to surface area of the drug particles. In micronization, an increase in particle surface area is achieved by reducing particle size. DCS includes a proposed equation to calculate target particle size (D90). If the D90 is below this value, oral absorption of the drug is not limited by the dissolution rate, even in sink conditions.

THE GOAL OF PARTICLE ENGINEERING IS TO FIRST **GATHER QUANTITATIVE DATA THAT CAN HELP GUIDE** IMPROVEMENT EFFORTS FOR THE DRUG.

The micronization process is a simple and well-established method that offers a consistent particle-size distribution without the use of solvents and without producing excessive heat.[6] Traditional mechanical techniques such as hammer, pin and conical milling may not produce the desired particle-size distribution suitable for for specialized applications, such as those intended for pulmonary delivery. Jet mills rely on impact and attrition of the API particles themselves to reduce particle size and, for solid-dose medications, are one of the most common and effective forms of micronization.[6] High-velocity particle collisions cause larger particles to break down, and by careful design, centrifugal forces separate larger particles and ensure they linger in the mill, while the newly created small particles are able to escape into the collection system. This self-regulating process helps ensure a consistent result.

Additionally, when improved control is desired, or when working with highly potent compounds, there are more enhanced micronization options; for example, cryogenic micronization, which is similar in principal to jet milling but performed at temperatures as low as -50°C. This is becoming increasingly popular for micronization of compounds that have low brittleness or are tacky at ambient temperature. The colder temperatures help increase brittleness and friability of the compounds resulting in a finer particle size. Another option is to use a multiprocessing classifier mill, like that housed in Catalent's Dartford, U.K. facility, which simultaneously micronizes and classifies powder substances and can be especially valuable when a narrow particle size range is required. Catalent has a range of

AS MANUFACTURERS OF OSDS LOOK FOR WAYS TO SUCCESSFULLY PROVIDE POORLY SOLUBLE MOLECULES WITHIN THE DOSAGE FORM, **THERE IS A GROWING DEMAND FOR THE APPLICATION OF SO-CALLED ENABLING TECHNOLOGIES,** I.E., THOSE THAT CAN MITIGATE THE POOR SOLUBILITY OF THE API.

different airjet mills at various scales including those that can micronize 250 mg or less of API, which may be suitable for companies looking at micronization during early development. Further, Catalent has achieved full containment in order to handle potent compounds. Micronization of potent drugs is difficult due to dust, which is a part of the milling process and has historically made the process inside containment impossible at larger scales.

Co-micronization, in which a small percentage of an excipient is blended with API prior to micronization, is an advancement on the traditional process. Compared with micronization followed by blending, the co-micronization process promotes enhanced interactions between API and excipients. The potential advantages include decreased agglomeration, avoidance of dry blending, enhanced hydrophilic character and solubility, enhanced dissolution rate, and better flow properties. By increasing rate of dissolution and/or solubility, co-micronization can improve bioavailability of poorly soluble molecules, where particle size reduction alone my not be sufficient.

Though equipment considerations remain important, however, equipment alone cannot satisfy cGMP guidelines and deliver consistent results. When scientists are looking into particle engineering services it is best to seek existing expertise from a company that not only uses specialized equipment, but also offers support for any custom protocol development that may be required depending on the potency of the API, validation, execution and, of course, reporting.

CONCLUSION

OSD medication, being the preferred dosage form for in-house manufacturing, continues to be the dosage form of choice. Enabling technologies such as particle engineering will continue to have a place in drug product development for poorly soluble APIs. Particle characterization and engineering can identify optimal particle size, provide a more thorough understanding of the drug, and point to bioavailability enhancement options through particle reduction processes – a simple, elegant solution to a modern-day dissolution-rate issue.

Ultimately, if the goal is to ensure robust and consistent bioavailability with the most cost-effective OSD, then micronization and co-micronization have a case for being the ideal solution. Catalent has many other enabling technologies in their portfolio, and are ideally placed to advise companies about which data need to be collected to make an informed decision about whether particle engineering is right for a given molecule. In addition, Catalent has capability all the way from preclinical development to commercial supply. Catalent now integrates particle engineering capabilities with it's existing expertise in characterization, giving customers options for molecule to phase 1 OSD materials with a fast turnaround. P

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NEXT-GENERATION OSD MANUFACTURING STRATEGY

→ BY **CHRISTA MYERS** AND **TODD VAUGHN**, CRB

The Facility of the Future has to be more agile, flexible and efficient than it is today. How to get there? By innovating — introducing new processing concepts, analytics and control — and pulling it together with attention to flow and ergonomics.

With some 60 percent of pharmaceutical therapeutics on the market delivered in oral solid dose (OSD) form, the category remains a pharmaceutical stalwart and its historical dominance is likely to continue for decades.[1] The pace of solid dose pharmaceutical development and market growth is robust. Since 2013, roughly half of all new molecular entities approved each year by the FDA have been solid dose forms, and drug innovators are investing R&D dollars toward more effective, patient-friendly and therapeutically effective adherence-promoting solid forms.[2]

There are few sectors in pharma that do not have some stake in OSD innovation and development. From the world's branded, generic and OTC producers to the supply chain's contract service and equipment providers, few are expecting anything less than continued growth and investment in this category. It is clear that oral delivery of solid dosage forms will remain the preferred route, but only if they can be formulated and manufactured in appropriate doses and at quality levels. Experts and other industry watchers understand that OSD manufacturing, new drug candidates, reformulations, combination drugs, bioavailability technologies and complex controlled-release formulations – not to mention emerging life-cycle–management strategies – will continue to fuel the sector's growth and uptake of manufacturing innovation.

NEW STRATEGIES FOR CAPACITY AND QUALITY

From answering regulators to competing in global markets, pharmaceutical developers are pursuing distinct strategies to remain compliant, competitive, relevant and successful. Much of this hinges on the ability to manufacture defect-free products at volume. With innovation dollars shifting from blockbusters to value leaders and with cost and price pressures mounting, the ability to manufacture OSD medicines at the lowest cost possible is a leading driver of recent pharmaceutical economics. To get there, pharma has been aligning production and processing assets in a coherent operations-focused manner, innovating to sustain progress quality and profitability in the post-blockbuster, Pharma 3.0 era.[3]

Trends in pharma OSD processing capacity reveal drug innovators and drug manufacturers slowly shedding dated, dedicated fixed-scale manufacturing and processing facilities, especially those challenged to sustain compliance cost effectively. The pharmaceutical manufacturing landscape is shifting, moving to replace and transition to more flexible cost-effective and efficient capacity. Discrete batch processing, which has characterized 99 percent of OSD manufacturing process since the first mass-produced tablet was pressed, has reached its technical and efficiency limits. Although there will always be applications that should and will remain batch-oriented, hybrid and continuous methods are ready for mainstream application in pharma.

Much of this legacy capacity is being supplanted by contract manufacturing and services providers. The world's generic producers are also being caught up in the movement to refine their quality profile as regulators push these high-volume manufacturers further. It is widely acknowledged that the CDMO sector is driving capital spending, but the industry's demand for access to best-cost operationally excellent capacity is spurring spending and organizational changes in most sectors, and that, in turn, is driving OSD manufacturing innovation.

ACCELERATING OPERATIONAL EXCELLENCE

While the pace of change and the adoption of advanced manufacturing and processing solutions may not be occurring as fast as some feel is possible or necessary, pharma's leaders are exploring next-generation manufacturing strategies in measured and deliberate ways. But change and advancement must come if the industry is to remain successful in meeting the expectations of regulators, healthcare providers, payers, and above all else, the patient.

As pharma's process and production ecosystem evolved, process cost and efficiency has only become a serious consideration when drugs come off of patent. Pricing followed more cost-plus models, with the industry charging what the market can bear. Once a drug comes off of patent, the commoditization of that drug begins. Companies are now being prompted to implement and institutionalize process technologies effective at maximizing quality at an effective volume cost, even when a drug first comes to market. There is incredible competition to be the leading prescribed medication.

For nearly two decades now, regulators have focused much of their oversight on the processes and technical means that companies employ to manufacture drugs. Central to its drug-quality, consumer-safety mission, the FDA in particular recognized that manufacturing quality and efficiency was key to advancing drug safety and effectiveness while helping to push the drug-cost curve down. However, with the industry beholden to batch process and a regulatory basis that was serving to further entrench the status quo, the FDA recognized it was going to need to reform its policies and create economical and practical pathways to the higher-order, higher-quality and lower-cost pharmaceutical processing the agency was promoting as the key to drug safety.

INDUSTRY RESPONSE

Alongside academia, Pharma's engineering community responded to the call, and industry groups, including the International Society of Pharmaceutical Engineers, began collaborating with the FDA to explore and recommend the best processing and technical strategies for manufacturing drug products, especially OSDs (those in highest demand and in production around the world). This dialogue has produced a number of tactical and technical recommendations that have real potential to drive quality up and costs down, including better, more pervasive application of process analytical technologies (PAT) in batch processing and continued emphasis on continuous manufacturing (CM) processing, and the quality by design methodology it supports.

Beyond the headlines, pharma process engineers have reached a particular crossroads in their pursuit of operational excellence and efficient, cost-contained high-quality processing. Again, drug makers' manufacturing strategies are revealing how they think they can best manage risk and sustain business and revenues. Some projects support adopting more sweeping processing advancements like CM, justified by market potential, while others serve to manage risk (i.e., financial) and exposure through an incremental but methodical optimization of batch-based processing.

Because batch processing in pharma is so well established, with plenty of capacity delivering value and revenue, there continues to be a great deal of investment in optimizing batch operations and quality-enhancing analytical equipment and controls.

Drug manufacturers' uptake of analytical technologies is supported by more affordable access to reliable instrumentation and controls. In the last few years, PAT technologies that measure and help control granule size have introduced a new level of transparency as well as the ability to control process variation within batch-processing operations. Coupled with data and information technologies, this further supports better quality and efficiency.

For many in OSD manufacturing, the viable strategy is to optimize batch process segments and align production and associated manufacturing steps to speed the flow of process and materials through the

FROM ANSWERING REGULATORS TO COMPETING IN FAR-FLUNG GLOBAL MARKETS, PHARMACEUTICAL **DEVELOPERS ARE PURSUING DISTINCT STRATEGIES TO REMAIN COMPLIANT, COMPETITIVE, RELEVANT AND SUCCESSFUL.**

BEYOND THE HEADLINES, **PHARMA PROCESS ENGINEERS HAVE REACHED A PARTICULAR CROSSROADS IN THEIR PURSUIT OF OPERATIONAL EXCELLENCE** AND EFFICIENT, COST-CONTAINED HIGH-QUALITY PROCESSING.

production train and manage any risk to product quality from either a process or operations standpoint. This is a strategy that AstraZeneca (AZ), for example, is pursuing vigorously. Over the past four years, AZ transformed its aging OSD facility in Delaware, completely transforming the facility in pursuit of high-level quality and cost control – as well as future-proof flexibility – as part of their international supply chain.

CRB was a key contributor to the success of this project, which through careful planning and execution transformed the facility without interrupting operations. OSD manufacturers like AZ are reframing what it means to reform their operations and achieve, by their own measure, operational excellence. It also shows that operations executives who take the time to do the studies can find a measured and risk-managing path to better product quality and sustainable cost-containment.

NEXT-GEN MANUFACTURING CONTINUES

Vertex, Hovione and Janssen have also successfully demonstrated their commercial commitment to CM; from this point going forward, no conversation or planning regarding next-generation OSD processing can exclude continuous manufacturing from the dialogue.[4] With so much experience with the methods and application of CM in other process industries, the movement to introduce its quality and efficiency drivers to pharma is gaining momentum. Regulators, especially the FDA, are advocating this solution, attributing the recent successful development and approval of CM facilities to the collaboration it has fostered with the industry and engineering community to promote more widespread adoption of the methodology. In CRB's experience, everything is in place for OSD manufacturers to seriously consider more 'all-in' manufacturing strategies based on CM because of its risk-based, science-based approaches and the inherent flexibility of continuous processes.

Whether addressing new product manufacturing, managing an aging processing infrastructure, or developing new capacity to meet decade-spanning business plans, capital will only be spent once the investment's potential is thoroughly vetted. Project success is also increasingly predicated on efficient execution. It is here that CRB, for example, deploys its knowledge, experience and engineering wisdom within a highly developed methodology, providing a clear, defined project management process that promotes speed and cost-effective execution to deliver on project time lines, process innovation, and development and compliance objectives.

As drug innovators and manufacturers navigate the Pharma 3.0 landscape, they are increasingly being tasked by society to lower costs – that is, lower drug prices through lower manufacturing costs. With that goal in mind, the OSD "Facility of the Future" has to move beyond the lab-batch and compound pharmacy roots. Pharma's uptake of state-of-the-art processing and facility designs and technology is accelerating, and that progress is already making an impact on pharma's ability to fulfill its promises and potential to society in general, as well as its specific obligation to patients worldwide. P

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FLEXIBLE PARTNERSHIP, INFLEXIBLE QUALITY

BY **NICK BYKERK, CPA** AND **VAL DITTRICH**, GRAND RIVER ASEPTIC MANUFACTURING, INC.

Driven by the demand for biologics, most of which still require parenteral administration, the sterile injectable market is projected to continue its 6% annual growth through 2020.[1] Though biologic injectables account for 52% of this market, which is projected to hit $363 billion this year, they are not the only drugs filling this pipeline.[2] Small-molecule injectable drugs, primarily those falling under the categories of oncology and anti-infectives, also command 38% of the overall market.[2] The divide between innovator drugs and generic, however, is perhaps more indicative of how the market is responding to the current competitive landscape.

Though innovator drugs will continue to contribute to this growth, especially in the way of advanced biologics, generic injectables are following suit with generic medications overall and are growing at a much faster rate. Led primarily by China (CAGR 13%) and other emerging nations (CAGR 12%), the growth of the overall generic injectables space is expected to continue at 10% annually.[3] With a steady flow of abbreviated new drug applications as key injectables approach or are already at the patent cliff, this number is only likely to grow, and manufacturing efficiency, agility and reliability will become the defining attributes of desirable supply chain partners.

Injectable drugs come with complex sterility requirements and, for these drugs – innovator and generic alike – to be truly successful in the market, they must meet quality expectations while making it to market as quickly as possible. To meet this new set of demands without having to establish the necessary expertise or invest in costly equipment, many pharmaceutical and biologic companies are turning to contract development and manufacturing organization (CDMO) partners that can assist with early development work and offer batch flexibility and speed while still flawlessly hitting quality targets. Currently, the total CDMO injectable market is growing at a CAGR of 11%, 4% higher than the overall global CDMO market.[2] With companies continuing to recognize the value of manufacturing partnerships, CDMOs are pressured to deliver on quality promises without hindering launch, which will require the mastery of a full suite of services and the ability to demonstrate added value in a typically cumbersome supply chain.

TO MARKET, TO MARKET, WITH A RELIABLE CDMO

First-mover advantage (FMA) is a coveted position for marketers in any industry. For those within the pharmaceutical industry facing a market that is littered with competition and, especially in the case of generics, is extremely price sensitive, FMA is almost a necessity. This position is so advantageous in many cases that researchers at Duke University studied promotional and market-share data to develop a pharma-specific formula for predicting the added benefits of FMA.[4] Though several factors can contribute, the researchers found that second-to-market drugs lagging behind their first-to-market counterparts by as little as two years can only capture 38% of the market at launch.[4] This can mean the difference between success and failure in the market and – especially when making the added investment to pursue an injectable formulation, of which there are currently 1,699 unique products on the market (including all doses) – can be a costly error.[5]

Currently, generic medications only comprise approximately 22% of total prescription sales, but their share of filled prescriptions has risen rapidly over the last two decades, from 19% in 1984 to 88% in 2015.[6] The volume-to-value relationship here highlights the cost competition in this market, most of which is caused by low-cost import products driving down costs and increasing the pressure on U.S. manufacturers.[6] This gap between volume and value also helps explain the growth of generics in the injectables space, as generic injectables are typically able to command a higher cost and face decreased competition when compared to their oral equivalents.[1] However, the push toward injectables is as driven by price and, in many cases, necessity as it is by patient demands for more convenient and effective options.

This new patient-centric focus will be critical for market success in the future, but finding the perfect balance between convenience, effectiveness and affordability (from the cost-to-value perspective) for medications can be challenging for companies without expertise or proper equipment. Relying on outsourced manufacturing should allow companies to reduce time to market and benefit from not only expertise, but also a collaborative partnership and unmatched quality. Working with a CDMO – such as Grand River Aseptic Manufacturing (GRAM), a Michigan-based, parenteral CDMO – capable of guiding a product from development through fill-finish is even more valuable, as potential pitfalls can be overcome in clinical stages, preventing potential delays or shutdowns. Of course, handing responsibility off to a third party carries its own risk, which is why true partnership through transparent communication is a critical component for these relationships.

This atmosphere helps explain why the 2017 Nice Insight Contract Development and Manufacturing Survey found reliability as the number one priority for respondents seeking an outsourcing partner.[7] Most interestingly, reliability has ranked second to quality for the last three years of this survey, and this shift in 2017 is perhaps due to reliability being viewed as an all-encompassing, rather than singular, trait. Speed remains critical and cost is important, but neither should come at

the expense of quality and, arguably, the three combine to form a *reliable* supplier. Quality, however, is at the crux of this reliability with injectables, as it is especially critical for this delivery method.

A CULTURE OF QUALITY IN EVERY VIAL

When engaging with a CDMO partner for the development and/or manufacture of a parenteral medication, biologic and pharmaceutical companies alike are purchasing a certificate of conformity as much as they are the finished product.[8] Quality and compliance are the foundation of a reliable CDMO or any contract partner, but the quality, purity and sterility standards applied to injectables are uncompromising. Over the last several years, the industry has seen quality issues and warning letters arise in injectable manufacturing facilities, especially in emerging markets like India, which has seen its share of FDA issues with, among others, Pfizer and Wockhardt facilities both receiving negative marks from the agency due to Current Good Manufacturing Practice (cGMP) violations.[9] In the case of Wockhardt, these findings even prevented export to the U.S., which was the primary purpose for the new facility.[9]

Currently, approximately 30% of injectables are being manufactured by CDMO partners, making the impact of a violation and/or a shutdown potentially devastating to companies and even more so to patients if a shortage were to occur. Recognizing the damage that can come with an FDA warning and the importance of maintaining quality in the face of increasingly aggressive market launch time lines, GRAM focuses heavily on the agility of its manufacturing processes while keeping quality as bookends every step of the way. To deliver on this commitment, GRAM views every client engagement as a partnership in need of transparency, undivided attention through a dedicated project manager, and quality by design (QbD) built into the day-to-day. With two state-of-the-art cGMP facilities and not a single 483 from its most recent FDA audit, GRAM offers everything from robust analytical and development services to lyophilization, terminal sterilization and even distribution, while treating every client product like it is their own.

Though product quality issues can arise for a myriad of reasons throughout manufacture (e.g., inferior active pharmaceutical ingredients, poor manufacturing processes, inadequate packaging, etc.), quality risks are heightened as the supply chain deepens and the drug changes hands.[8] As companies look to mitigate risk in the chain and simplify manufacturing, full-service CDMOs such as GRAM, who offer quality aseptic processing along with complete custom labeling, packaging and kitting (a big advantage given the looming implementation of serialization requirements under the Drug Supply Chain Security Act), become increasingly valuable.

In pharma, 'quality' is a word that is easily and frequently thrown around but, as a well-rounded concept, it is often difficult to deliver in full. As patient demands for convenience and affordability mount and the industry shifts from the ever-popular vial – currently accounting for 73% of all injectables – to prefilled syringes that are already gaining in popularity, this need for quality from start to finish may evolve, but it will not diminish. To keep up with these changes, CDMOs will remain a vital part of the injectables supply chain, and those with core operational efficiencies designed to handle the full range of injectables (i.e., small molecule and biologics) will offer the most value. With a range of services and the agility required to respond quickly to customer needs and market demands, GRAM is prepared for the injectables market and, most importantly, the quality that should define it going forward. P

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NEW VENTURES IN THE MICROBIOME

BY **EMILIE BRANCH**, NICE INSIGHT

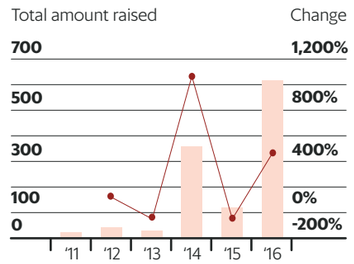
The human body harbors up to 100 trillion microbial organisms throughout the gut, skin, oral cavity, respiratory system and urogenital tract, among other organs and systems. Collectively these microorganisms are known as the microbiota, and the sum of all of their genomes is known as the human microbiome.[1] These organisms play an important role in human health, including metabolism and immunity, and are implemented in the gut-brain axis where the central nervous system communicates with the gastrointestinal tract.[2] Disruption in the microbiome can lead to disease, and has been linked to depression, asthma, psoriasis, and even cardiovascular disease.[3] Therefore, knowledge and manipulation of human microbiota presents a great potential for the development of therapeutics to treat a wide range of diseases and ailments.[4] The 2008 Human Microbiome Project launched by the National Institutes of Health (NIH) caused a significant uptick in research, which stirred the pharmaceutical industry's interest in the field. This opened the market for three distinct types of companies and start-ups: **(1)** therapeutics-based companies focused on development of microbiome products, including devices, drugs, probiotics, and prebiotics; **(2)** research-based companies that amass knowledge and data for potential partnerships with pharmaceutical firms; and **(3)** direct-to-consumer service providers that offer microbiome sequencing.

Biotherapeutic firms have begun to **use the microbiota to influence the cancer microenvironment**, modulating immune responses

State of the Market

Few therapeutic products exist today that take advantage of the considerable research that has come about in the wake of the Human Microbiome Project. Nonetheless there has been significant investment.[5] This year in particular has seen marked increases in funding for microbiome companies and start-ups. A good example of this increased funding is Second Genome, a company that set out to develop therapies for microbiome-related diseases. As of 2016 alone, Pfizer, Roche and others have invested over $42.6 million (a majority of $59 million total the company has raised since its inception in 2010).[6] Venture-capital investment in microbiome companies has grown faster than other areas of investment by venture capital firms. According to the Wall Street Journal, "From 2011 through 2015, venture funding in microbiome firms soared 458.5% to $114.5 million, while overall venture investment grew 103.4% to $75.29 billion. This year, microbiome investment has surged again despite a decline in overall venture funding. The $616.9 million raised for microbiome companies to date so far in 2016 is more than all of the venture investment in the microbiome space in 2011 through 2015 combined."[5]

Venture Capital Investment (in $M)



Source Dow Jones VentureSource; Securities and Exchange Commission; the companies

Companies with the most VC Investments since 2012

Human Longevity Inc.	$300.0M
Indigo Agriculture Inc.	$156.0M
Seres Therapeutics Inc.	$133.5
C3 Jian Inc.	$90.0
Synlogic Inc.	$69.4

Source Dow Jones VentureSource; the companies

What's Being Done in the Industry

Microbiome companies and start-ups offer a wide array of products and services. They can be roughly grouped into therapeutics-based companies, research-based companies, and direct-to-consumer service providers. In terms of the first group, biotherapeutic firms have begun to use the microbiota to influence the cancer microenvironment, modulating immune responses. Furthermore, therapeutics that adjust microbiota colony populations have shown promise at enhancing remedial effects in patients suffering from gastrointestinal and other ailments and diseases, either through probiotics (delivering microbes via capsules, pills or suppositories) or prebiotics (substances that promote growth of certain type of microbes). There are also ventures that use synthetic biology to program bacteria for smart drug-delivery systems.[6]

Alternatively, an entire sector is focused on microbiome research. These companies strive to understand the multifarious interactions between different microbial populations, the connections between the microbiome and diseases, and to use these findings to develop new technologies. Much in the business paradigm of 23andMe, several companies are focused on bringing DNA microbiome sequencing to individual clients in order to illuminate imbalances in their personal microbiomes.[5] Many of these same companies – again, very much in the 23andMe business model – are amassing knowledge and data about the microbiome in order to partner with pharmaceutical firms interested in pursuing some of the aforementioned therapeutics.[7]

Conclusion

Predictions look bright for the microbiome market, in part due to the advancements made by companies in the development of microbiome-based therapeutics, devices, technologies, research and services. So much so that established pharmaceutical companies are increasing their focus on microbiome research and development.[8] Powered by advancements in synthetic biology and microbial ecology, microbiome-based therapeutics are progressing towards the clinical setting.[2] The global microbiome market is expected to reach $658 million by 2023, at a compound annual growth rate of 22.3% during the 2019–2023 period.[9] P

ABOUT THE AUTHOR

Emilie Branch
Strategic Content Manager, Nice Insight

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

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OPERATIONAL EXCELLENCE IN OUTSOURCED FILL-FINISH SERVICES

→ BY **GUY TIENE**, NICE INSIGHT

NICE INSIGHT IS IN CONVERSATION WITH OSKAR GOLD, SENIOR VICE PRESIDENT KEY ACCOUNT MANAGEMENT AND MARKETING/ CORPORATE COMMUNICATIONS AT VETTER PHARMA INTERNATIONAL, A GLOBAL LEADER IN THE FILL-FINISH OF ASEPTICALLY PREFILLED SYRINGE SYSTEMS, CARTRIDGES AND VIALS, ABOUT HOW OUTSOURCED SUPPLY OF SUCH SERVICES CAN HELP COMPANIES OF ALL SIZES.

Flexibility, responsiveness and operational excellence are increasingly being demanded by drug developers. The challenge faced by companies like Vetter Pharma International is to deliver these to customers. Oskar Gold, Senior Vice President Key Account Management and Marketing/Corporate Communications, says that Vetter believes that partnership is always the key to success, with operational excellence being decisive in both the development and commercial phases.

"Particularly in the early drug development phases, a number of issues that can affect the entire development project scope can arise and thus flexibility is critical," Gold says. "Also, it is important that a sponsor and service provider with a common target in mind act as one to successfully perform a drug development project that can get the drug on the market as fast as possible, where it can improve or even save patient lives."

Increasingly, contract development and manufacturing organizations (CDMOs) like Vetter are acting as the interface between small biotech firms and large drug manufacturers. There is a variety of reasons for this, in Gold's opinion.

"By definition, a CDMO has long-term experience with a variety of complex compounds and knowledge of most recent regulatory guidelines. CDMOs have also installed targeted development services portfolios either within or close to the markets where innovation is happening. Thus, a leading CDMO can provide the appropriate capacities and services across markets."

IT IS IMPORTANT THAT A SPONSOR AND SERVICE PROVIDER WITH A COMMON TARGET IN MIND ACT AS ONE TO SUCCESSFULLY PERFORM A DRUG DEVELOPMENT PROJECT THAT CAN GET THE DRUG ON THE MARKET AS FAST AS POSSIBLE, WHERE IT CAN IMPROVE OR EVEN SAVE PATIENT LIVES.

AT THE MANUFACTURING LEVEL, WHERE THE ACTUAL PROJECTS ARE COMPLETED,TRUST-BASED AND WELL-MANAGED RELATIONSHIPS PROVIDE THE NEEDED INTELLECTUAL FUEL NECESSARY FOR A SUCCESSFUL PROJECT OUTCOME WHILE HELPING TO OPTIMIZE COSTS AND IMPROVE EFFICIENCIES.

A "solution provider" like this can help sponsors of all sizes to align their requirements and bridge gaps, Gold contends. For smaller biotechs, partnering with one can offer the support needed for faster and more efficient drug development, adding critical value from the earliest stages via a combination of efficiency, long-term thinking, high quality and safety. Larger companies can benefit from this approach at a later stage when acquiring a drug substance or, indeed, the small biotech.

There are many who say that there is currently an excess of fill-finish capacity. Based on its own experience in recent months, including dialogue with customers, Vetter does not entirely agree. Its manufacturing sites in Germany and the U.S. are experiencing continuous short-, medium- and long-term demand for these services.

However, the company has indeed seen a shortage of fill-finish capacities for certain types of delivery systems and containers, such as lyophilized vials. For this reason, it announced at the end of 2015 a strategy to invest significantly in the expansion and upgrading of its manufacturing facilities over about ten years, preparing these facilities for the expected future requests and the associated need for high-quality drug product manufacturing.

Gold points to a *PharmSource* analysis that contains data from the clinicaltrials.gov website. This shows that phase I and II trial starts by emerging (bio-)pharmaceutical companies were 55% higher last year than five years before.

"Because such companies are often highly dependent on external service providers for nearly all of their process development, formulation and manufacturing requirements, we see the future of CDMOs as being in very good shape, as long as they stay ahead of regulatory requirements, as well as performing in a committed and dedicated way," he says.

Vetter continues to acquire or move strategically to acquire processing capacity in the U.S. near Chicago. This reflects the important role the U.S. market plays for the pharmaceutical industry in general and for Vetter in particular. Approximately two-thirds of all drug development projects take place in the U.S. and more than half of Vetter's customers are headquartered there; the company currently manufactures about 50 customer products with FDA approval.

This is one of the reasons behind Vetter's existing small-scale clinical manufacturing facility at the Illinois Science+Technology Park in Skokie, which was its first such facility in the U.S. The ongoing purchase plans would complement rather than duplicate this facility.

"In fact, several of our customers have expressed their desire that we offer commercial manufacturing opportunities in both the U.S. and Europe. Thus, the current project supports our 'ability to act' preparations that put us in the position to offer our customer base greater flexibility in global manufacturing for the future, due to an increase in geographical manufacturing opportunities," Gold adds.

Vetter recently was honored by AbbVie, receiving its highest Supplier of the Year "Triumph" award. Last year, it also won the WorldStar Award for its syringe closure system Vetter-Ject and the 2016 CMO Leadership Award in the four categories of quality, capabilities, expertise and compatibility.

While agreeing that winning any recognized award is always an honor, Gold says that the AbbVie Triumph award is particularly significant "since it recognizes past and present efforts on behalf of one of our most important customers. With this award, which is granted within a field of more than 1,000 contractors, our customer acknowledges its top performing contract suppliers for efforts that consistently add measurable value and regularly exceed best-in-class performance for the company and the patients that rely on their products."

For Vetter, he adds, this is particularly significant since the practice of managing customer relations has never been more important to CDMOs than it is today. Factors – including the high value of drug substances, escalating costs of development, product safety and security of supply in a complex and globalized world, as well as an increased competition – have added new intricacies to the business.

"At the manufacturing level, where the actual projects are completed, trust-based and well-managed relationships provide the needed intellectual fuel necessary for a successful project outcome while helping to optimize costs and improve efficiencies," he concludes. P

ABOUT THE PANELIST

Oskar Gold
Senior Vice President Key Account Management & Marketing/ Corporate Communications, Vetter Pharma International

Oskar Gold studied at schools in the U.K., France and Germany, then completed graduate studies in international business administration at INSEAD in Fontainebleau, France. Before joining Vetter, where he is in charge of global business development, he managed the European business development of a pharmaceutical component manufacturing company, serving in various functions, including vice president and managing director of group companies. He has also taught and lectured on international business strategy and marketing at a European university.

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Stay Tuned: **Pharma's Almanac TV** Goes Live

BY **STEVE KUEHN**, NICE INSIGHT

Pharma's Almanac is now more interactive than ever, with the debut of our own channel and network. We look forward to introducing the larger-than-life personalities of our industry to the world through this palpable source.

If you were at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting in Denver in November, you surely would not have missed the That's Nice booth. There was a large company team, pop art imagery, the opportunity to stand in a miniature wind chamber picking up fake money in order to win a cash prize or research services, a white picket fence, large paper flowers and, above all, that yellow Lamborghini.

Aside from drawing admiring looks, of which there were plenty, there was a real reason for the Lambo: to showcase the launch of Pharma's Almanac TV (PA TV). Almost back-to-back throughout the show, one or another member of the Pharma's Almanac team was conducting an interview on camera for the website (www.pharmasalmanac.com) with leading industry executives.

Thus, for instance, we spoke with Rolf Hilfiker, CEO of the Swiss firm Solvias, who discussed the increasing recent interest solid-state chemistry holds for the company's customers at ever-earlier stages of the drug development continuum. Matthew Morganelli, Director of Sales at Korsch, explained their novel tablet-pressing technology that addresses demands for bi- and tri-layer tablets in combination therapies, while Dr. Paul August, Vice President of Biology at Icagen, elaborated on their 'disease-in-a-dish' models.

We wanted to introduce ourselves, and our clients, to our community, **creating a personal experience for all involved.**

Picking a few others at random, Abby Thompson – Global Marketing Communications Manager at CordenPharma – spoke on their latest developments in oligonucleotide and drug product manufacturing; Adam Covitt, Vice President at Federal Equipment, discussed strategizing around used equipment; Marga Viñes, Business Development Manager at Grifols, updated us on the challenges of quality in their operations; and Tobias Bachle, Sales Director at Pantec Biosolutions, spoke about their breakthrough technology for laser-assisted drug delivery.

The diversity was impressive and could only really be captured in this medium. There will be plenty of others to see as we roll out PA TV over the coming months. Television as a format has a unique immediacy and personal appeal that meshes with the immediacy and face-to-face interaction that trade shows still offer, despite all the technology development that was meant to make them redundant in time. As such, it is a natural complement to the magazine and the other channels of communication That's Nice offers.

Our PA TV channel has debuted to bring Pharma's Almanac to life for our readers in a way the printed pages of the magazine or a regular website experience simply cannot do. We wanted to introduce ourselves and our clients to our community, creating a personal experience for all involved. Stay tuned – PA TV will become a big part of what we do on the show floor at exhibitions over the coming years. The Lamborghini, alas, has now gone to its rightful owner, but we will no doubt find something spectacular next time. P

Idle No Longer: Strategizing Around Used Equipment
Adam Covitt, Vice President, Federal Equipment Company

Filling a Market Need
Abby Thompson, Global Marketing Communications Manager, CordenPharma

Breakthrough Drug Delivery Technology
Tobias Bachle, Sales Director, Pantec Biosolutions

The Importance of Quality
Marga Viñes, Business Development Manager, Grifols Partnership

Visit www.pharmasalmanac.com for more.

MERGER & ACQUISITION

CATALENT BUYS ACCUCAPS, JOINS PSCI

▼ Accucaps Complements Catalent's Existing Softgel Capabilities

CATALENT HAS AGREED to acquire Accucaps Industries – a Canadian maker of over-the-counter (OTC), high-potency and conventional pharmaceutical softgels – on undisclosed terms, subject to approval from the Canadian government. The company has also become the first CDMO to join the Pharmaceutical Supply Chain Initiative (PSCI).

According to Catalent, buying Accucaps will "substantially complement" its global OTC and prescription softgel capabilities and capacity. Accucaps brings in 500 employees at two facilities in Ontario, which carry out integrated softgel development, manufacturing and packaging, and house blistering, bottling and other packaging capabilities. Catalent already has 11 other softgel facilities.

In the same field, Catalent has since concluded a deal to examine different softgel delivery technologies – including its Opti-Shell gelatin-free technology for Jotrol, Jupiter Orphan Therapeutics' novel formulation of resveratrol – ahead of manufacturing doses for phase II clinical studies and human pharmacokinetic studies. Jotrol is being developed to address resveratrol's poor bioavailability and dose-limiting gastrointestinal side effects, and studied in multiple programs for the treatment of rare diseases. P

Pharmaceutical Supply Chain Initiative (PSCI)

The PSCI dates back to 2006 and brings together companies seeking to develop responsible business pratices within the pharmaceutical supply chain in health and safety, the environment, labor and ethics. Most major biopharmaceutical companies are already members.

Since the PSCI was opened to top-tier suppliers in late 2015, DSM Sinochem Pharmaceuticals and West Pharmaceutical Services have joined. Members sign up to core principles on applying GMPs to, among other things, waste management, air emissions and wastewater discharges, though actually doing so remains voluntary.

MERGER & ACQUISITION

ACG OWNER FOR CMC BIOLOGICS

CMC BIOLOGICS, a Danish firm specializing in the clinical and commercial manufacturing of monoclonal antibodies, coagulation factors and other therapeutic proteins, is changing hands after its shareholders, including Monitor Clipper Partners, European Equity Partners and Innoven Partenaires, agreed to sell to Japan's Asahi Glass Chemical (AGC). No financial terms were disclosed.

CMC WILL RETAIN its brand identity and no changes are envisaged in terms of its operations, leadership and employees. The company has two commercial-phase manufacturing facilities and one early-phase manufacturing facility, employing about 500 people. Its services include cell line and bioprocess development, formulation and comprehensive analytical testing, plus the CHEF1 expression system for mammalian production.

THIS IS THE SECOND MAJOR BUY for AGC in this field in recent months. In September 2016, the company acquired the German biopharmaceutical CMO Biomeva. Based in Heidelberg, Biomeva offers process development for therapeutic protein expression, cGMP-compliant fermentation, purification and bulk filling, analytical testing and cell banking.

BOTH BUYS WERE DESCRIBED in terms of seeking to combine the newly acquired firm's capabilities with AGC's in large-scale market supply. They represent the company's first moves into biologics in Europe. AGC is active in fine chemicals for pharmaceuticals, among many other areas of chemicals, as well as in glass and high-tech materials. Under the ongoing AGC Plus initiative, the life-science business was designated one of its strategic areas for future growth. P

ALLIANCE

Wacker Grows Further in Cysteine Fermentation

▸ Natural Amino Acid Cysteine to Be Produced by Wacker Biosolutions

The company plans to invest about €30 million to modernize the facility and add production equipment over the next few years, creating about 35 new jobs.

Wacker Biosolutions, the life sciences and biotechnology division of the Wacker Group, has bought a large-scale fermentation plant from Antibióticos de León at León in northern Spain. This has a capacity of about 800 m^3. No further terms were disclosed. The company plans to invest about €30 million to modernize the facility and add production equipment over the next few years, creating about 35 new jobs.

Wacker will use the site to make the natural amino acid cysteine by fermentation for use in flavor, personal care and pharmaceutical applications. In pharma, it is mainly used as an expectorant in cough medicines though it has also been mooted as an ingredient in liver damage treatments, as it has been shown to counteract the toxic effects of acetaldehyde.

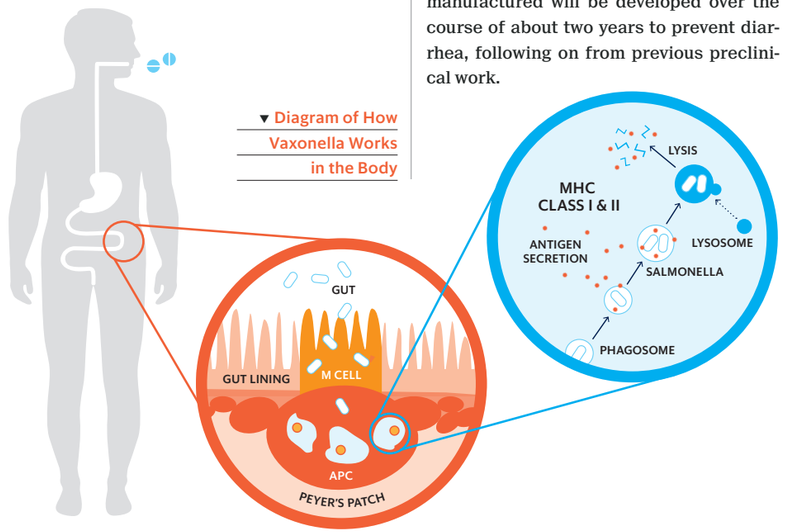
The company described the acquisition as "a major step in satisfying globally growing customer demand for cysteine during the years ahead, and in supporting the commercialization of other bioengineered products," as well as more generally increasing the proportion of specialty products in its total business.

The move was prompted largely by demand for cysteine that is made in ways acceptable to vegetarians and free of contamination by pathogens. Conventional production is still largely done by extracting the product from human or animal sources — such as hair, feathers or pig bristles — using hydrochloric acid. Wacker, uniquely, produces it by fermentation in a patented biotech process that won the Federation of German Industries Environmental Prize in 2008, using only plant-based and inorganic starting materials. P

> **Wacker will use the site** to make the natural amino acid cysteine by fermentation for use in flavor, personal care and pharmaceutical applications.

ALLIANCE

U.K. & MEXICO FIRMS IN VACCINE ALLIANCE



▼ Diagram of How Vaxonella Works in the Body

Prokarium, a U.K.-based biotechnology company focusing on oral delivery vaccines, and Probiomed, a Mexican biopharmaceutical company, have started a collaboration to scale up the manufacture of orally administered vaccines in a formulation that could remain stable at 40°C for several weeks. The first vaccine to be manufactured will be developed over the course of about two years to prevent diarrhea, following on from previous preclinical work.

The collaboration is supported by the U.K. government's Newton Fund, which is administered by the agency Innovate UK, and by the Mexican government's own innovation agency Conacyt. The companies said that the results "will be widely applicable to many different vaccines for difficult-to-target diseases worldwide."

Diarrhea, which is most commonly caused by the *Shigella* or enterotoxigenic *E. coli bacteria* and non-typhoidal Salmonellosis, is so common an affliction among tourists in Mexico that it is jokingly known as 'Montezuma's revenge' but is a serious threat to people's health and even their lives in many Third World countries. It is estimated that there are over 1 billion cases worldwide every year.

An oral vaccine, the two companies said, would greatly reduce the cost and increase the scope of treatments, by potentially saving some of the 1.3 million lives lost each year because of syringe reuse and over $500 million in additional healthcare costs. The need for medical professionals to administer injections and a refrigerated supply chain means that in practice many cannot access treatment at present. P

ALLIANCE

Saneca Pharma Wins Menarini Contract

Slovakia-based CDMO Saneca Pharma has signed a five-year supply agreement for enteric controlled-release pellets with the Menarini Group, an Italian pharmaceutical company.

▼ Pellet Production at Saneca's Plant

It will consequently invest at its Hlohovec site to boost the scale of operations for wurster coating of the pellets by extrusion spheronization.

Before securing the contract, Saneca had demonstrated its capabilities in enteric coating, which prevents dissolution in the stomach while allowing it in the small intestine, to Menarini at 100 kg batch scale. Precise financial and infrastructure investment details were not disclosed.

Subsequently, Saneca received a €1.5 million grant from the Slovak Ministry of Education, Science, Research & Sport in partnership with organic synthesis specialist Tau-Chem, which it will use to strengthen its pharmaceutical development services and establish a new R&D department. About 25 new employees will be taken on at Hlohovec.

Saneca will use the money to look at energy-efficient production methods and the use of renewable raw materials for opiates and synthetic drugs. Drawing on its expertise in opiates, it will also explore abuse-resistant techniques for finished dosage forms. This year, the company plans to double its R&D expenditure.

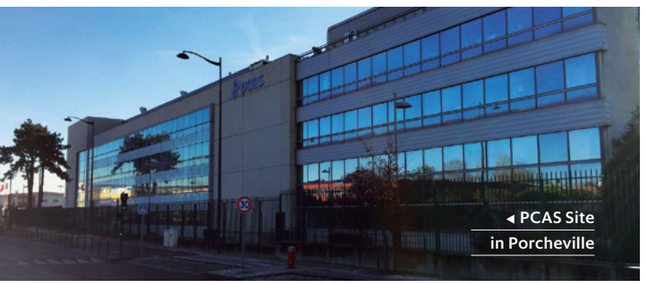
In September 2016, Saneca had announced plans to invest in its API capabilities to meet demand for smaller batch sizes and streamlined scale-up, enabling it to take projects right through development to commercialization. This included several smaller reactors to deal with 1-30 kg batches in its new kilo lab. The investment was made with EU funding and in collaboration with the Slovak Academy of Science. P

> **Saneca will use the money** to look at energy-efficient production methods and the use of renewable raw materials for opiates and synthetic drugs.

EXPANSION

PCAS ADDS R&D SITE

France's PCAS has revealed plans to acquire an R&D center near Paris, which will become its global R&D platform. The site, at Porcheville, is almost adjacent to another company site at Limay. Its location dates back to the 1970s and had been an R&D center since 2004, passing most recently from Sanofi to the global CRO Covance in 2010. It was last inspected by the FDA in February 2015 and by the French equivalent, the ANSM, in March 2016.



◂ PCAS Site in Porcheville

According to CEO Vincent Touraille, Porcheville will become "the central platform for PCAS' R&D projects" by the end of 2017. Previously, these teams had been rather scattered across company sites, with pharma-related R&D at Limay, Longjumeau and Couterne in France and Turku in Finland.

The center will be responsible for innovation and both product and industrial process development, thus enabling PCAS to ramp up its R&D subcontracting services. It features equipment for the development of complex molecules, plus seven kilo labs, 13 m^3 of industrial pilot works, and 4.2 m^3 of 'R&D pilot scale' and 8.8 m^3 of 'industrial pilot' capacity.

These labs will be used for testing new synthesis processes prior to routine manufacturing, something which is expected to be of specific interest to biotechs. The new site will also feature units specialized in crystallography and analytical method development. About 25 new employees have been taken on. In addition, a dedicated generics team will be created to help develop the catalog of proprietary products aimed at this market. P

EXPANSION

FAREVA'S AEROSOL PLANT STARTS UP

FAREVA RICHMOND, a U.S.-based subsidiary of the French CDMO Fareva, officially inaugurated its eleventh aerosol facility worldwide on December 11, 2016. This is located in a vacant distribution facility adjacent to the main plant at its Henrico, Virginia site and cost $40 million to build. Between 80 and 100 jobs have been created to add to the 600 already there. About 30 have already been filled, according to a local newspaper.

The expansion will have a capacity of about 100 million aerosol cans/year for the pharmaceutical and cosmetic markets. Specific capabilities include three aerosol packaging lines, one with 'bag on valve' capability, a flameproof bulk-manufacturing workshop, plus grade water, compressed air, steam and propellant gas storage to U.S. Pharmacopeia standards. There is also a 5,000 ft^2 R&D laboratory for product development, employing about 20 scientists, engineers and technicians.

Fareva is now considering installing up to four additional lines in a second phase of expansion, depending on market conditions and how quickly contracts can be signed. This, if implemented, would cost $15-$20 million, increase capacity to 250 million cans and create about 150 more new jobs.

The company first moved into the U.S. in 2011 by acquiring the site, which had belonged to Wyeth and was facing closure after Wyeth's merger with Pfizer. The facility is best known for producing branded over-the-counter (OTC) medicines like Robitussin cough medicine, the hemorrhoid relief cream Preparation H and ChapStick lip balm, all of which it does under a legacy contract from Pfizer. P

BY THE NUMBERS

$40M
Cost of Fareva Richmond's new facility in Henrico, Virginia

80-100
New jobs have been created to add to the 600 already there

2011
First acquisition of a facility in the U.S.

100M
Aerosol cans/year new capacity

▲ Robitussin is one of several well-known OTC products made at the site

EXPANSION

SARTORIUS EXPANDS ON TWO SITES

Pharmaceutical and laboratory equipment supplier Sartorius has seen expansion by two subsidiaries in short order. Sartorius Stedim Biotech (SSB), in which it owns a majority stake, has opened a new bioanalytical and biosafety testing laboratory in Boston, while Sartorius Stedim Cellca (SSC) has acquired over 6,000 m^2 (64,000 ft^2) of space at Science Park III at Eselsberg near Ulm in southern Germany to build a new laboratory and office complex.

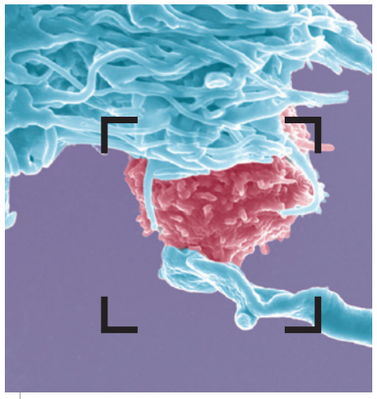
SSB's new laboratory covers about 830 m^2 (9,000 ft^2) of space and will house 15 scientists. The company said that it "is designed to accommodate the rising demand for the company's BioOutsource brand specialized assay platforms in North America and facilitate the ongoing expansion of this unique service offering." Boston was chosen because of its importance as a biotech hub.

This laboratory features many kinds of advanced analytical instruments for services such as antibody- and complement-dependent cell cytotoxicity and surface plasmon resonance assays. It will also provide GMP-compliant *in vitro* and polymerase chain reaction–based assays for the detection of adventitious agents.

The new German facility, meanwhile, will approximately double SSC's space when it opens towards the end of 2019. Hitherto SSC, a division of SSB that offers platform technologies like cell lines for biopharmaceuticals, had been based in a rented building in Laupheim. Managing Director Hugo de Wit cited the site's proximity to universities and research institutes in Ulm's Scientific Park and easy reach to international customers as reasons for the choice. P

ALLIANCE

FOUR TO WORK ON HIV VACCINES



▲ Dendritic (Blue) and T Cells (Red) Can Both Be Affected by HIV

French CDMOs Novasep and GTP Technology have signed an agreement with two compatriot associations to produce candidate vaccines against HIV.

Under this, they will develop and produce a prophylactic and a therapeutic vaccine to cGMP standards for use in phase I-II clinical trials on behalf of the Vaccine Research Institute (VRI) and the National Agency for Research on AIDS and viral hepatitis (ANRS).

Financial terms were not disclosed. Novasep has been working with GTP, which specializes in customized recombinant proteins and process development services for biopharmaceutical companies, since signing a collaboration agreement in early 2016.

The vaccines emerged from years of international research and collaboration, notably with the Baylor Institute for Immunology Research in Dallas. They target and activate dendritic cells via monoclonal antibodies (mAbs) coupled with HIV antigens. Depending on the type of antigen and mAb used, the vaccine will induce a potent neutralizing and non-neutralizing antibody response as well as a T-cell response, giving a preventative or therapeutic impact.

"The candidate vaccines developed in the framework of the VRI and ANRS vaccine program have allowed us to take a major step forward. The manufacture of sterile injectable vaccine batches will enable us to begin clinical trials on human subjects around 2019," said Professor Jean-François Delfraissy, Director of the ANRS.

Separately, Novasep has sold its TangenX subsidiary for $39 million to Repligen. TangenX is based in Shrewsbury, Massachusetts, and makes tangential flow filtration (TFF) technologies to reduce industrial purification costs in biopharmaceutical manufacturing, notably the Sius single-use TFF cassette. Novasep had owned TangenX since 2006 but no longer considered it core. P

MERGER & ACQUISITION

LONZA ACQUIRES CAPSUGEL

Lonza has made one of its largest-ever acquisitions in Capsugel, a supplier of advanced oral dosage delivery technologies, from private equity firm Kohlberg Kravis Roberts.

Capsugel is based in Morristown, New Jersey. It has about 3,600 employees at 13 facilities on three continents.

The $5.5 billion deal, which is expected to close in Q2, subject to regulatory approvals, includes refinancing Capsugel's $2 billion debts. Combined, the two firms had revenues of about $4.7 billion and adjusted EBITDA of about $1.1 billion in 2015. Lonza added that the deal is in line with its strategy "to accelerate growth and deliver value along the healthcare continuum by complementing its existing offerings and by opening up new market opportunities in the pharma and consumer healthcare and nutrition industries."

CAPSUGEL'S STRONG PRESENCE in hard-capsule technologies will help Lonza to reach out to customers in both large and small molecules, according to Lonza CEO Richard Ridinger. He added that customers will "gain from the simplicity and efficiency of working with one company that can provide world-leading support from APIs to excipients and dosage forms."

THE MAJOR SYNERGIES are expected through innovation, cross-selling of products and service and an integrated value offering of ingredients and dosage forms. The two firms believe that this will give them top-line savings of about $100 million/year in the mid- to long term, in addition to about $30 million/year in corporate, procurement, IT and efficiency gains over three years and another $15 million/year in tax savings. P

"Capsugel's strong presence in hard-capsule technologies will help Lonza to reach out to customers in both large and small molecules."

RICHARD RIDINGER, CEO, LONZA

COMPANY PROFILES

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

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

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

Avara Pharmaceutical Services was founded by a team of industry veterans who, through personal experience, understand both sides of the contract manufacturing market. A state-of-the-art contract development and manufacturing organization, Avara provides API and bulk drug formulation and manufacturing as well as primary and secondary packaging services for solid dose drugs, including highly potent compounds. The company's manufacturing technologies include granulation, coating, blending, encapsulation, compression and drying of tablets and capsules.

www.avara.com
+1 734 282 3370
101 Merritt 7
Norwalk, CT 06851

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

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

Fermion is a privately held, globally operating company focusing on Active Pharmaceutical Ingredients (APIs). Fermion develops, manufactures and markets APIs for generic, specialty and branded pharmaceutical companies and offers fully integrated contract development and manufacturing services from phase I to commercial scale. Fermion's headquarters, R&D facilities and two manufacturing sites are located in Finland. Fermion is a fully owned subsidiary of Orion Corporation.

www.fermion.fi
+358 10 4261
Koivu-Mankkaan tie 6 A FI-02200
Espoo, Finland

Glatt is a market leader in life science systems for the refinement and processing of powders. With 14 branches and subsidiaries worldwide, the company supports customers in pharmaceuticals, food and feed processing, and fine chemicals. As a pioneer in fluidized bed technology, Glatt has over 60 years of experience in leading-edge solutions for developing, refining and manufacturing solids. The company's Pharmaceutical Services Division operates a finished dosage form R&D and manufacturing facility and offers services that include formulation/process development, scale-up, process optimization, and clinical and full-scale cGMP manufacturing.

www.glatt.com
+1 201 825 8700
20 Spear Road
Ramsey, NJ 07446

Brammer Biopharmaceuticals LLC is a contract development and manufacturing organization dedicated to cell and gene therapy. The company specializes in in-depth biologics manufacturing, which enables large pharma and biotech clients to accelerate the delivery of novel medicines. Founded by Mark Bamforth (CEO) and Steven Kasok (CFO), previously cofounders of Gallus Biopharmaceuticals, the company is positioned to accelerate the development of these emerging technologies. Brammer Biologics is building a facility in Lexington, MA.

www.brammerbio.com
+1 386 418 8199
45 Hartwell Avenue
Lexington, MA 02421

Catalent is a global provider of drug delivery technology for drugs and biologics. The company has over 30 locations across five continents and is headquartered in Somerset, New Jersey. A leader in drug delivery solutions, Catalent has developed unique delivery technologies that include softgel solutions, Liqui-Gels® capsules, Vegicaps® capsules, Zydis® fast dissolve, controlled-release and inhaled-dose forms. Catalent provides integrated solutions to take a product from design to clinical trial, to plant and to pharmacy.

www.catalent.com
+1 732 537 6200
14 Schoolhouse Road
Somerset, NJ 08873

For over 30 years, **CRB** has specialized in delivering high-quality bioprocess facilities that are safe, reliable and sustainable. CRB provides services across the entire project life cycle, from conceptual design through preliminary and detailed design, construction, commissioning and validation. The company has more than 900 employees across 14 offices and hundreds of project locations around the world. CRB offers a range of services from packaging solutions, fill/finish design and aseptic processing to operations improvement solutions.

www.crbusa.com
+1 816 880 9800
1251 NW Briarcliff Parkway, Suite 500
Kansas City, MO 64116

Grand River Aseptic Manufacturing is a full-service parenteral contract manufacturer, approved by the FDA for aseptic manufacturing, with and without terminal sterilization. With a state-of-the-art cleanroom and highly trained staff, GRAM provides clinical trial and commercial material in vials or syringes for the life sciences industry. The company provides a range of services from pharmaceutical development, manufacturing, and analytical testing to regulatory filing support.

www.grandriveraseptic mfg.com
+1 616 678 2400
140 Front Avenue SW, Suite 3
Grand Rapids, MI 49504

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

www.grifols.com
+1 34 93 05712200
Avinguda de la Generalitat, 152
Parc empresarial Can Sant Joan
08174 Sant Cugat del Vallès,
Barcelona, Spain

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

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

Icagen is an integrated early discovery partner, offering its clients specialized technologies and deep scientific expertise to solve myriad challenges and optimize efficiency moving from target to lead. The company has locations in the heart of Cambridge, MA and Research Triangle Park, NC. The Durham facility is home to their ion channel and transporter expertise, including their proprietary Xrpro® X-ray fluorescence technology. The company benefits from a solid IP estate, including 58 issued and pending patents.

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

Marken maintains the leading position for direct-to-patient services and biological sample shipments, and offers a state-of-the-art GMP-compliant depot network and logistic hubs in 45 locations worldwide. Marken's 683 staff members manage 50,000 drug and biological shipments every month at all temperature ranges in more than 150 countries. Additional services such as biological kit production, ancillary material sourcing, storage and distribution, and shipment lane qualifications — as well as GDP, regulatory and compliance consultancy — add to Marken's unique position in the pharma and logistics industry.

@ www.marken.com
+1 800 627 5361
4307 Emperor Boulevard, Suite 210
Durham, NC 27703

M+W Group is a leading global high-tech engineering and construction company with 6,000 employees in more than 30 countries, offering a full range of services from concept and design to turnkey solutions. Services offered by the company include consulting & planning, design & engineering, (pre-) construction & project management and service, maintenance & installation. Founded in 1912 and headquartered in Germany, M+W now has locations in over 30 countries worldwide.

@ www.mwgroup.net
+44 1249 455150
Methuen South, Bath Road
Chippenham Wiltshire
SN14 0GT, United Kingdom

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

@ www.servier-cmo.com
+33 1 55 72 60 00
50 Rue Carnot
92284 Suresnes, France

SPI Pharma serves over 55 countries with formulation innovation, technical assistance and troubleshooting support. SPI Pharma's products include antacid actives, excipients, taste-masking technology, drug delivery systems for tablets, fast-dissolve technologies and a variety of other creative offers for patient-friendly dosage formats. They focus solely on the pharmaceutical market, ensuring their best-in-class products provide exceptional quality by meeting or exceeding global regulatory requirements.

@ www.spipharma.com
+1 800 789 9755
503 Carr Road, Suite 210
Wilmington, DE 19809

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

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

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

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

SPECIAL THANKS TO:

- Aesica
- Altasciences Clinical Research
- Celanese
- Cook
- DFE Pharma
- Dishman Group
- Dow Corning
- Frontage Labs
- Interphex
- IPS-Integrated Project Services, LLC
- Millipore Sigma
- Minafin S.P.R.L.
- Patheon
- PCI Pharma Services
- PCT
- Piramal Discovery Solutions
- Recipharm
- Robinson Brothers Ltd
- Vetter

Pharma's Almanac Online
Nice Insight's Content Community
www.PharmasAlmanac.com

Over the last few years, **CDMOs have entered strategic partnerships and completed acquisitions** to enable proximity to clients and their end markets.

Easy accessibility to the manufacturing site, F2F discussions with the CDMO team and tax or other benefits of outsourcing locally increases the ease of doing business. Maintaining an excellent track record with global regulatory agencies is also a requisite for CDMOs to easily facilitate launch of drug products across different regions globally. Access to facilities in Asia and in the West to provide economical solutions to the client is an added advantage. Overall, service providers must have a positive impact on the flexibility and efficiency of pharmaceutical firms. Piramal has created a global network of development and manufacturing facilities located in North America, Europe and Asia that offer a multitude of services covering the entire drug life cycle, from Drug Discovery & Development to Commercial Manufacturing of Active Pharmaceutical Ingredients and Finished Dosage Forms. Our development centers and manufacturing sites have accreditations from regulatory bodies in the U.S., Europe and Japan.

Ramesh Subramanian, Ph.D.
VP, Strategic Marketing and Global Head,
Business Development, Piramal Discovery Solutions

Q

LOCAL VS. GLOBAL MANUFACTURING

What do CROs/CDMOs need to do to ensure that they provide **effective global support but with locally oriented services?**

Stefan Peterli, Ph.D.
Vice President of Strategic Business Development, Minafin S.P.R.L.

Business is **global**, technology is **local**.

While our clients are all over the globe, our manufacturing units for intermediates and APIs in France, Belgium, Germany and the U.S. are regulated locally from the labor and SHE point of view. cGMP regulations are national (local health authorities) and global (ICH Q7). In order to properly serve international clients, we rely on experienced project managers for client interactions on a technical level. These project managers are located at the manufacturing plants to ensure tracking of project details with the local team on a daily basis and interaction with the client on at least a weekly basis. Key account managers handle commercial aspects and do not necessarily have to be located at a plant, but instead are traveling frequently to visit clients and attend trade shows.

PCI Pharma Services provides services for products destined for over 100 countries around the world, which includes manufacturing services, clinical trial supplies and commercial packaging services. This creates a need for robust understanding of the local regulations, import/export requirements and other cultural concerns and considerations. Likewise, supplying such a multitude of locations also brings significant regulatory requirements and auditing from individual countries' regulatory agencies. As a full-service CMO, we have to strike the right balance in ensuring our staff and facilities are very geographically accessible to the pharmaceutical and biotech clients we serve, as well as staying oriented to the geographies and end markets for which our products are destined. Furthermore, the global pharmaceutical supply chain continues to evolve as the global economy evolves, affecting both upstream and downstream supply. Our best strategy is to constantly take inventory of market trends and stay continually engaged with our customers to stay ahead of the curve.

Justin Schroeder
Executive Director of Marketing, Business Development & Design, PCI Pharma Services

Scenario One
Look to establish CDMO-owned centers in the global areas of interest. The areas to be looked at would obviously be based on the area with the best reach to their customer base. This scenario gives the CDMO the best control of their own destiny but can be costlier upfront.

Scenario Two
Develop regional centers globally through partnerships or collaborations with existing CMO entities in the region. This may provide the ability to establish presence in the global market with lower infrastructure costs, but will require clearly negotiated agreement for items such as regulatory responsibility, governing quality system, etc.

Considerations for Either Scenario

- **Specific global areas to be targeted based on customer reach and need**
- **Local regulatory and government requirements**
- **Site-logistic access**
- **Workforce stability**
- **In the case of partnerships, the partner's financial stability, covered through due diligence**
- **Cost effectiveness – in terms of investment, cost of goods, infrastructure, local incentives**

For a CRO or CDMO to do this effectively they would need to look at two scenarios and then, **based on the level of funding and resources available**, choose one of the two scenarios.

William J. Monteith
Chief Operating Officer, PCT

ATTRIBUTES THAT FACTOR INTO INITIAL CDMO SELECTION (2017)

Regulatory Compliance	**72%**
CDMO/CMO Understands the Customer's Requirements	**72%**
Operational, Methodological & Therapeutic Experience	**72%**
Financial Stability	**71%**
CDMO/CMO Industry Reputation	**71%**
Cost	**71%**
Contractual Approach — Assured IP Protection	**70%**
Risk Adherence	**70%**
Supply Chain Transparency & Logistics Management Capabilities	**69%**
Geographic Convenience — CDMO/CMO Location Proximity	**68%**
Size and Structure of CDMO/CMO	**68%**
Cultural Fit with the CDMO/CMO	**67%**
References from Colleagues or Coworkers	**65%**
Global Presence	**63%**
One Stop Shop — Provides Complete Spectrum of Services R&D to Commercial	**57%**

Source: 2017 Nice Insight CDMO Survey

Q: What do CROs/CDMOs need to do to ensure that they provide **effective global support but with locally oriented services?**

Establishing a global supply solution is one of the important topics of discussion in the industry, and certainly one that our customers (and in particular the larger pharma companies) are talking about. Pharmaceutical companies face many potential roadblocks that cannot necessarily be addressed without involving multiple capabilities, which often means accessing skills and technologies in different geographic locations. The key is for CDMOs to offer a wide breadth of capabilities, while still delivering a locally oriented service.

In Europe, markets are so fragmented that a supply chain model without at least a packaging step in Europe can prove to be very inflexible and, in most cases, unable to address needs from multiple commercial channels. Mandatory retesting of products manufactured outside of Europe, as well as serialization requirements, are adding additional layers of complexity that are not easy to handle remotely without reducing the chance of meeting customer expectations.

The U.S. market requires large-volume products that can be formulated in various geographic locations, providing that manufacturing sites have been inspected and approved by the FDA. Although a wide range of options are offered by CDMOs and much development work and commercial manufacturing is taking place in Europe, we observe that many customers are opting for U.S.-based solutions principally for clinical supply, but also for the packaging step of commercial demand.

As the Japanese and Korean markets require a particularly high level of quality that is not necessarily delivered by most manufacturing sites, many companies located in these markets are looking for at least a local packaging step to guarantee that requirements are met.

In terms of emerging markets, several countries now require that a good manufacturing practice (GMP) certificate is granted to pharmaceutical manufacturers by their own administrations before a marketing authorization request can be submitted for a new product. Such GMP certificates may take multiple years to obtain.

Likewise, other countries are restricting import licenses for products that can technically be manufactured locally. In some other markets, only locally made products have access to government tenders or can benefit from higher subsidized prices.

Finally, some countries are suffering from unstable currency or high import taxes that make localization a valuable option. As many markets are too small to support an investment in production by a single pharmaceutical company, CDMOs that can pool together a number of customer requirements into a single facility are a more viable option.

In order to help our customers achieve high-quality products in a cost-effective way, Recipharm is focused on offering solutions to address all of these constraints and has a global, experienced team that is committed to delivering locally oriented services. By combining a wide range of capabilities with scale and a global presence, we can minimize the risks associated with working with multiple partners in multiple locations.

Mark Quick
Executive Vice President of Corporate Development, Recipharm

Jean-Francois Hilaire
Executive Vice President, Head of Strategy & Global Integration, Recipharm

Song Li
CEO, Frontage Labs

OVER THE LAST 10 YEARS, **GLOBALIZING CLINICAL TRIALS** INTO EMERGING MARKETS HAS SEEN A **STEADY INCLINE**.

Despite an increase in the number of trials in areas like Asia Pacific, Eastern Europe and Latin America, conducting these studies outside of a more established market can prove challenging.

China has become the second-largest pharmaceutical market in the world, home to 17% of the world's population. It is an ideal region for study recruitment and accelerated trial start-up times. Top pharmaceutical companies are taking advantage of this by placing project management teams in China to oversee trials being conducted there. It is important that sponsors look for CRO partners that have global capability support while also demonstrating a strong localized presence in the targeted areas.

With multiple sites in the U.S. and China, Frontage has delivered optimal value to our clients by addressing the diverse challenges inherent in these studies. We are well-known in China as a bridge to assist our partners forwarding their products to the international and China markets. We possess dedicated resources in DMPK, CMC, bioanalytical and early-stage clinical services on both continents. We have adapted our processes to adhere to local regulatory and oversight requirements.

Supply chain has always been the backbone of the global pharmaceutical industry and all firms strive to ensure on-time delivery of drugs. New product approvals, pandemic threats, low-dose drugs, multiple dosage forms, uncertain market demand and geographic spread are driving the demand for customized manufacturing and supply solutions. Focus has now shifted from large-volume drugs to low-volume highly potent drugs treating rare and orphan diseases. To be able to cater to specific requirements, manufacturers must implement lean, adaptable facilities that can switch quickly between multiple products in multiple dosage forms. Criteria to be considered while designing a manufacturing facility include adequate space for orderly placement of equipment and materials to prevent mix-ups and contamination as well as suitable size, construction and location to facilitate cleaning, maintenance and proper operations. Above all, proper adherence to GMP regulations must be kept in mind even before designing and engineering the pharmaceutical manufacturing facilities to be approved as compliant – this is in the best interest of manufacturers to avoid approval delays with local authorities in regions where they intend to market their drug products.

Ramesh Subramanian, Ph.D.
VP, Strategic Marketing and Global Head, Business Development, Piramal Discovery Solutions

I think that one of the biggest factors impacting facility and equipment design is the regulatory need to assure that the product can be produced the same at every location, cost-effectively. For that reason, the cell therapy industry is evolving towards modular design of facilities for maximum flexibility while still providing design consistency, automated processes to reduce operator error and minimize process variability, and — in the case of sterile manufacture — closed-system processing.

***Note:** Answered in terms of cell therapy manufacturing, not pharmaceuticals.

William J. Monteith
Chief Operating Officer, PCT

LOCAL VS. GLOBAL MANUFACTURING

How is the need to provide local drug-product supply in multiple regions around the world **impacting pharmaceutical manufacturing facility and equipment design?**

The Minakem GMP factories provide drug substance according to client specifications in the case of custom manufacturing contracts, or in the case of generic APIs according to pharmacopeia standards (e.g., EP or USP). API delivered with appropriate certficiation (e.g., a CEP) gives the client the certainty that the API has been produced according to international standards as defined by the ICH Q7 guideline. While the Minakem group is not currently producing drug product, it certainly recognizes the need for local drug-product manufacturing in factories adjusted to local market size. Such local factories are, in certain countries, mandated by the local government to be allowed to sell drugs in that country. They should, however, always be at the highest quality and compliance standards.

Stefan Peterli, Ph.D.
Vice President of Strategic Business Development, Minafin S.P.R.L.

WE SEE THE BIGGEST IMPACT COMING FROM THE REQUIREMENTS OF INDIVIDUAL COUNTRY REGULATORY AGENCIES. For example, requirements brought forth by countries such as Turkey or Brazil may not necessarily be areas of focus for the FDA or MHRA/EMEA. These specific export country regulatory requirements can considerably affect workflows, infrastructure and operational design for our sites. Being a supplier to so many countries, we have to ensure our operations are compliant for the many markets for which our products are destined.

Justin Schroeder
Executive Director of Marketing, Business Development & Design, PCI Pharma Services

CLOUD COMPUTING

What impact do you think the move to cloud computing will have **on the ability of contract service organizations to better meet the needs of their customers**?

Utilizing cloud computing would allow CROs to provide their customers with **more comprehensive, flexible, targeted and faster services** for a fraction of a cost of going a non-cloud route.

Cloud computing offers CROs the ability to select their solutions from a wide array of existing choices; begin using cloud infrastructure or systems without the need of going through (often cumbersome) builds and implementations; scale the solution delivery and costs according to the current needs; utilize existing vendor controls such as disaster recovery, security, automated updates, etc.; and allow access to data and systems from any connected device, etc.

The cloud computing business model of investing heavily into building sophisticated computing infrastructure and systems, and providing users with access to such resources for a fraction of the total cost, clearly benefits cloud users and allows them to pass improved services and lower costs to their customers.

The benefits of using cloud computing in the CRO space are not any different from utilizing the cloud in any other space, and can be safely achieved as long as the CRO remains vigilant when addressing considerations and challenges that are unique to life sciences–regulated environments.

Paul Labas
Director, IT Compliance and CSV,
IPS-Integrated Project Services, LLC

Simon Lane
Vice President, Information Technology, Altasciences Clinical Research

I think the principal impact of the move to the cloud for many applications and services is the flexibility it adds to organizations to adapt to their clients' needs. Without the need for large legacy systems, and with the proliferation of offerings available, cloud computing provides agility to CROs that has not been seen before. The historical evolution of CRO systems has been a very slow, on-premise, waterfall progression. All of a sudden, these legacy systems are being replaced by one or multiple vendors that offer what are – in the CRO world – revolutionary developments. Furthermore, the advent of SaaS models allows the smaller player to be able to offer the same level of computing services as their much larger rivals from the start, something that was previously almost impossible. Likewise, the large CROs also have greater flexibility in what they can offer their clients. There is no requirement to invest a large amount in their own infrastructure in anticipation of the market; the infrastructure is already available, and this provides the CRO with the ability to service clients and requirements that were previously out of reach. Cloud computing is a game-changer and it is here to stay.

Cloud computing will help us to become more efficient and focus on our core business of delivering APIs while externalizing certain tasks such as mail, domain controller, web hosting and payment solutions. IT in support of core activities such as production and analytics will continue to be operated in-house for performance and confidentiality reasons.

Stefan Peterli, Ph.D.
Vice President of Strategic Business Development,
Minafin S.P.R.L.

CLOUD COMPUTING IS CERTAINLY A **GROWING TREND IN TECHNOLOGY** AND MAKING HEADWAY INTO THE CONTRACT PHARMACEUTICAL-SERVICES MARKET.

It has established a presence in project management applications and information sharing, training and compliance applications and the emergence of many others. From a corporate IT perspective, being a highly regulated industry, there is always strong consideration for risk mitigation and application of robust data security for situations where the use of the cloud is an off-network third-party option. That is why cloud computing has probably seen slower adoption in our market as compared to more progressive technology-driven businesses. That being said, probably the biggest application we see for true third-party cloud computing is in logistical supply chain management. Our services are one facet of a complex supply chain, and cloud computing helps connect the dots to help provide end-to-end visibility.

One application in the clinical trial space is in Interactive Response Technology (IRT). IRT is commonly the interconnected hub of information that allows clinical trial stakeholders to monitor and progress the execution of clinical trials. The IRT system provides the central pathway for individual investigational sites, CROs who are administering the trial and collecting data; clinical supply companies like PCI Clinical Services who are preparing and delivering the medicines; courier companies; and sponsor companies to exchange information, monitor patients, order and enable transactions for supplies, share data, etc. These various groups and locations are commonly all over the world, and it is necessary to ensure that the data being exchanged is blinded (and often randomized) to guarantee the integrity of the trial. IRT is the central connected hub network that ensures that trials are executed efficiently and effectively with a multitude of touch points.

Justin Schroeder
Executive Director of Marketing, Business Development & Design,
PCI Pharma Services

We are excited about the **benefits that cloud computing can bring**.

Primarily it will offer greater flexibility and access to numerous IT applications used by customers, in addition to the potential to significantly improve data transfer. Applications will be more scalable, which will benefit everyone, and there will no longer be a need to build up an expensive infrastructure if your demand is increasing. There are the added benefits of being able to book high-demand systems and, of course, that system and/or version updates can be planned and performed externally. Overall it will help reduce the IT administration burden, especially on backup and hosting maintenance, etc.

Ralf Liedke
IT Director Germany, Aesica

Cloud computing has been around for a while. However, its adoption by the pharmaceutical industry has taken longer than expected. Cloud computing has changed the way service providers and sponsor companies work, especially in terms of data transfer and security. Service providers have been challenged over the years to handle large volumes of data and documents associated with client projects. Due to increased outsourcing over the last decade, considerable efforts were required to maintain documents for each project, including those spanning various clinical phases. Cloud-based solutions allow for continuous and transparent content management. They facilitate sequencing of information based on timelines, dates and versions, while also assuring data integrity over the long run. They also allow for customers to access these documents at any point in time, thereby easing the burden during regulatory audits. Customers can also access cloud platforms 2-3 years after the completion of a project. This helps minimize any discontinuity that may arise due to the exit of a team member. At Piramal, we have implemented cloud-based solutions for some customers and found that they simplified the data management process for both our collaborators and our project management teams.

Ramesh Subramanian, Ph.D.
VP, Strategic Marketing and Global Head, Business Development,
Piramal Discovery Solutions

CLOUD COMPUTING

What challenges are associated with **implementing cloud computing within CROs/CDMOs**?

FROM SHARING PERSONAL PHOTOS ON AMAZON WEB SERVICES TO COMPLEX COMPUTATIONS WITHIN NASA'S NEBULA CLOUD COMPUTING PLATFORM, **THERE ARE CERTAIN CONCERNS THAT ARE COMMON TO CLOUD COMPUTING MODELS IN EVERY INDUSTRY.**

Data protection, systems availability, adequate disaster recovery, network speeds and systems performance, change control – all of these considerations must be identified and addressed within every cloud service. In addition to the above, CROs and their clients are tasked with meeting complex regulations relevant to the use of computerized systems and electronic data within life sciences industries. These unique challenges include compliance with such regulations as FDA 21 CFR Part 11, computerized systems validation, vendor and sub-vendor management, long-term data retention and availability, etc. It is the system users and data owners, not the cloud services providers, who are ultimately responsible for regulatory compliance and data integrity. However, a compliant cloud ecosystem can only be established and maintained through definition, communication, documentation and fulfillment of specific responsibilities by all key players – regulated client organizations, CROs and the cloud providers.

Paul Labas
Director, IT Compliance and CSV,
IPS-Integrated Project Services, LLC

Challenges for installing cloud-based solutions include the **time that is required to implement such a change**, and potential reluctance from the client's end.

Customers may prefer traditional options of using emails, password-protected mechanisms, server-based tools, local proxy, etc. Generally clients feel that time-tested formats are more reliable, considering the fact that such business documents are very crucial, and they prefer having control of such tools for safekeeping, transfer and IP protection. For some, the comfort and convenience of using time-tested, existing models overrides the potential benefits of moving to new cloud systems. At times, IT policies at the clients' end could be a hindrance — they usually have restrictions and aren't flexible enough to provide access to cloud-based tools to their employees working on projects. This increases the turnaround time and lowers ease of use.

We at Piramal, though, have been fortunate enough to be engaged with customers who are willing to implement cloud computing and are proactive enough to initiate such system-level changes. We have been supporting companies globally with our development and manufacturing sites across regions connected to secure clouds. Once initiated by the client, our site teams promptly align themselves with the client's cloud-based systems and use them regularly for regulatory needs and project planning purposes.

Ramesh Subramanian, Ph.D.
VP, Strategic Marketing and Global Head, Business Development, Piramal Discovery Solutions

As with any solution, security and risk management is paramount. Once the decision has been made to utilize a secure and robust cloud solution, much of the challenge can be the interactivity with various ERP systems, company-specific processes and industry vernacular. Each company or node in the supply chain operates differently, so sometimes applications can really take on a life of their own in the process of integrating supply chains. For example, a third-party cloud application developer may have already executed integration with your particular brand of EPR system, but in actuality the use of that ERP system from one company to another may vary considerably and be much more complex for integration, causing considerable scope creep and additional product development. Ensuring that there are enough resources and ownership from all parties in the execution of the integration is a critical step for success, so that all parties experience a seamless cloud solution integration.

Justin Schroeder
Executive Director of Marketing,
Business Development & Design,
PCI Pharma Services

Simon Lane
Vice President, Information Technology, Altasciences Clinical Research

The challenges with cloud computing are closely related to the advantages it offers. It offers flexibility and agility, but these have still to be tempered by the traditional CRO requirements of data integrity and control. There may be a tendency to create a parallel IT, or to forgo the IT group completely due to the apparent simplicity of the offerings, but this could be a mistake. While the traditional IT group may not always be adapted to the cloud computing world, there are still some fundamentals that are required: security (confidentiality), interoperability and availability. These features or basics are readily available in most cloud offerings, but thought and process still have to be applied to the implementation of these essentials, and unfortunately — because of the ease of the initial setup of a SaaS offering — these are often overlooked until much later when they have become problematic. The challenge with cloud computing is therefore to ensure that the requisite discipline in structure and usage is maintained as it would be for a legacy application. The backend development may have been completed for the CRO, but the requirement for operational discipline has not gone away.

CDMOs NEED TO EVALUATE THE RISK AROUND THEIR INTELLECTUAL PROPERTY THAT CLOUD COMPUTING IMPOSES AND **ENSURE THE SECURITY OF THE IP OF THEIR CUSTOMERS.**

Qualification and validation activities also need to be reviewed to ensure that they remain compliant. Within this, evaluation of both supplier and host is important, and solution suppliers need to be auditable. Cybersecurity is also vital to protect against external system attacks. Cloud computing does also increase demands on certain IT infrastructure; for example, there may be a requirement to enhance certain elements such as bandwidth if not already sufficient. Finally, disaster strategies will need to be reworked to incorporate cloud solutions, which will require more than just backup/restore procedures for internal servers. Redundancy of connection lines needs to be built in, as well as additional network availability to external sources.

Ralf Liedke
IT Director Germany, Aesica

From a regulatory compliance point of view, we need to have access to our archived data 10 years back. Depending on the cloud partner, this can become difficult in the case of switching to a different host or when we would like to internalize the data.

For solutions such as Office 365, which is being gradually phased in, we experience bandwidth problems using the online application and local files. We therefore prefer to install the heavy client for every user locally to avoid too much dependence on a wide bandwidth.

When we use hosting in the cloud, we insist on servers located in Europe. In fact, for mail and domain controllers we use a private cloud solution located in France.

Stefan Peterli, Ph.D.
Vice President of Strategic Business Development, Minafin S.P.R.L.

NEW REQUIREMENTS FOR EXCIPIENTS

What will be the impact of the requirements that drug manufacturers gain a similar level of supply chain understanding for excipients as they must have for APIs?

The need to generate full supply chain transparency will lead to increased scrutiny of excipient suppliers' supply chains. The level of involvement and oversight required to get excipient suppliers to provide the right transparency depends on the specific characteristics of the suppliers. Adapting to the new standards might be more challenging for smaller or nondedicated pharmaceutical excipient suppliers (many suppliers also have food, cosmetic, etc. products in their portfolio) and will require a more involved approach from the drug manufacturer. In the end the new requirements will force drug manufacturers and excipient suppliers to work together more closely in solid, open partnerships.

William van den Bremer
Global Supply Chain Manager, DFE Pharma

Dirk Hair
Technology & Innovation Manager, Product Development Medical and Pharmaceutical, Celanese

As an excipient supplier, this change is bringing more consistency and alignment in requirements from the drug manufacturers, and an opportunity to further enhance our service model. Changes related to Good Manufacturing Practices (GMP) and supply chain have been further enhanced by the release of standards specifically for excipient manufacture, such as NSF/IPEC/ANSI 363–2014 GMP for Pharmaceutical Excipients.

Drug manufacturers need to gain a higher level of understanding of their total excipient supply chain, more so than they have in the past, which requires more knowledge of supplier manufacturing practices, quality programs, regulatory capabilities, logistics, etc. Risk assessments must be performed to determine the appropriate level of expectations based on each excipient and its intended end use. Suppliers must then be evaluated to identify any gaps and mutually agreed plans developed to address them. Such activities require close cooperation between suppliers and their pharmaceutical industry customers. Formal quality agreements are often one end result. The industry has also been active with respect to the development of clear guidelines and tools to facilitate the process and help suppliers and drug manufacturers systematically perform these assessments, put appropriate practices in place and document their activities. One direction that needs to be worked on is standardized supplier information packages such as questionnaires and quality agreements that can eventually be developed to further simplify and harmonize the process for both parties.

Patricia Rafidison
Global Regulatory Compliance Manager, Dow Corning

Ramesh Subramanian, Ph.D.
VP, Strategic Marketing and Global Head, Business Development, Piramal Discovery Solutions

The impact will be on time and cost both. Currently, as far as FDA submissions of finished forms are concerned, the need is to have U.S. DMF-approved excipients.

So in a way the quality and GMP aspect is taken care of. But beyond ensuring that the source is a U.S. DMF-approved source, the formulation manufacturer has limited knowledge of the supply chain for the [excipients]. Deeper understanding of the supply chain here will help manage the supply of finished dosages well. The same becomes critical when it comes to a global project when there are a limited number of suppliers for excipients that cater to the GMP and quality standards of a wider regulatory requirement of different countries. It is only prudent to consider the excipients of primary packaging material in the same context. Usually, this is an oligopoly market with fewer large suppliers controlling this market – examples: resins, polymers, etc.

Patricia Rafidison
Global Regulatory Compliance Manager, Dow Corning

Excipients represent a broad diversity of substances. Therefore, appropriate Good Manufacturing Practices, based on IPEC guidelines or equivalent, should always be considered and preferably coupled with using a risk-based approach in order to meet current and future industries' expectations. Many excipients are also handled by distributors, and it can be challenging to establish full traceability in order to ensure product integrity. Consequently, it is necessary for drug companies to assess the quality of the supply chain depending on the type of supplier, the excipient technology, the distribution channels and the intended use. While they may purchase many excipients from multiple suppliers, a one-size-fits-all approach isn't, in many cases, practical. In addition, suppliers will be carefully considering any actions they must pursue that require extensive investment. Finally, lack of harmonization of requirements around the world adds significant complexity for excipient suppliers and drug manufacturers alike. Overcoming these challenges requires good cooperation and two-way communication between both parties, which in turn requires building of trust – something that does not occur quickly or easily.

NEW REQUIREMENTS FOR EXCIPIENTS

What are the greatest challenges drug manufacturers face **when working to meet the new requirements for excipient supply chain security**?

Ramesh Subramanian, Ph.D.
VP, Strategic Marketing and Global Head, Business Development, Piramal Discovery Solutions

There are various challenges ranging from batch sizes and minimum order quantity to quality inspection and financial stability of these companies. The greatest of all would be supply chain issues of low-volume excipients where the manufacturers have set campaigns in the year and any miscalculation would be detrimental for supply in the market. Identifying these excipients to have a supply chain risk mitigation or de-risking plan in place is critical for a drug manufacturer.

PER THE IPEC GUIDELINES, ALL PARTIES IN THE SUPPLY CHAIN SHARE THE RESPONSIBILITY TO ENSURE THE QUALITY AND SAFETY OF MATERIALS AND PRODUCTS. However, in the end, the drug manufacturers have the responsibility for setting up a risk-management program that assesses risks in their downstream supply chain. The large and globally extended networks of suppliers make it a challenge for drug manufactures to implement risk-management programs efficiently across their supplier base. Working with fewer preferred suppliers that can offer full control and transparency over their downstream supply chain can decrease the effort required to meet the new requirements for drug manufacturers. However, it can also restrict the availability of excipient suppliers meeting the standard. An additional trend is the increased regulatory focus on drug availability that is pushing drug manufacturers to critically assess business continuity with their critical suppliers. DFE Pharma supports drug manufacturers by having our own business continuity plan, including supply chain mapping and risk assessments for our manufacturing network and suppliers.

William van den Bremer
Global Supply Chain Manager, DFE Pharma

These requirements are resulting in an increased number of audits by the drug manufacturers' audit teams, with increased scope. As an excipient supplier that is highly responsive to emerging requirements, this change provides further evidence that our customer-driven engagement model meets or exceeds these evolving requirements.

Dirk Hair
Technology & Innovation Manager, Product Development Medical and Pharmaceutical, Celanese

Nice Symposium Oral Solid Dose Thank You to Our 2017 Sponsors

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

Nice Symposium, a new industry think tank forum for leaders of outsourced pharmaceutical service providers and their customers, was held January 31, 2017, in Durham, NC.

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