pharma's almanac

A NICE INSIGHT SUPPLEMENT

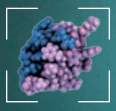
Q2 2016 EDITION

GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS

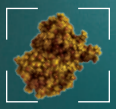
INNOVATIVE & EXPERT PARTNERS 2016 EDITION

BIOLOGICS SPECIAL FOCUS

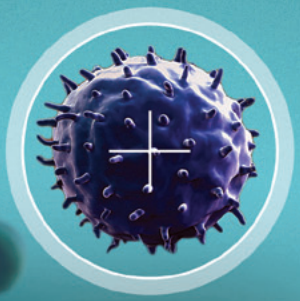
PRECLINICAL – RESPONDENTS' BIOLOGICS PIPELINE



69% **CRO** OUTSOURCING FOCUS ON HORMONES



75% **CDMO** OUTSOURCING FOCUS ON NBEs



PHARMA OUTSOURCING

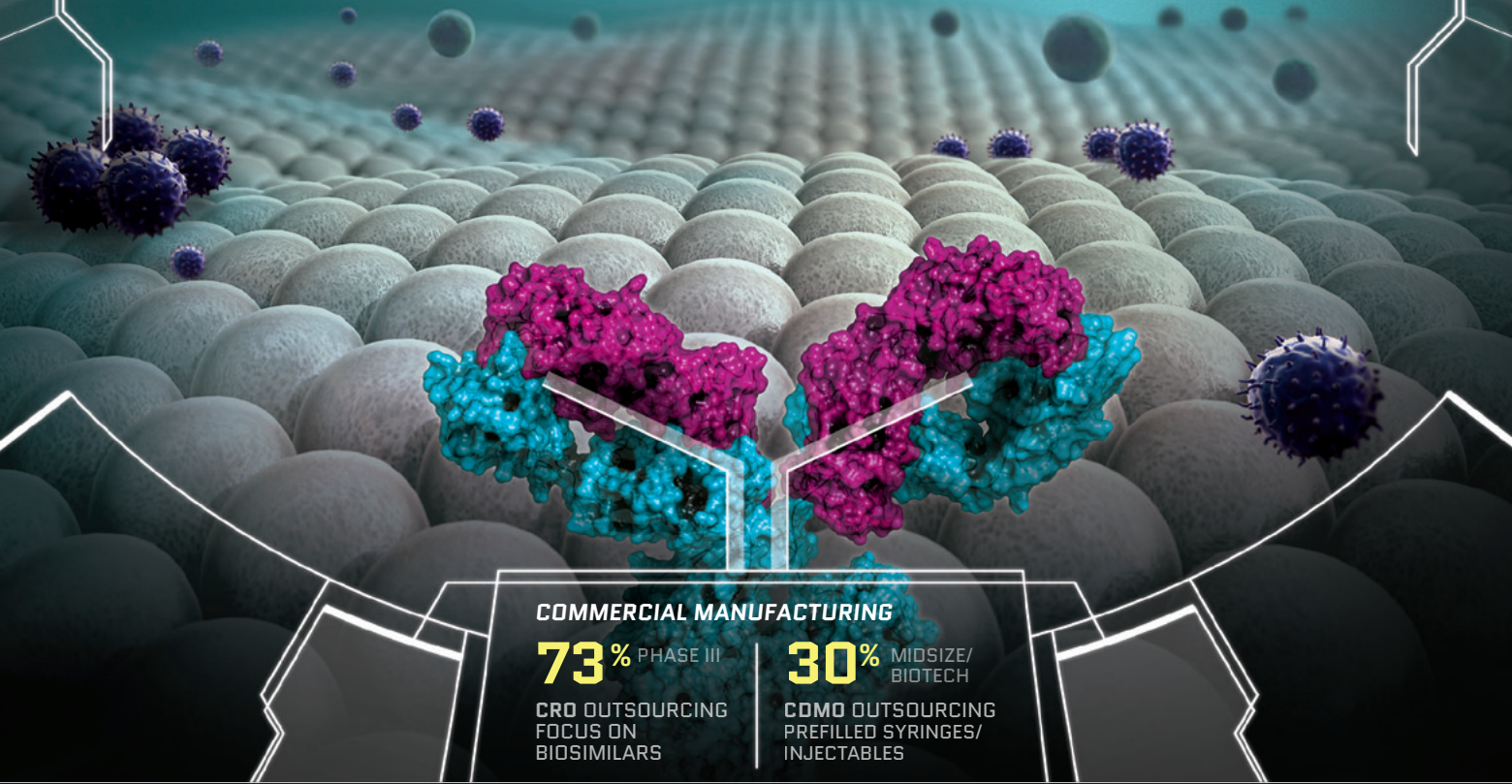
CLINICAL – OUTSOURCING PHASES

PHASE II

49 % TNF OUTSOURCED BY **CROs**

PHASE I-III

64 % OF ANTIBODY DRUG CONJUGATES OUTSOURCED BY **CDMOs**



COMMERCIAL MANUFACTURING

73% PHASE III

CRO OUTSOURCING FOCUS ON BIOSIMILARS

30% MIDSIZE/ BIOTECH

CDMO OUTSOURCING PREFILLED SYRINGES/ INJECTABLES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GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS
Q2 2016 EDITION

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CDMO INDUSTRY LEADERS

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Nice Insight is the market research division of That's Nice LLC, the leading marketing agency serving life sciences. We publish Pharma's Almanac, a special supplement that contains results from our annual industry surveys on buyer needs, supplier evaluation and selection criteria, and ratings for CROs, CDMOs, pharmaceutical excipients, and products/services for pharmaceutical equipment.

Pharma's Almanac is distributed by American Pharmaceutical Review and Pharmaceutical Outsourcing, reaching 40,000 unique readers. American Pharmaceutical Review is the leading review journal for business and technology in the pharmaceutical industry throughout North America that is read by 34,000 senior executives, technical personnel, scientists and others for the latest trends and developments in the process of pharmaceutical manufacturing. Pharmaceutical Outsourcing is a journal dedicated to pharmaceutical and biopharmaceutical contract services distributed to 15,000 readers for contract manufacturing, contract research, formulation/development services, contract analytical testing and other areas. The net total distribution of both publications is 40,000.

COLLABORATORS AND INNOVATORS WANTED

→ BY **STEVE KUEHN**, EXECUTIVE CONTENT DIRECTOR

Those developing biopharmaceutical therapies are building on scientific momentum that started some thirty-plus years ago. The supply chain that is discovering, developing and marketing new biologic medicines has never been more dynamic. The future of the pharmaceutical industry is guided by innovators and collaborators in the space.

The amazing intricacy associated with the development and manufacture of biopharmaceuticals is being managed in new and exciting ways. Industry observers agree that with biologics, "process is the product." The most successful in the sector are investing much in the way of time, resources and technical effort to align operations and processes for success, no matter their role in the supply chain.

What's exciting is that as biopharmaceutical science advances, the more it succeeds. The billions being poured into biopharmaceutical development is unprecedented; this torrent of investment is driving the industry higher, at an accelerating rate. What's interesting is how big a role contract research organizations (CROs) and contract development and manufacturing organizations (CDMOs) are playing in providing this lift to the sector's fortunes. CROs and CDMOs are providing the industry with the finest labs, clinical trial managers and operationally excellent manufacturing processes to push products to commercial success. Picking the right partners and then empowering them with collaborative tools and procedures is a start, but drug owners and makers both understand that the real imperative is to integrate their organizations in new, more transparent ways.

Biopharma's supply chain has its complexities, but is unbundled in its primary segments of research, clinical development and manufacturing. Each one plays to its strengths, and in collaboration are helping to create more new biological entities. This is also playing a significant role in bringing more economy and value to consumers, as the first wave of biosimilars reach commercial reality. With more such medicines losing patent protection every year, both branded players and an extensive army of contract service providers will be busy deciding which biologic therapies are commercially viable enough to apply the capital resources to produce as the original.

Who's going to win in this marketplace? For contract service providers, the "W" will be bestowed on those organizations that have the systems, technologies and SOPs to connect most closely with drug innovators. There's been a drive in the industry to simplify and strengthen biopharmaceutical supply chains by building more strategic, long-term associations with contract service providers.

What does the next biopharmaceutical season hold? How will the current "crop" of biological medicines do in the coming months? True to its progenitor, Pharma's Almanac has again been compiled by Nice Insight to bring you context, meaningful data and perspective to support the efforts of the industry's cultivators and help reveal and predict what the near future for biopharmaceuticals is, as well as its potential in revolutionizing health care. P

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CONTRACT SERVICE PROVIDERS

KEY TO TRANSLATING NEW IDEAS INTO EFFECTIVE MEDICINES

BY **CYNTHIA A. CHALLENER, PH.D.,** THAT'S NICE

Despite strong growth in the overall biopharmaceutical market and the biopharma contract services market, manufacturers of biologic APIs and drug products face innumerable challenges, from increasing cost pressures to expanding regulatory requirements and limited formularies. In this 3rd edition of the Pharma's Almanac, we provide in-depth discussions of the trends — positive and negative — driving the biopharmaceutical market and the use of CROs/CDMOs. Contract service providers representing the full value chain also offer their unique insights into the practices and strategies that are helping overcome the various challenges and enabling the accelerated development of novel medications.

Nigel Walker, founder of marketing firm That's Nice LLC and Nice Insight, the company's research arm, discusses how the biopharma industry is responding to both market drivers and constraints.

In a special focus on biologics, Nice Insight editors review the integral roles that CROs and CDMOs are playing in translating innovative technologies into highly successful treatments.

Brammer Bio CEO Mark Bamforth, along with Steve Kasok, CFO and Richard O. Snyder, CSO, explains why successful realization of commercial cell and gene therapies is predicated on the ability of big pharma and new biotech firms to establish partnerships with CDMOs with specialized expertise.

Rigorous integration is also essential within full-service CDMOs if they are to effectively support drug substance and drug product development, manufacturing, testing and packaging, reports Syed Husain Chief Commercial Officer of Alcami – the new alliance formed from the merger of AAIPharma Services and Cambridge Major Laboratories.

Advances in biotechnology are also impacting the production of small-molecule drugs, according to Rob Wilson, Senior Director of Business Operations for Codexis, Inc. The ability to rapidly develop specialized, engineered enzyme biocatalysts is improving efficiency and reducing costs in discovery, development and manufacturing.

The various facets of effective collaboration that differentiate ideal suppliers from qualified vendors are discussed by a virtual panel of top executives from contract providers Avara Pharmaceutical Services, Xcelience (a division of Capsugel Dosage Form Solutions), Vetter Pharma International and UPM Pharmaceuticals.

Oliver Technow, President, Scott Doncaster, Vice President of Manufacturing Technologies and Engineering, and Heather Delage, Vice President of Business Development for Biovectra, remind us that close relationships must be supported by the unique combination of specialized capabilities and demonstrated performance to achieve partnerships that can be competitive in the marketplace.

Cyrus K. Mirsaidi, President and CEO of BioDuro, outlines how integrated contract research and development organizations (CRDOs) with specialized expertise and innovative technologies can accelerate the biopharma drug development process and reduce overall costs.

Ash Stevens' Vice President of Operations, Vince Ammoscato, and Senior Process Safety Engineer, Sean Lapekas, underscore the importance of conducting comprehensive process safety evaluations.

Bruce Miles, Lead, Mergers & Acquisitions Integration with Think Tank Partner, Nice Consulting, highlights factors driving the success of new organizations like Alcami that are formed via mergers and/or acquisitions.

The design of better packaging, administration devices and the use of advanced manufacturing technologies must be employed to allow production of the affordable, convenient and easy-to-use drug forms necessary for increasing patient adherence, according to Kevin Haehl, General Manager of Unither Pharmaceuticals.

Oriol Prat, Director of Contract Manufacturing with Grifols Partnership, outlines the challenges associated with the outsourcing of fill/finish activities and the importance of selecting a contract service provider with a clear track record of quality performance.

Trends in the pharmaceutical industry are changing equipment and technology needs and thus purchasing patterns. This is challenging manufacturers to rethink their equipment management strategies. Matt Hicks, Chief Operating Officer of Federal Equipment, discusses these key issues and a range of potential solutions.

GlaxoSmithKline Biopharmaceuticals' Process Development Head, Erich Blatter, discusses why biopharma CDMOs must have the expertise to achieve efficient and effective upstream and downstream process development, enabling "right first time" technology transfer.

That's Nice LLC and Nice Insight discuss how the adoption of single-use equipment is facilitating the implementation of flexible manufacturing solutions to achieve cost-effective, aseptic production.

In three roundtable articles, industry leaders provide insights on enhancing bioavailability, the biosimilars landscape and antibody-drug conjugates.

Nice Insight researchers provide details about the recently completed 2016 Pharmaceutical Equipment Survey, including the demographics of respondents, types of equipment considered and the evaluation of company awareness and perception.

Guy Villax, CEO of Hovione, discusses the FDA's shift from a focus on quality metrics to one that combines metrics with quality culture, and why leading CDMOs embrace innovative technologies and practices, including the introduction of Quality Culture into FDA's lexicon.

Scale-down modeling is described by John Moscariello, Vice President of Process Development, and Gustavo Mahler, President and CEO of CMC Biologics, as an indispensible tool for biopharmaceutical process development, characterization, optimization and validation.

The list of top CDMOs and CROs are ranked according to customer perception as determined by The 2016 Nice Insight Contract Development & Manufacturing Survey and The 2016 Nice Insight Contract Research — Preclinical and Clinical Survey. P

→ ABOUT THE AUTHOR

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Scientific Content Director

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

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VIRTUAL PANEL

FROM QUALIFIED TO IDEAL: THE IMPORTANCE OF PARTNERSHIP

→ BY **GUY TIENE,** NICE INSIGHT

NICE INSIGHT'S VIRTUAL PANELISTS WEIGH IN ON WHAT MAKES CONTRACT SERVICE RELATIONSHIPS WORK BEST

Outsourcing is often critical to the success of a product and partnership can be just as critical to the success of an outsourcing relationship. According to the 2016 Nice Insight CDMO Outsourcing Survey, nearly 70% of outsourcing projects were sent to a combination of preferred providers and strategic partners, with the latter being awarded 26% of the business. Further, 95% of survey respondents were interested or very interested in becoming involved in a strategic partnership in the next 18 months.

STRATEGIC TIES AN IMPERATIVE

According to Peter Soelkner, Vetter Pharma Intl's managing director, there is a real distinction between what constitutes a "qualified" supplier versus an "ideal" supplier. "As we see it, the ideal supplier is differentiated by one very important term – 'strategic partnership,'" says Soelkner. "That means an ideal supplier will put the customer first when creating the partnership, making almost every effort to see things from their perspective." As Soelkner explains, Vetter is challenging itself to view the partnership through the lens of the customer, making decisions that are in the interest of the customer, while at the same time making decisions that make good business sense for the company.

Vetter is a contract development and manufacturing organization (CDMO) and a fill finish innovator of aseptically pre-filled syringe systems, cartridges and vials. With production facilities in Germany and the United States, Vetter serves the top 10 (bio-) pharmaceutical companies as well as a growing list of small and midsize companies. Its portfolio spans state-of-the-art manufacturing from early clinical development through commercial filling and final packaging of parenteral drugs.

> AN IDEAL SUPPLIER WILL PUT THE CUSTOMER FIRST WHEN CREATING THE PARTNERSHIP, MAKING EVERY EFFORT TO SEE THINGS FROM THEIR PERSPECTIVE.
>
> Peter Soelkner – Vetter Pharma International

→ ABOUT THE PANELISTS

Bill Pasek
Executive Vice President, Avara Pharmaceutical Services

Frank Sorce
Vice President of Business Development, UPM Pharmaceuticals

Peter Soelkner
Managing Director, Vetter Pharma International

Derek Hennecke
CEO and President, Xcelience, a division of Capsugel Dosage Form Solutions

> AN OPEN, HONEST AND TRANSPARENT RELATIONSHIP IS WHAT I THINK WILL ENSURE LONG-TERM SUCCESS BETWEEN TWO ORGANIZATIONS VERSUS ONE TRYING TO WIN.
>
> Bill Pasek – Avara Pharmaceutical Services

NARROWING IT DOWN

There's plenty of evidence to point to the fact that a primary goal of today's pharma and biotech companies is to reduce the number of suppliers and contract manufacturers that they partner with. "In past years [pharma companies] have come to realize that it is far better to develop partnerships with only a few suppliers whom they deem to be strategic in focus, not simply tactical. This intent has led to the creation of programs by pharma and biotech companies alike on how to successfully assess and choose partners." In this process, says Soelkner, such companies are continuously screening suppliers, creating databases and utilizing electronic bidding – all with the goal of creating a base of only a few qualified service providers. "Over the last decade, they have also begun evaluating existing suppliers with scorecards and key performance indicators such as 'adherence to cycle time' or 'supply plan adherence,' explains Soelkner.

Any supplier wanting to play an important role in today's strategically driven market must accept these and similar challenges. Successfully doing so offers promising opportunities to play an important part in any future outsourcing decisions.

PARTNERS, OF COURSE

For Bill Pasek, Executive Vice President and CCO at Avara Pharmaceutical Services, partnership is key: "An open, honest and transparent relationship is what I think will ensure long-term success between two organizations versus one trying to win." A private, wholly owned subsidiary of American Industrial Acquisition Corporation (AIAC), Avara Pharmaceutical Services provides bulk drug formulation and manufacturing, along with primary and secondary packaging capabilities for solid-dose drugs.

Avara's manufacturing and packaging capabilities are focused on oral solid and includes a high-containment module. Equipped with the latest solid-dose manufacturing technologies that include granulation, coating, blending, encapsulation, compression, tablet and capsule drying, Avara says its broad experience with supply chain, commercialization, product launch and product transfer allows it to sustain exemplary levels of product quality and regulatory compliance.

A contract services provider has to have the right tools and know how to use them, but it's the quality of the relationship, the close collaboration, says Pasek, of what makes a supplier not only qualified, but also ideal. In fact, though Pasek stresses that quality is critical, he regards it more as "the price of admission" to even be considered for outsourcing projects, further stressing the significance of partnership. For a CMO to be considered a quality business partner you must deliver on time, in full, at the agreed price and exceed customer expectations.

MORE FORMAL COLLABORATION

Although most in the industry are beginning to understand that more formal levels of collaboration between sponsor and contractor are desirable, when it comes right down to it, some drug owners aren't ready for the kind of partnerships required to be successful in today's pharmaceutical markets. "While we're seeing movement toward partnership and overall risk sharing in deal structures, that movement is not yet universal. We've had several potential clients approach us with potential partnerships, [but] a lot of potential partnerships and arrangements we felt would be very one sided," says Frank Sorce, Vice President of Business Development at UPM Pharmaceuticals.

Based in Bristol, Tennessee, UPM Pharmaceuticals is an independent contract development and manufacturing organization serving the pharmaceutical and biotechnology industries. UPM provides high-quality pharmaceutical drug

> WHILE WE'RE SEEING MOVEMENT TOWARD PARTNERSHIP AND OVERALL RISK SHARING IN DEAL STRUCTURES, THAT MOVEMENT IS NOT UNIVERSAL.
>
> Frank Sorce – UPM Pharmaceuticals

development services that include formulation development, cGMP manufacturing and packaging, analytical method development and testing from concept through commercialization.

Derek Hennecke, CEO and President, Xcelience, a division of Capsugel Dosage Form Solutions, finds clients – especially small and virtual companies whose needs continue to evolve – must have a huge level of trust in their development partners. "Knowing that their projects will be handled on a case-by-case basis by a partner that has a range of technologies, depth in formulation know-how and integrated product development capabilities is an imperative. A partnership mindset is valued in the design and feasibility assessment stages – and often can entail working with clients in redefining problem statements – as well as later stages of product development, clinical and commercial supply," explains Hennecke.

Xcelience offers a suite of services enabling clients to partner with a single CDMO for all clinical outsourcing needs. Services include preformulation, analytical services, formulation development, GMP manufacturing, small-scale commercial manufacturing, clinical supplies packaging and logistics. According to Xcelience, the company takes pride in delivering the highest standards in science and service with an emphasis on quality, cost and speed.

Much has been learned about what drives customer satisfaction with outsourced contract manufacturers post-engagement. For example, while a solid regulatory record and cost are critical in pre-engagement selection, we see companies being challenged with on-time delivery and tasked to meet project deliverables high post-engagement. What's important here? Soelkner agrees that a strong regulatory record and cost factors can often times be important selection factors for a contract manufacturer. "However, this is not always the case," explains Soelkner. "What must also be taken into consideration and properly differentiated since it decisively affects the selection criteria, are the characteristics of the market in general, the form of administration of the drug itself, the specific product characteristics and complexity, and many other factors."

Technical acumen and a consistent policy of continuous improvement is crucial and something most CDMOs and contract services providers must provide to stay relevant and competitive. "A service provider must invest in high-quality materials, to achieve the high safety requirements and cGMP standards," says Soelkner. "Technical expertise is also important since today's customers expect state-of-the-art equipment, laboratories and filling lines in aseptic manufacturing. And, of course, good performance in timeliness and reliability is crucial."

"I think that the clients and suppliers are both much more sophisticated than they were in the past," says Hennecke, "and deal structures have evolved in step with their developing relationships. There is no longer a simple buy vs. build choice in models but many options in between that can best fit a given situation." According to Hennecke, a transactional approach – the "old" model as he puts it – generally tends to result in poor outcomes for all parties in the pharmaceutical industry. If the drug does well, the pharmaceutical company will do well, but not necessarily the partner. And if the drug fails, both companies will suffer. It is encouraging that the industry has matured to look at a broader team collaborative approach, with sustainable risk and reward sharing.

> THERE IS NO LONGER A SIMPLE BUY VS. BUILD CHOICE IN MODELS BUT MANY OPTIONS IN BETWEEN THAT CAN BEST FIT A GIVEN SITUATION.
>
> Derek Hennecke – Xcelience

Ultimately it is a two-way street and the partnership has to offer both sponsor and contractor the best structure to meet not only each party's shared goals, but their individual business imperatives as well. In the end some of those opportunities aren't right, says Sorce: "We've turned a lot of those down because it just didn't make sense for us to do that."

As market pressure continues to make a well-ordered supply chain and the need for competent contract services partners a guiding principle, it's clear the necessity for new levels of collaboration and partnership will only continue to grow in importance throughout 2016 and beyond. In a constantly evolving market with rapidly changing demands, the stability that comes from solid partnerships can be a true differentiator, and a value proposition should not be ignored. P

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QUALITY CULTURE WINS OVER COMPLIANCE

→ BY **GUY VILLAX**, HOVIONE

It's Official! FDA has introduced Quality Culture in its guidance – although still in draft, it signals a sea change at the agency.[1] No longer will FDA focus solely on compliance. Pharmaceutical manufacturers will be recognized for excellent performance. Pharma companies that rely on contract service providers will be able to use Quality Metrics and New Inspection Protocol Project (NIPP) performance scoring to make better decisions when it comes to selecting CDMOs.

In the last half-century, the two most significant changes in the global pharma sector have been [1] the emergence of a generic medicines industry that fills more than 80% of global prescriptions and [2] the ability of regulators to keep up with science and – in over the last decade – shape the drug approval pathway to reflect policy. We have seen the rise of the approval hurdle for blockbuster me-too drugs that give patients negligible marginal benefits.[2] Instead NDA sponsors now can use a number of mechanisms for accelerating the approval of drugs that address unmet medical needs or have mechanisms of action linked to a specific gene possessed by a specific patient population.[3]

In the same half-century, on the other hand, pharmaceutical manufacturing on the whole changed very little despite valiant efforts by FDA to take the industry into the 21st century. Any changes that did occur involved generally enhancing GMP

standards, which have improved steadily across the board in all geographies. Most of this progress can be attributed to the International Conference on Harmonization (ICH) and increased harmonization of standards globally. However, I believe significant change is on the horizon.

In 2014, my article *Why Dr. Hamburg Needs Her Dean's List* [4] focused on the inability of regulators to get pharma manufacturers[5] to do more than just comply. FDA currently only gives pharma manufacturing facilites three possible classifications in an inspection: the first is "no action needed," meaning that manufacturing issues will not be the reason for non-approval, while the two other inspection outcomes are negative and generally indicate set-backs to an approval are likely.

Today, FDA still provides no feedback when plants do better than comply, and so FDA is unable to send a signal of encouragement for those that want to be role models. FDA's message has to date been all about meeting its regulations and ICH guidelines. The graph below from the previously mentioned article illustrates the problem and how an FDA Dean's List could solve it.

QUALITY OVER COMPLIANCE

Inspections have traditionally paid little attention to quality cultures signals. I even recall a very good, but bruising, inspection[6] in which the message my team and I received was something like "patients want capsules full of compliance." It has been tough to fight such attitudes, yet I keep telling my people "patients want capsules full of quality," because if we think quality, then compliance will take care of itself. Quality is what happens when nobody is looking, and it is what makes sure we catch the unexpected. Compliance only deals with what is expected, and is therefore insufficient to truly protect the patient.

FDA started to "walk the talk" on the need for a new manufacturing paradigm in 2002 when it launched its Vision for the 21st Century. Since that time, the agency has pushed forward a number of innovations: Parametric Release of Human and Veterinary Drug Products, Process Analytical Technology (PAT), and Quality by Design (QbD). Interestingly, ICH contributions also moved from product-focused guidelines (impurities, stability...) to "how to do" (ICH Q7 to 11), and currently "how to develop" (ICH Q12).

Quality has thus evolved from focusing on the what (defining the product) to the how (improving how it is produced). To date, the heavy lifting has been performed by the regulator. For the most part, FDA has been behind these innovations, and for this reason it remains the gold standard of regulators. Yet there has been little adoption of these innovations. Except for regulation-driven requirements, e.g., wide adoption of risk-assessment and meeting constantly escalating GMP standards, there has been virtually nil traction in adopting new paradigms, including PAT, QbD, parametric release or continuous manufacturing.

TODAY WE HAVE A **RE-STRUCTURED INDUSTRY** IN WHICH BIG-PHARMA IS NO LONGER LEADING DRUG INNOVATION, AND THE **SMALL PHARMA FIRMS THAT INNOVATE NO LONGER DEVELOP OR MANUFACTURE IN-HOUSE.**

All of these initiatives may be sound ideas, but because the industry generally does not perceive any short-term gain, they are not adopted. The root casuses for this are many: lack of global harmonization and FDA being a poor communicator; furthermore, the drug industry being both very conservative and very profitable: if forced to choose between risk and manufacturing cost reduction, reduced risk is preferred. As a result, many new useful innovations are standing idle because there is no driver to get them adopted.

CHANGE IS IN THE WIND

Last March, FDA gathered industry associations to inform them of changes in its approach to inspections.[7] Funding through the Generic Drug User Fee Act (GDUFA) has enabled FDA to dramatically strengthen its compliance oversight. There are now two distinct, independent but overlapping inspection dimensions: a pre-approval inspection (PAI) program and a surveillance program.

In addition, FDA has created a cadre of specialist inspectors (headquarters-based, not district-based) and is implementing the New Inspection Protocol Project (NIPP). The industry has been informed that "*... while continuing to document observed deficiencies, [FDA] inspections should also identify practices that exceed basic compliance... the inspection process focuses on measuring and describing the state of quality... industry outreach/training on positive manufacturing behaviors.*"

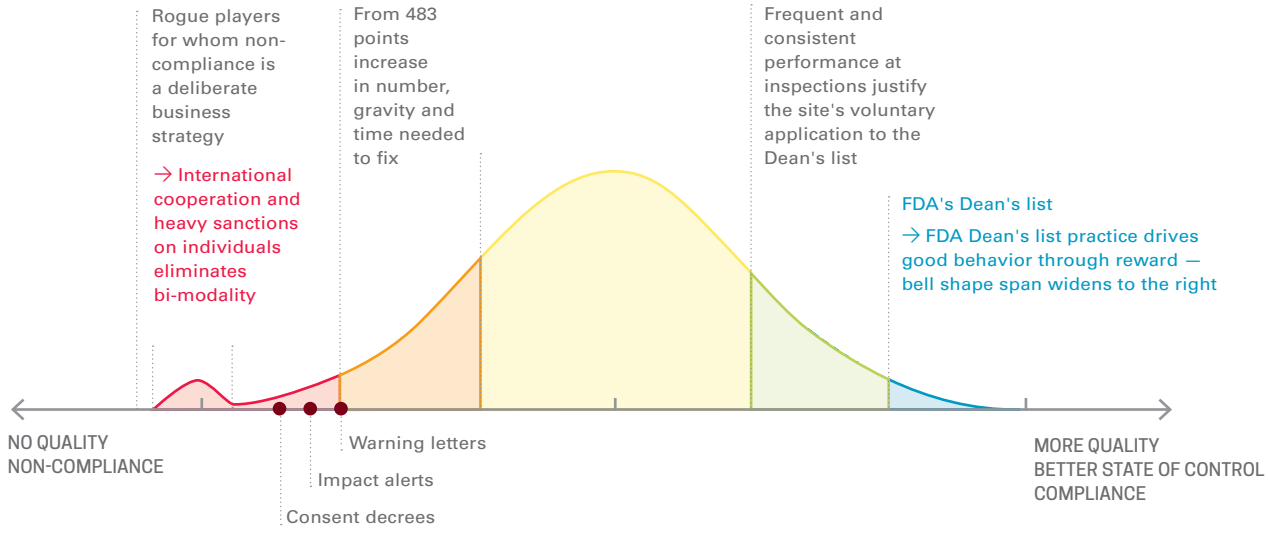
FDA explicitly says that "*Elements of an inspection [include] quality culture, maturity of the process development program, lifecycle risk management and oversight.*" "*[During inspections] Scoring will take place at the element level and for the 6 [quality] systems, 29 Elements were developed... There are six performance levels (1-6): three levels of failure (critical, major, minor), one acceptable level, two levels of exceeding basic compliance.*"

Furthermore, FDA says that "*...good practices that exceed cGMPs*" contribute to quality performance. The agency also indicates that although its initial focus will be on sterile drugs[8], one should expect this approach to become a generalized best practice of FDA.

CDMOS ARE CRITICAL TO NEW PHARMA INNOVATION

Today we have a re-structured industry in which big pharma is no longer leading drug innovation, and the small pharma firms that innovate no longer develop or manufacture in-house. Instead, small pharma companies partner with CDMOs both to generate the knowledge required for the CMC section of new drug applications (NDAs) and use their production capacity to launch new drug products. The business

→ **FIGURE 1 PHARMACEUTICAL MANUFACTURING SITES STRATIFICATION BY LEVEL OF COMPLIANCE (2014)**



model of the new innovative pharma companies is defined by high risk/high reward, speed to market and maximum returns. The key success factors are knowing what vendors present a good fit with the project and developing strong partnerships.

This model allows CDMOs to take risks and invest in what many consider to be exotic capabilities – capital expenses for out-of-the-ordinary equipment/technologies that solve unique problems and considerable operating expenses for expert individuals that can link the use of sophisticated technology with fundamental understanding of these out-of-the-ordinary processes.

A specialist CDMO offering a specialist technology can quickly fill its capacity by serving all, even if there are only a very few drug-development projects that require a highly specialized capability. The time when big pharma had everything in house is long gone, primarily because even if you can afford the plant you cannot afford to have the experts on hand waiting just in case a project comes along that requires their specialized skills – and experts will remain state-of-the-art only if they are always busy.

COMPETITION WELCOME

This restructuring of the industry has created a situation in which companies can exploit a vast range of innovative technical opportunities. Soon the key driver for their adoption will be competition. The industry structure is no longer based on captive development and captive manufacture; innovators now rely on specialist CDMOs that have the technical solutions across all scales supported by talented individuals with deep know-how.

These CDMOs tend to be heavy investors in new plant and equipment, actively fund R&D in a narrow number of technologies, and employ armies of highly experienced and dedicated multi-disciplinary teams that have developed strong methodology to support the design and development of robust production processes. These teams tackle a large number of projects; each year they may in fact support a dozen process validation campaigns and supply clinical trial materials for a hundred compounds in every phase of clinical development.

Such CDMOs have a fully industrialized approach to generating the CMC section of NDAs. For them, developing an extensive understanding of the process is not just a "nice to have", it is a pre-condition for meeting profitability goals. CDMOs make money on a manufacturing profit and loss (P&L) not on a patent; they need to be lean, deliver right-first-time and make sure they operate with high capacity utilization. What has remained mostly an illusive holy grail to the big pharma plants in Puerto Rico and Ireland is a survival pre-condition for today's CDMOs.

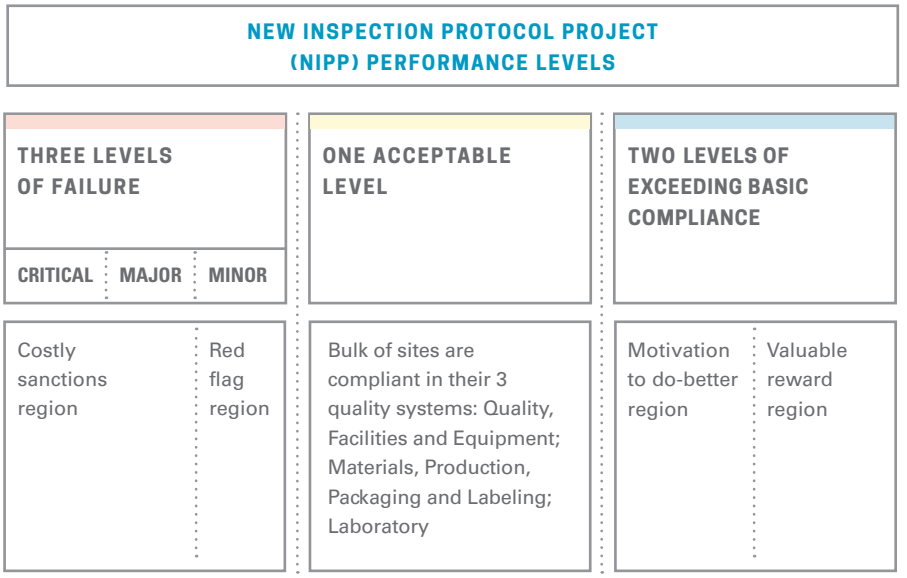
Not surprisingly, these CDMOs totally embrace the Innovation that FDA has been trying to convince industry to adopt for the last 15 years as it makes good business sense.

QUALITY AS A DIFFERENTIATOR — THE RISE OF QUALITY CULTURE

Why do CDMOs embrace PAT, QbD and Quality Metrics, and why are they delighted with the introduction of Quality Culture into FDA's jargon and guidance? Because it gives them an opportunity to differentiate in a measurable way.

CDMOs are in the service business, and thier activities only become industrial when all of the problems are solved. So for the most part, what matters is how each CDMO's employees perform. The company culture of a CDMO has always been very apparent to clients when they visit or conduct audits. In some cases, clients have been

→ **FIGURE 2 WHAT AREAS UNDER THE CURVE MATTER?**



COMPANY PROFILE

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 USA, 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. In the inhalation area, Hovione is the only independent company offering a complete range of services.

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heard to say *"at XYZ CDMO, the service is uneven, it all depends on who they put on the team for our job, and you only find out when it's too late"* – with the changes taking place at FDA, clients of CDMOs will be able to get a site-specific trended measurement of quality performance made by the ultimate arbiter.

BEING GREAT, WITH MEASURED PERFORMANCE

Quality Metrics and the NIPP performance inspection scoring will enable the ranking of sites that will allow objective comparison between those sites that are a good fit for each sponsor's project. Market pressures will make sure all of this data becomes public, and organizations will make sure it is compiled and made widely available. The differentiation will no longer be just between compliant and non-compliant. Quality Metrics and NIPP will differentiate between bad, OK, good and great.

Furthermore, this data will allow innovators to make better decisions when it comes to selecting CDMOs for their pharma intermediates, APIs and drug products. FDA has indicated that performance ahead of compliance will be rewarded. As a result, manufacturers will finally realize direct benefits of going beyond compliance, for being early adopters of new technology, and for nurturing a fertile quality culture at every one of their sites. With measurable quality, differently rated sites will be able to price their services based on the value they provide to the client. In addition, with public quality rankings – and the ugly side of globalization raising its head in the shape of fake pharmaceuticals – the increasingly well-informed patient will be looking for effective pharmaceuticals made by quality manufacturers.

DEFINITIONS OF QUALITY TERMS

Quality by Design (QbD): Quality should be built into a product with an understanding of the process by which it is developed so that manufacturing is performed within a defined design space, this is made possible through the knowledge of the risks involved in manufacturing the product and how best to mitigate those risks.

Parametric Release: Process by which a firm achieves real-time release by relying on critical process controls in lieu of quality control testing of samples of finished products.

Process Analytical Technology (PAT): A mechanism to design, analyze and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (CPP) that affect Critical Quality Attributes (CQA).

Quality Culture: The collective attitudes, beliefs and behaviors of an organization and of individuals in the organization related to delivering quality pharmaceutical products to the patient.

The changes are, in fact, already taking place. For example, a small pharma company that displays many of the innovative attributes described in this article recently announced that it is contracting with a CDMO for continuous tablet manufacturing.[9] Such agreements are evidence of how much the industry has changed.

Innovators do not want to manufacture; this activity is now left to specialists. Interestingly, the CDMO chosen to make tablets using a continuous process is not well known for making dosage forms, but rather APIs. Most likely the determining attributes for this vendor selection were based on soft attributes, not hardware, such as a focus on deep science; a fertile quality culture; a demonstrated commitment to client service; a track record of QbD filings; extensive knowledge of automation, PAT and math modeling; and years of demonstrated reliability. P

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Guy Villax CEO, Hovione

Guy Villax has been the Chief Executive Officer of Hovione since 1997. Prior to that, he held positions with Price Waterhouse in London and Hovione in the Far East. Guy has been a Member of the Board of CEFIC's European Fine Chemicals Group since 2004, as well as a Member of the Board of Rx-360 since 2010 and is currently Vice-Chair. He has a degree in accounting and financial management from the University College at Buckingham.

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5. Throughout this article, pharma manufacturer refers to all drug-related establishments that FDA inspects – finished dosage drug manufacturers, API manufacturers, analytical labs, bioequivalence sites, etc.
6. This inspection was performed by FDA investigator Thomas Arista, a biotechnology expert, at Hovione's Portugal facility during September 2005.
7. On 4th March 2016, the leadership of CDER gathered industry representatives (GPhA, EFCG, BPTF and PBOA) to discuss inspection matters. The materials presented can be accessed at: http://go.hovione.com/fda-quality-forum; industry association information can be obtained at: Generic Pharmaceutical Association (GPhA) http://www.gphaonline.org; Pharma & BioPharma Outsourcing Association (PBOA) http://www.pharma-bio.org; Bulk Pharmaceuticals Task Force (BPTF), an affiliate of the Society of Chemical Manufacturers and Affiliates (SOCMA) http://www.socma.com/AssociationManagement/?subSec=9&articleID=2889#Chain-Safety; European Fine Chemicals Group (EFCG) http://www.efcg.cefic.org.
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OVERVIEW

NICE INSIGHT

INNOVATION AT THE HEART OF BIOPHARMACEUTICAL INDUSTRY GROWTH

NICE INSIGHT HIGHLIGHTS KEY TRENDS DRIVING GROWTH IN THE BIOPHARMACEUTICAL MARKET

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

CDMO BIOLOGIC PRODUCT PIPELINE FOCUS ON

57% ADC

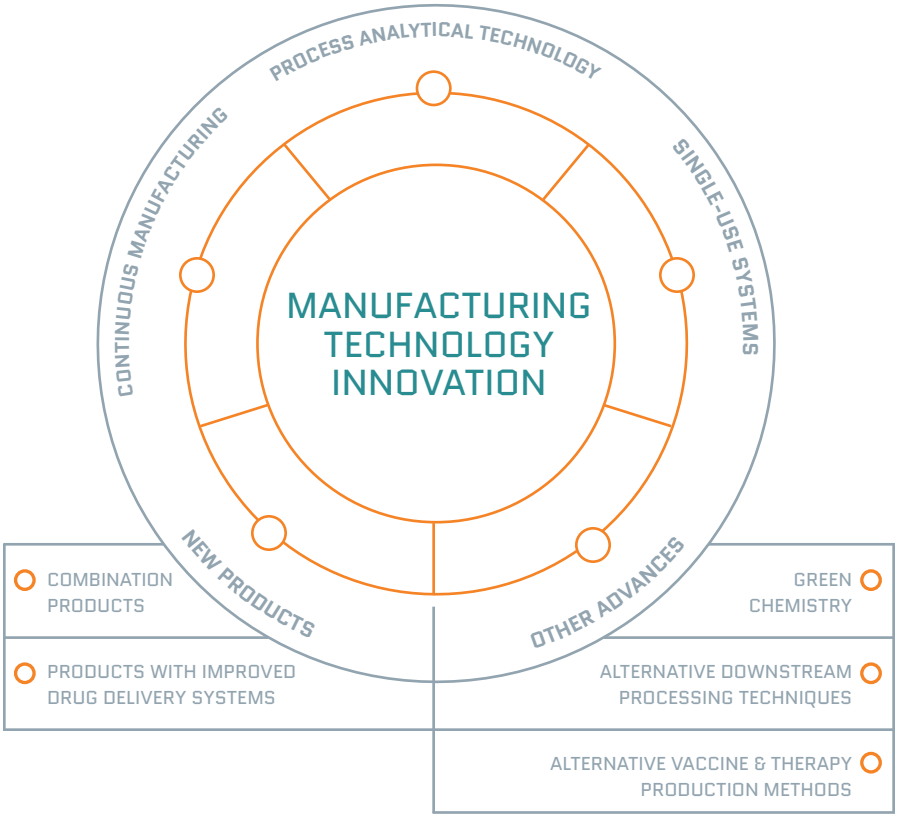
56% VACCINE

51% mAbs

The global biopharmaceuticals market was valued at $162 billion in 2014 and predicted by Persistence Market Research to grow at a compound annual growth rate of 9.4% from 2014 to 2020 to reach $278 billion.[1] This healthy growth rate is attributed to the increasing prevalence of chronic diseases, for which biologic drugs are more effective than traditional small-molecule treatments, the aging of the global population, and increased investment in R&D technological advances, particularly in the area of targeted and personalized therapies. However, intense pressure to reduce the costs of these very expensive drugs and rapid expansion of biosimilar sales is acting to restrain even greater market growth. The industry is responding with the installation of state-of-the-art flexible, small-volume manufacturing capabilities based on single-use systems, and exploring continuous processing technologies in modular facilities, which can be readily replicated anywhere in the world. Increased outsourcing to leverage unique expertise as well as lower-cost development and production capacity remains a key strategy for many small-to-large companies involved in biopharmaceutical manufacturing.

Part of this strong growth is also due to globalization of the biopharmaceutical industry. There is significant investment in the expansion of existing, and the addition of new capacity in many emerging markets. This growth is occurring despite significant challenges. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), it takes more than 10 years to receive regulatory approval at an average cost of $2.6 billion, double the cost from 10 years ago. This also reflects the fact that just 12% of investigative medicines that enter Phase I clinical trials end up as commercial products.[2] It is also worth noting that constructing conventional, large-scale biopharmaceutical manufacturing

FIGURE 1 KEY AREAS OF MANUFACTURING TECHNOLOGY INNOVATION



facilities typically costs $200 to $500 million (vs. $30 to $100 million for similar-scale, small-molecule plants) and takes approximately four to five years to complete.[3] Indeed, BioPlan Associates reported that bioprocessing-related budgets were higher in 2015 than the previous year across all areas, including capacity expansion, equipment expenditures, process design, new personnel hiring and facility construction.[4]

MEETING THE CHALLENGES POSED BY NEXT-GENERATION THERAPIES

Monoclonal antibodies (mAbs) remain the largest class of biopharmaceuticals with sales of ~$50 billion in 2014, and account for ~90% of global mammalian cell-culture capacity.[4] Introduction of mAb biosimilars is also anticipated to drive strong growth in the biosimilar sector.[5] Even so, as our understanding of disease mechanisms increases, numerous next-generation therapies are being developed that will require significant advances in biomanufacturing technologies. For instance, antibody-drug conjugates (ADCs) and therapeutic vaccines are taking cancer treatment to new levels. According to PhRMA, there have been three ADCs approved to date, with 24 in clinical trials. In addition to Provenge, the therapeutic vaccine approved in 2010 for prostate cancern,[13, 14] other cancer immunotherapy drugs are in clinical trials.[2] In early 2016, Immunomedics' investigational ADC, Sacituzumab govitecan, for the treatment of triple-negative breast cancer, was awarded breakthrough therapy designation by the FDA.[6] Notably, of the 2016 Nice Insight CDMO Outsourcing Survey[7] respondents that have biologic drugs in their pipelines, 57% are developing ADCs and 56% are developing vaccines, compared to 51% with mAbs under evaluation.

In addition to ADCs, numerous gene and cell-based (e.g., chimeric antigen receptor T-cell (CAR-T)) therapies are progressing through clinical trials. Alternatives to Chinese hamster ovary (CHO) cells for recombinant protein expression, such as duck embryo quail sarcoma and chick embryo fibroblasts, have the potential to be more productive and specific. Baculoviral insect cell systems have also been shown to be suitable for large-scale production of mAbs.[8] Transient transfection (introduction of genetic information through pores in cell membranes) has allowed for large-scale production of recombinant proteins, prior to degradation of the genetic material.[8]

SEVERAL MEGA-TRENDS CONTINUE TO IMPACT THE GROWTH AND STRUCTURE OF THE BIOPHARMACEUTICAL INDUSTRY.

BEHIND THE SCENES IN 2016

Several mega-trends continue to impact the growth and structure of the biopharmaceutical industry. The diseases being addressed by biologic drugs are of increasing complexity, making the development of successful therapies more challenging. At the same time, governments and payers are seeking justification for high drug costs ($50,000 to $100,000 annually for some biopharma products) and placing ever-growing pressure to reduce prices.[2]

Merger and acquisition (M&A) activity continues at a heightened pace in the bio/pharma industry, but fewer mega-deals are expected. According to Deloitte, the greater prevalence of complex medicines and increased therapeutic competition are just two of four overarching commercial trends impacting biopharmaceutical manufacturing. The other two include the growth of orphan drugs (FDA designations up from 131 in 2004 to over 250 in 2013) and the emergence of personalized medicine.[9] Both orphan drugs and personalized medicine result in the development of smaller-volume products and create a need for flexible, multi-product manufacturing capabilities for efficient use of labor and equipment.

FLEXIBLE SOLUTIONS

All of these trends are driving the need for increased manufacturing efficiency and productivity. In fact, dramatic increases in cell-culture titers over the last decade have led to bottlenecks in downstream processing. Recent indicators suggest, however, that downstream productivity is also improving and, that while chromatography columns still represent capacity constraints, concerns are abating.[3] The adoption of single-use technologies, continuous processes monitored using process analytical technology (PAT) and the installation of smaller, replicable modular facilities that can be constructed in a fraction of the time, and at a much lower cost than conventional, permanent plants are, according to PhRMA, driving manufacturing flexibility and scalability while improving quality and efficiency.[2]

Single-use technologies are already widely used for process development and clinical-scale manufacturing, and are increasingly employed in newer flexible manufacturing facilities. As titers have increased, needed reactor volumes have decreased, enabling the use of disposable technologies for commercial production. When compared to traditional stainless-steel equipment, single-use technologies have been shown to reduce capital and operating costs by 40%-50% and 20%-30%, respectively, and time-to-build by 30%.[7]

While end-to-end continuous processes are still a ways off, advances are being made in both upstream (high-density/intensified and hollow-fiber perfusion) and downstream (continuous chromatography, in-line concentration, tangential flow filtration, etc.). The FDA notably encourages the adoption of continuous manufacturing.[10,11]

Modular and flexible manufacturing systems, meanwhile, are seen by many as providing a way for biopharma manufacturers to standardize manufacturing across multiple sites, achieve in-country manufacturing more rapidly and ensure efficient operation of multi-product facilities at lower costs, while maintaining high protection against cross-contamination. Components such as processing equipment, control systems, cleanrooms and HVAC systems are produced as separate modules and shipped to the site of construction. Autonomous modular facilities designed to include HVAC and other utilities help ensure true flexibility, as they do not need to be constructed within an existing structure to gain access to these systems. Recently, a pre-fabricated KUBio plant manufactured by GE Healthcare Life Sciences for JHL Biotech was assembled from 62 containers in Wuhan, China, in 11 days. According to GE, the cost of a KUBio plant can be as much as 45% lower than a comparable, traditional facility.[12]

CONCLUSION

With a robust clinical pipeline, expectations of 10 to 15 new biologic drug products receiving approval each year and greater numbers of biosimilars reaching the market[3], the outlook for the biopharmaceutical market is bright. Pressures to reduce costs and be quicker to market with innovative, targeted therapies are, however, driving significant change in the manufacturing strategies of biopharma manufacturers. Companies that move swiftly to adopt modular facilities, single-use technologies and continuous processing are likely to be the biggest winners. P

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

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RESEARCH DATABASE

RECOMMENDATIONS

→ BY **GUY TIENE,** NICE INSIGHT

As the pharmaceutical industry grows, the research surrounding it follows suit. To stay ahead of industry trends and keep abreast of the myriad changes in drug development, including approvals and expirations, it is recommended that a contract development manufacturing organization (CDMO) or contract research organization (CRO) subscribe to one or many of the following databases, listed below. As the adage goes, you are only as powerful as the information you have at your disposal.

Data analysis has become increasingly big business; it is impossible to be an industry leader without the ability to analyze the industry. However, the real key to analysis is finding the gap — where is there an opportunity, or where is a pattern repeated? From internal fluctuations in company leadership that predict tomorrow's mergers and acquisitions, to clinical trial success rates that indicate a company's future drug pipeline, maintaining data as a means of staying on top of trends should be regarded as de rigueur standard of practice.

The list below includes databases recommended by That's Nice for tracking sales trends, revenues, overall global market intelligence, therapeutic indication, dose manufacturing and packaging, as well as the top companies and producers in each space.

GLOBAL RESEARCH ORGANIZATIONS AND DATA PROVIDERS

BIOMEDTRACKER BMT allows for deep customization. Notable filters include disease indication and clinical trial phase, as well as market cap and molecule/compound type. The database allows for biotech and pharma investment opportunities by accessing drug pipelines and future catalysts.

BIOPHARM INSIGHT This database provides detailed visual reports on topics such as phase success rates, sales forecasts, clinical trials, expected catalysts, etc. Furthermore, clinical studies concerning a specific drug as well as the direct competitors to that drug can be easily accessed.

CITILINE Citiline features data related to drug development pipelines, clinical trials and clinical trial investigator profiles. The site provides clinical trial algorithms to predict timelines, from patient enrollment through study duration period and trial completion.

DATAMONITOR DataMonitor's search tool allows queries by both drug and company. The database also divides companies based on size and specified regional markets. Results include revenue and forecast analysis and rankings of top companies and producers.

EVALUATE PHARMA Evaluate Pharma offers consensus forecasts, global market intelligence, financial data and valuation tools for the pharma and biotech industry. Users can perform custom searches based on region, therapeutic area and orphan indication, as well as access revenue numbers for U.S. and WW sales.

GLOBAL DATA Global Data is one of the largest databases. The database provides access for researching patents, product pipeline, clinical trials, M&A and market forecasts for emerging markets.

IMS SMART SOLUTIONS IMS Smart Solutions can be tailored for macro to granular level market analysis. The tool provides solutions to measure brand and competitive performance, provides portfolio planning throughout the organization, and performs launch planning and assessment.

INFORMA LIFE SCIENCE ANALYSIS Informa Life Science Analysis' diverse portfolio covers the pharmaceutical (drug discovery, clinical development, regulatory affairs, biopharmaceutical, generics and business strategy), medical devices and diagnostics, fine chemicals and agrochemicals, and veterinary medicine arenas.

MEDTRACK MedTrack's integrated platform provides a detailed insight into pharmaceutical sales, drug pipelines, sales, epidemiology and patents.

NICE INSIGHT Nice Insight tracks customer perception and awareness for top CDMOs, CROs, equipment and excipient companies, and scores competitive ranking.

ORC INTERNATIONAL ORC International provides business intelligence on shifting markets and consumer trends.

PHARMATELL Pharmatell allows for rapid data analysis, business development alerts and expert analysis of current industry topics to aid in making informed strategy decisions.

PHARMSOURCE ADVANTAGE PharmSource provides access to detailed reports on global pharma / bio R&D sales trends and analysis. Searches can be done on a number of parameters, including molecule size, service provider, clinical/commercial dose manufacturing and packaging.

PROFOUND Profound's database is almost entirely comprised of articles and reports concerning market topics, split by industry/location/publisher. Reports come in the form of abstracts and full texts. All content must be paid for on an individual basis to gain access.

S&P CAPITAL IQ S&P Capital IQ allows users to gather detailed current and forecasted data on stock prices, financials and company investments.

THOMSON REUTERS CORTELLIS Thomson Reuters Cortellis is a tool mainly concerned with the analysis of R&D and drug patents. The user can search results by phase, indication, action and molecule type. The database does not contain any financial information.

THOMSON REUTERS INTEGRITY Thomson Reuters Integrity allows a simple search by drug name and molecule type. Advanced search parameters include current phase, therapeutic group and condition.

THOMSON REUTERS NEWPORT Thomson Reuters Newport contains information on APIs. The user can categorize results by region and therapeutic category. Advanced search options allow results to be refined by API manufacturer and sales. P

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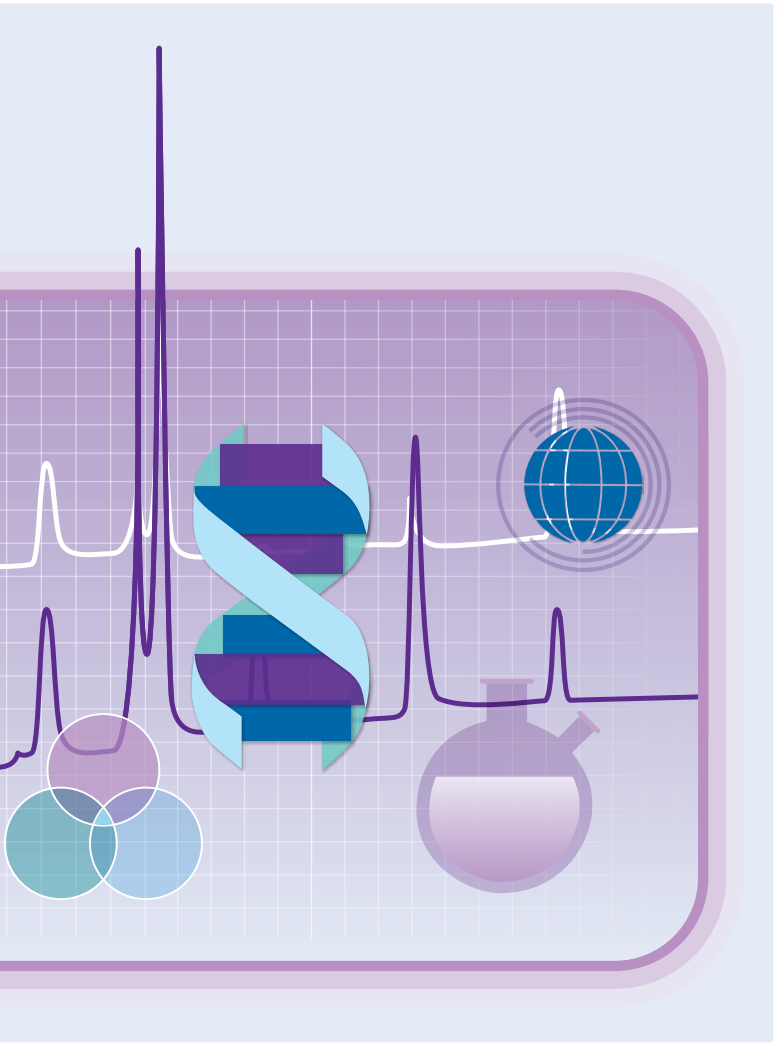

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ENABLING RIGHT-FIRST-TIME TECH TRANSFER WITH EFFECTIVE SCALE-DOWN MODELING

→ BY **ERICH BLATTER**, GLAXOSMITHKLINE BIOPHARMACEUTICALS

The growing expectation from payers, governments and patients that new medicines provide significantly improved results compared to existing drug products is placing increasing pressure on biopharmaceutical manufacturers to be first to market. Accelerating drug development and commercialization while maintaining safety and quality has consequently become a necessity. The use of contract development and manufacturing services can facilitate this process, but only if the contract development and manufacturing organization (CDMO) has the skills and expertise to achieve efficient and effective upstream and downstream process development and "right-first-time" technology transfer.

INTRODUCTION

Biologic drugs are large molecules with complex structures and product profiles produced via a series of upstream and downstream unit operations. A given drug is defined by its structurally derived product quality attributes. The product quality attributes – not limited to glycosylation, glycation, charge profile, aggregation etc. – are defined during the upstream and downstream processes. The process conditions used during manufacture influence the final product's characteristics. The ability to predict and model the effects of process conditions on product quality in the laboratory prior to GMP manufacture is critical to the success of a technology transfer. Biopharmaceutical contract development and manufacturing organizations (CDMOs) must, therefore, have extensive knowledge about the impact of process conditions on product characteristics, in-depth experience with all of the operations at both the laboratory

and commercial scale, and a deep understanding of how laboratory results translate to production performance.

Expertise in process modeling is crucial for the successful development of biopharmaceutical processes. De novo process development begins at bench scale. Effective bench-scale models are designed to accurately predict the performance of production-scale runs, and thus allow rapid development and optimization of processes in preparation for scale up and transfer to the manufacturing plant. Once a process is transferred to manufacturing, a scale-down model can be qualified for use in characterization and validation.

"Right-first-time" technology transfer, whether of an established process from a customer facility to the CDMO or from the process development lab to the production facility within the CDMO, is a crucial capability for competitive biopharmaceutical contract service providers. CDMOs that have a track record of consistently achieving smooth technology transfers assist their biopharma partners by delivering high-quality drug substances with shortened commercialization timelines and lower costs.

BENEFITS OF SCALE-DOWN MODELING

Scale-down models are used in the development of both upstream and downstream biopharmaceutical manufacturing processes to identify the impacts of different process parameters on product quality attributes (PQAs). A scale-down model is qualified by a rigorous comparison with representative production runs and must pass a panel of pre-specified acceptance criteria. Qualified scale-down models are used not only to characterize and optimize processes. They are also necessary for conducting viral clearance, resin cleaning, lifetime validation studies, troubleshooting, including investigation of the root causes of deviations, and continuous process improvement.

EXPERIENCE MATTERS

Developing effective upstream scale-down models that accurately predict performance at production scale requires a strong understanding of the relationship between shear, mixing and mass transfer at the different scales. All parameters cannot be scaled at once. Scale down of the recovery process is performed with a continuous centrifuge sized for 100 – 200 L scale with appropriate filtration. Downstream chromatography scale down models are developed by reducing column diameter and holding resin load, column heights, linear flow rates, relative buffer volumes and composition constant. Thus, equivalent product can be made in a 5 L or a 20,000 L bioreactor and purified in a 1.6 cm or 1.6 meter column. It is far easier and cheaper to study a process at small scale. Also, studies that require spiking-like viral clearance can only be performed at small scale. Viral safety assessment, study design and execution are important parts of most projects.

A real-world understanding of both the laboratory and plant equipment and operating conditions, and the differences between them, is therefore essential for the effective application of scale-down and scale-up modeling during biopharmaceutical process development. Problem solving skills and the ability to apply them are also invaluable, because process development teams must be able to develop processes within any constraints established by the customer that yield products with the desired characteristics at acceptable cost levels.

The scientists in the GSK Biopharmaceutical Technology Laboratory have an

THE PROCESS CONDITIONS USED DURING MANUFACTURE **INFLUENCE THE FINAL PRODUCT'S CHARACTERISTICS.**

average of over 15 years experience. This experience in process development and technology transfer of an extensive array of processes and conditions is highly beneficial for the rapid development and successful transfer of new processes into manufacturing. Having worked through both straightforward and challenging scale ups and transfers gives the team the tools to handle the twists and turns a project may take.

THE ADVANTAGES OF INTEGRATION

As a CDMO that operates as an independent group within a large pharmaceutical company, GlaxoSmithKline Biopharmaceuticals has found that integration of upstream and downstream process development has been tremendously helpful for accelerating development efforts and transferring manufacturing-ready, optimized processes into the plant more quickly. The process development laboratory has an open design containing both the upstream and downstream equipment. With shared laboratory space and open, continuous communication, everyone is part of the same team and gains a greater understanding/awareness of the needs and concerns of the others in the group. As a result, upstream and downstream scientists work together to dial in the correct product quality, titer and purity needed for each project. A well-coordinated effort leads to shorter development times and an increased success rate.

PROCESS MODELING AT GSK BIOPHARMACEUTICALS

The Biopharmaceutical Technology (BPT) laboratory within GSK Biopharmaceuticals has developed a process development/process assessment system using scale-down models for common upstream and downstream unit operations, including various types of cell-culture processes (batch, fed-batch, high/low titer, etc.), continuous centrifugation/depth filtration for harvesting, chromatography, various downstream filtration steps including UF/DF and single-pass tangential flow filtration. Additionally, the lab can assess the effects of media pasteurization (preferred for any media/feeds used in the production facility to prevent virus contamination), and controlled rate freezing of final products in bags.

The laboratory has the ability to model processes coming in from different sources by having the flexibility in the bench scale bioreactor design to mimic different agitation strategies, gassing strategies and processes. The lab is equipped to allow processing of volumes up to 200 L (e.g., 5, 15 and 200 L bioreactors, 1 to 30 cm chromatography columns and ultrafiltration/diafiltration) for development, material generation or toxicology lot production. As a result, the company is uniquely positioned to model processes that will be transferred to its 1,600 and 20,000 L reactors and to customer or other contract manufacturing facilities.

The highly experienced process development team at GSK Biopharmaceuticals has a great understanding of bioprocess technology, and how lab-scale processes with certain characteristics translate to the manufacturing/commercial scale. Use of robust scale-down models and advanced on-site analytical capabilities, including process analytical technology (PAT), helps the team achieve "right-first-time" technology transfer. The starting point for a project could be anywhere from preclinical to late stage processes. Process fit to manufacturing is assessed by performing a series of consistency runs in the laboratory. If the process runs correctly in the laboratory, the probability of success in manufacturing is extremely high.

In all cases, the laboratory group retains a focus on manufacturing and remains aware of how processes will translate from the lab or pilot scale to the manufacturing facility, whether at GSK or somewhere else. As a result, commercial-scale production conditions are always under consideration to ensure that all processes are aligned with the needs of the manufacturing plant. It is common to ensure that processes will fit into multiple plants. After a process is manufacturing ready, the laboratory team interfaces with the tech-transfer team to create a process flow diagram, batch records and all documentation needed to transfer the process to the plant. The laboratory team also provides floor support during the first manufacturing runs to ensure the process performs as expected.

> EXPERTISE IN THE DEVELOPMENT AND APPLICATION OF **SCALE-DOWN MODELING** IS CRUCIAL FOR THE **SUCCESSFUL ACCELERATED DEVELOPMENT** OF BIOPHARMACEUTICAL PROCESSES.

CONCLUSIONS

Robust process modeling is effective for accelerating process development, validation and achieving smooth technology transfer. They also enable effective problem resolution. CDMOs with comprehensive scale-down modeling capabilities, such as GSK Biopharmaceuticals, are positioned to rapidly bring biopharma partner processes into their facilities (or other manufacturing sites), whether they require extensive process development or only slight modifications to provide similar product profiles in any plant. P

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Dr. Erich Blatter is the head of the BioPharmaceutical Technology Laboratory at GlaxoSmithKline (GSK) in Rockville, Maryland, USA. He brings over 25 years of expertise in protein chemistry, process development and technical transfer. Dr. Blatter has been involved in the development, characterization and commercialization of drugs from internal pipeline and CMO clients. Development of biosimilar drugs and scale up of commercial products are a specialty. Dr. Blatter holds a BS in biochemistry from the University of Rochester, a Ph.D. in biochemistry from Rutgers University and was a Merck postdoctoral fellow.

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DOSE AND FORM MATTER: FUTURE OF CARE DEMANDS OPTIMAL DRUG DELIVERY

→ BY **KEVIN HAEHL,** UNITHER PHARMACEUTICALS

Contract manufacturers, the pharma industry they support and the healthcare community are working hard to address medication non-adherence and improve patient outcomes; but more can be done to ensure innovative medicines achieve their full potential.

It's well established that children, seniors and even cogent, non-impaired adults are prone to use their prescribed medications incorrectly. Medication non-adherence is a significant and ongoing risk to patient safety – its consequences create significant waste in health care, and cost even more in terms of poor patient outcomes. The healthcare industry has been studying this problem for decades, yet in spite of all the papers, studies and data, the challenge continues, with non-adherence rates and associated costs still on the rise.[1]

STAKES ARE HIGH, RISKS EVEN HIGHER

Among the more exciting trends in pharma is how increasingly important the biopharmaceutical sector has become to the future of the industry. Over the past decade, some 300 new prescription medicines have been approved for use by the FDA, and in recent times the agency has accelerated its approval process, completing more approvals in 2014 than any other year in its history.

According to PhRMA, a high percentage of New Molecular Entity-focused development activities are potentially first-in-class (those described by a unique

pharmacological class distinct from those of any other marketed products): 78% of projects in phase I, 69% in phase II and 45% in phase III were potentially first-in-class. This means that if all goes well, the best ones are approved and, being first-in-class, have the potential to become blockbuster medicines, improving outcomes for many patients.[2]

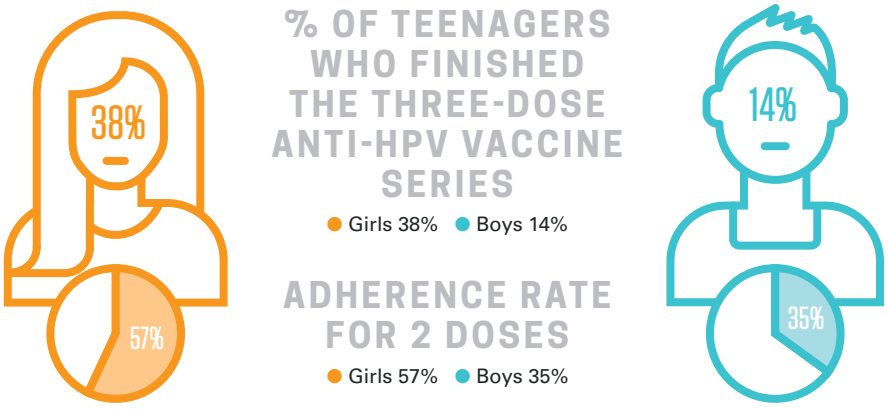
POTENTIAL GAINS IN JEOPARDY

The pace of investment and corresponding drug development have contributed to a range of new treatments, resulting in improvements in the length and quality of life and reduced disease burden for individuals and society. But the extent of these dramatic gains may be in jeopardy as actual patient outcomes fail to match clinical results—the same ones that set expectations and measure the net societal health benefits of a given medication. Surprisingly, the results observed in clinical trials for these new and novel therapies do not always translate into what is being experienced by consumers in the marketplace. While there are a variety of causes, one key is that medications in the "real world" are not taken in a controlled manner like in clinical trials. When patients don't take medicine as prescribed, they don't get the desired results; the question is why would any pharma innovator invest a billion dollars or more on a new drug only to jeopardize future returns because of an inferior dosage form?

ROOTS OF NON-ADHERENCE

The causes of poor adherence, according to a WHO report, are often complex. Recently, the WHO analyzed contributing factors related to the specific condition being treated, health systems, social and economic conditions, the therapy itself, as well as the contribution of the patient. The report indicated that the simplicity of the dosage regimen and side effects were the greatest therapy-induced factors related to adherence.[3] The organization noted that the complexity of self-administration increases rapidly with the use of multiple therapies for the same condition or those with multiple conditions in the same patient.

Last July, the Centers for Disease Control and Prevention called adherence rates in the U.S. "unacceptably low," citing a report that showed only 38% of teen girls and 14% of teen boys finished the three-dose Anti-HPV vaccine series. Comparatively, the adherence rate for two doses was 57% for girls and 35% for boys. CDC's report reveals that even patients with access to care givers and medical guidance have trouble adhering. In response, the required three-dose course was trimmed by dose, a change to improve adherence.



Awareness is helping, and while physicians, pharmacists and others providing care to patients are playing their part to fight non-adherence, the industry must remain proactive, pursuing new opportunities and innovating consumer-friendly dosage forms to mitigate this chronic healthcare issue.

MULTI-FACETED APPROACH BEST

Education of patients about their diseases, the action of the medications, the expected response time and the consequences of failing to adhere to prescriptions are crucial for increasing adherence. Physicians must consider their patients carefully and learn how best to communicate with each individual, taking into account his/her risk factors for nonadherence. Similarly, modern technology allows pharmacists to more actively monitor adherence for customers who regularly purchase medications from them.

Simplifying medication regimens and increasing the convenience and access to medications are two popular strategies for improving patient adherence. For example, the number of medications can be reduced by using combination therapies and finding alternative drugs that can treat multiple diseases. Similarly, formulation and dosage strategies to lessen daily dose frequency are proving effective (as the CDC report showed). For example, switching to extended-release versions of current medications can reduce the dose frequency. Prescribing a convenient and easy-to-use dosage form in pharmaceutical packaging designed to encourage adherence has become a cost-efficient and effective tactic by drug makers. Better adherence leads to higher volumes and efficiencies, which improve drug affordability—an important factor that supports everyone's access to health care.

BETTER COMPLIANCE BY DESIGN

Simple things like deploying easy-to-open, easy-access containers can have a significant and positive impact on geriatric patient adherence. Similarly, better-tasting formulas or easier-to-swallow forms can result in improved compliance. The pharmaceutical manufacturing industry needs to follow the lead of other consumer-focused industries, such as personal electronics, by designing better packaging and administration devices, then using advanced manufacturing technologies to manufacture affordable, convenient and easy-to-use drug forms.

Unither Pharmaceuticals, for example, specializes in the development and contract manufacturing of unit-dose pharmaceutical products. The company also offers a range of dosage forms and delivery systems that are convenient, affordable and easy to use.

Unit-dose delivery of medication is widely used in healthcare facilities in the U.S.

UNIT-DOSE DELIVERY OF MEDICATION IS WIDELY USED IN HEALTHCARE FACILITIES IN THE U.S. AND EUROPE TO PREVENT MEDICATION ERRORS.

and Europe to prevent medication errors. It's clear the benefits of single-dose packaging are an advantage for many patient populations, such as helping the elderly to live more independently. Single-dose delivery systems are accurately filled to hold only the quantity of drug intended for a prescribed single dose and are meant to be opened only once. Many dosage forms – oral, topical and injectable – can be packaged as unit doses: blister or pouch packages for oral solid formulations, plastic syringes with rubber tips and squeeze tubes for oral liquid medications, sterile blow-fill-seal forms for ophthalmic and inhalation therapies, pre-filled syringes and cartridges for injectables, and stick-packs for liquids, suspensions and gels for oral and topical administration.

Study after study shows single-dose packaging helps reduce medication errors.[3,4] Medications, especially tablets delivered by the hundreds in bottles, can be problematic for many, and even the simple act of sorting for one or two pills can expose medicine to loss, contamination and plain old gravity if the bottle is dropped. Single unit-dose medications can be clearly labeled and also include information on the dosing regimen, including calendars and other prompts such as color coding to guide consumption. For active patients away from home, single-dose packaging provides great convenience and portability. There is also reduced concern over contamination when traveling because each dose is surrounded by protective packaging. In many cases, the use of unit-dose technology allows for the removal of artificial preservatives and longer shelf life. The most effective pharmaceutical packaging designs also serve as deterrents to counterfeiting and incorporate child-resistant features, while still allowing easy access for elderly patients. Another type of single-dose package that is portable, easy to open and administer are stick-packs. The premeasured sticks can be filled with powders or liquids. Liquid stick-packs reduce the likelihood of spilling a spoonful of medication while trying to gain a resisting child's compliance or when administering liquids to geriatric patients with tremors. The Healthcare Compliance Packaging Council (HCPC), established in 1990 to promote the many benefits of unit-dose packaging, highlights several case studies demonstrating increased patient adherence for various types of medications (e.g., birth control pills, certain antibiotics, hormone replacement therapies, steroids, etc.) through the use of modern packaging solutions, and particularly compliance-prompting packaging that reminds people whether they have taken their medications.[4]

Pharma is becoming increasingly aware of the need to develop consumer friendly dosage forms. The market success of Humira is a good example. Cited by Drug Development & Delivery's 2015 "Global formulation Report," analysts noted that while the formulation for Humira has remained largely constant since its launch, AbbVie has consistently developed improvements in the drug/device configuration to better match outpatient needs and be easier to administer.[5] Launched in early 2003 with a vial presentation, the study notes a switch was made in mid-year 2004 to prefilled syringes. In 2006, according to the report, the company launched a single-use disposable pen presentation. Even with twice-monthly maintenance dosing, the study said the requirement for patient self-injection has not limited the uptake of Humira and its climb to the number one sales position (total sales since launch $65 billion).

AbbVie's experience with Humira highlights how an effective dose delivery strategy can sustain increasing sales and improve patient outcomes. This best practice is being led by contract manufacturing and packaging service providers who are at the forefront of this trend, engaging patent holders and drug owners to consider this vital aspect of their therapy at the earliest stages. Unither, for example, invests a great deal to pursue dose form and packaging-related compliance strategies for its customers, including sterile single-dose vials using blow-fill-seal (BFS) technology and liquid stick-packs, two forms that have the potential to promote dose adherence and improved patient outcomes.

Although the pharmaceutical industry has been widely successful in innovating new drugs to treat disease, it must now focus on the user experience before non-adherence has a chance to slow the dramatic health care gains biopharmaceuticals and other new medications can have on future generations of patients. P

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Kevin Haehl, General Manager, Unither Pharmaceuticals, is responsible for developing and growing Unither's contract pharmaceutical manufacturing business for North America. He has over 25 years of broad experience across pharmaceutical manufacturing, sales support, engineering, process development, financial, quality, and supply chain. Prior to Unither, Mr. Haehl held management positions at Evonik and Eli Lilly & Company, and worked in engineering at DuPont.

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ACCELERATING DRUG DEVELOPMENT AND MANUFACTURING WITH ENGINEERED ENZYMES

→ BY **ROB WILSON, Ph.D**, CODEXIS, INC.

In 2016, the (bio)pharmaceutical industry continues to face escalating demands to improve productivity, build pipelines faster, streamline infrastructure, reduce costs, and shorten time to market. At the same time, sponsor companies must meet increasingly rigorous regulatory expectations and conduct more complex clinical trials. Although the industry has traditionally been slow to embrace new processes and technologies, effective methods to accomplish these objectives are extremely valuable.

One way to help satisfy these demands is to employ custom-engineered enzymes as catalysts in novel, efficient manufacturing processes – a technology introduced to the industry over a decade ago. Since then, advances in genetics, high throughput biochemistry, and computational methods have enabled the creation of highly improved – and even completely novel – biocatalysts which improve efficiency and reduce cost in the discovery, development and manufacturing of active pharmaceutical ingredients (APIs) and drug products.

In this article, Codexis, Inc., a world leader in the field of protein engineering, biocatalytic process development services and enzyme production, highlights how technological advancements over the past decade have met many critical industry needs, and how long-held preconceptions about the use (and usefulness) of enzymes

A COMMON AND **SIGNIFICANT CHALLENGE** IN THE MANUFACTURE OF PHARMACEUTICAL PRODUCTS IS THEIR **INCREASING LEVEL OF STRUCTURAL COMPLEXITY**, REQUIRING MANY STEPS IN THE SYNTHESIS OF A GIVEN MOLECULE.

in the synthesis of APIs have been eroded.

Biocatalysis is the acceleration of a chemical reaction by an enzyme. Until quite recently (the 1990s), biocatalysis was limited to enzymes found in nature. The limited utilization of biocatalysis as an effective option within chemical manufacturing processes was in part due to misconceptions about yield, reliability, scalability, specificity, and cost – all of which are now readily addressable with focused and directed enzyme engineering and process development.

Codexis deploys state-of-the-art protein engineering technology to create completely novel, customized enzymes and processes to reduce the number of steps involved in API manufacture, thereby optimizing efficiency and reducing cost. The company leverages the latest breakthroughs in genomics and proteomics, along with data analytics, high throughput robotics and computational modeling to rapidly develop highly efficient enzymes, customized for specific molecules and optimized for challenging process conditions.

IMPROVING PROCESS EFFICIENCY

"Time is of the essence" has never been more applicable than in today's drug development process environment, due to fierce industry competition and pressures to build pharmaceutical pipelines more efficiently and more rapidly advance drug candidates to market. In the past, enzymes were not often incorporated into the development and manufacturing process because developing new enzymes for each different molecule was believed to take too long. Indeed, the application of enzymes in commercial manufacturing processes was often relegated to second- or third-generation developments that only the most highly resourced pharmaceutical companies could afford to implement and develop.

A common and significant challenge in the manufacture of pharmaceutical products is their increasing level of structural complexity, requiring many steps in the synthesis of a given molecule. Processes found in traditional chemical synthesis can often involve 8 to 12 steps. Enzymes developed by Codexis can revolutionize synthesis routes and often eliminate steps from these processes, resulting in more streamlined, cleaner processes for the manufacture of pharmaceutical products.

Much has changed over the last decade. The unique combination of breakthrough technologies in gene synthesis, molecular biology, high throughput analytics and bioinformatics has resulted in the rapid development of high-performing and cost-effective custom enzymes. This has provided solutions to problems that classical biocatalytic approaches would never have been able to overcome. Today, by using these highly advanced technologies, enzymes from a rapidly growing toolbox can more quickly and easily be identified and

CODEXIS:

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CodeEvolver® is a "directed evolution" technology platform that replicates nature's sequence of cycles involving mutation, selection and recombination, to create enzymes with improved target performance properties. By testing thousands of enzyme variants under process-relevant conditions (e.g., high concentration of substrate and solvent), improved enzymes can be quickly identified and evaluated for further improvement. A key differentiator of the Codexis CodeEvolver® technology over other methods is the deployment of highly proprietary methods to mine the wealth of structure-activity information contained in the large enzyme libraries produced using CodeEvolver® methods. CodeEvolver® enables the identification of beneficial modifications that are hidden within otherwise underwhelming enzyme variants. Highly tailored improved enzyme libraries can be designed and tested rapidly, resulting in more efficient incorporation of beneficial mutations and much faster improvement in overall enzyme performance. The cycle of design and testing concludes when an enzyme is created that meets or exceeds the targeted performance criteria (e.g., stability, selectivity, yield and/or productivity).

customized to particular uses. Codexis' access to a substantial database of enzymes and structure-activity data provides an excellent starting point for customization. This rich informational baseline is leveraged in combination with molecular modeling and advanced high throughput screening methods, as well as powerful, proprietary data analytics to yield rapid and dramatic improvements in enzyme performance.

IMPROVING PRODUCTIVITY

Another benefit provided by using customized enzymes in biocatalysis is that these enzymes can be developed to provide much higher volumetric productivity than natural variants. Thus, a much smaller quantity of custom enzyme can produce more product in less time as compared to alternative options. Engineered biocatalysts also can enable much higher throughput. Due to enzyme limitations, typical biocatalytic processes often operate in the range of 1%–5% product produced per reactor volume. In contrast, using engineered biocatalysts can result in between 15% and 30% of the reactor being filled with the molecule of interest. Additional benefits include cleaner reactions, with the production of a smaller proportion of impurities, water, solvent, and extraneous protein. As a result, modern biocatalysis can enable a very significant increase in manufacturing efficiency and throughput – often delivering at least 10- to 20-fold productivity improvement.

OPTIMIZING ENZYMES WITH CODEEVOLVER®

Codexis engineers custom enzymes utilizing its proprietary CodeEvolver® protein engineering platform. This platform incorporates many advanced technologies to speed the process of enzyme optimization for use in pharmaceutical production processes. The technology relies upon implementation of complex methods coordinated between various aspects of the workflow, including *in silico* modeling and molecular dynamic simulations to assess the ability of candidate enzymes to catalyze a reaction of interest.

CONCLUSION

Through the use of its proprietary technology and protein engineering knowledge, Codexis is able to respond to industry demands for cost reduction, helping its customers bring improved products to market much more rapidly and in a much more environmentally friendly manner. Codexis' products and services are helping the (bio)pharmaceutical industry to advance innovation, and develop greener manufacturing processes that bring better medicines to patients more rapidly, more cost-effectively, and more efficiently. Codexis is also leveraging its technology to reach into additional, related markets. P

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Rob Wilson earned his Ph.D. in organic chemistry from the University of Leeds in the UK, and has been with Codexis for over 9 years in a variety of business-operational roles of increasing responsibility, in postings across Europe, Asia and the USA. Prior to Codexis, Rob worked for 7 years in business-technical roles for a major UK-based supplier of cGMP intermediates and APIs to the Pharma industry. Today, Rob leads a broad-based team at Codexis, responsible for marketing, pipeline management, alliance management, project management, product management and supply chain execution. His experience and expertise in customer needs evaluation, business analysis and project execution enable Codexis' successful engagement with its core Pharma customers as well as in its increasingly important new markets.

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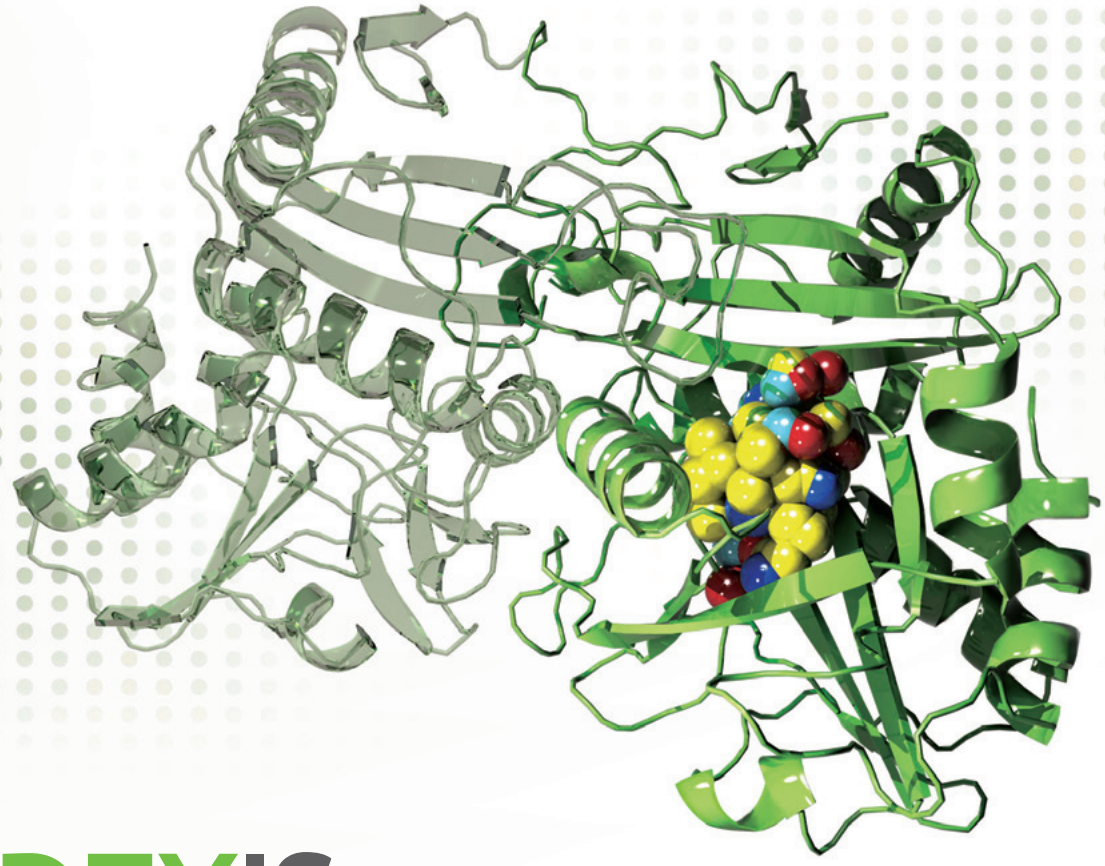

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INTEGRATING DRUG DISCOVERY AND DEVELOPMENT TO IMPROVE EFFICIENCY & CANDIDATE SUCCESS

→ BY **CYRUS K. MIRSAIDI**, BIODURO

Industry research shows that an estimated 94% of drugs that pass animal and non-animal preclinical tests will fail in human tests,[1] and only 11.8% of products that enter clinical development receive regulatory approval. With an estimated cost of development to bring a drug product to market of $2.6 billion and an investment of up to 15 years,[2] the failure rates are devastating.

Considering the increasing pressures on the industry to reduce clinical time and cost, it is clear the industry must find ways to improve these dismal success rates and speed the course of development. A 10% improvement in cycle time and success rates can reduce the total capitalized cost to bring a new drug to market by $634 million.[2]

Although the pharmaceutical and biotechnology industry has traditionally been slow to embrace new processes and technologies, effective methods to improve productivity, build pipelines faster, streamline infrastructure, lower costs and shorten time to market are extremely valuable – an industry imperative in today's marketplace. To achieve the needed efficiency, the traditional linear path to early drug development will no longer suffice.

To meet today's demands, including more rigorous regulatory expectations,

drug sponsors are relying more heavily on integrated development services from outsourcing contractors, such as BioDuro, that have the specialized expertise, technologies and innovations to improve efficiency. BioDuro, a U.S.-owned research and development contractor with laboratories in San Diego, Beijing and Shanghai, is a full-service preclinical research and clinical development service provider that offers discovery and development solutions from lead generation through to dosage form development and manufacturing. This article explains how companies such as BioDuro, a pioneer of integrated drug discovery and development services, saves considerable time and costs by utilizing innovative methodologies.

OVERCOMING INEFFICIENCIES IN CLINICAL DEVELOPMENT

The FDA has issued guidance documents describing specific ways for drug developers to advance the earliest phases of clinical research to evaluate scientific advances discovered in their laboratories much more efficiently.[3] Yet the drug development process remains highly inefficient, fraught with delays and rising costs. Late-stage failure for novel compounds is high. Attrition rates are as high as 40%, due to drug metabolism and pharmacokinetic (DMPK) issues alone.[4]

Often, various steps in the development process are provided by different service contractors in a sequential manner. This traditional pathway of drug development is no longer adequate.

To speed the development pathway, drug development service providers, such as BioDuro, are integrating discovery and development services by conducting interdisciplinary studies in areas such as formulation development and DMPK. BioDuro, a hybrid contract research and development & manufacturing organization (CRO-CDMO), takes a multidisciplinary approach, integrating project management throughout full development services in a seamless transition between processes, utilizing the same team of experts in all contributing areas. Its combined team of experts provide solutions in discovery chemistry, biology, DMPK, pharmacology, formulation development and cGMP drug product manufacturing.

INCORPORATING EARLY DMPK STUDIES AND TRANSLATIONAL MEDICINE

BioDuro integrates various key disciplines required to achieve the program goals of development, including drug discovery, early-stage characterization, preformulation and formulation testing, *in vitro* testing, drug design and DMPK studies. Uniting the key disciplines involves integrating chemistry, physical sciences, computer-aided drug discovery (CADD), biology, ADMET/PK and disease models.

Since the preclinical studies, formulation development, *in vitro* and animal tests are conducted in tandem by the same outsource partner along parallel paths, drug sponsors save considerable time – and consequently costs – by utilizing a single team of experts throughout development.

Another benefit of this integrated approach is that the early completion of characterization and other studies provides valuable information earlier, to guide formulation development and the final dosage form. As a result, companies can realize at an earlier stage whether the formulation will work or carries too much risk, which can save millions of dollars.

USING **TRANSLATIONAL MEDICINE** TO BRIDGE THE GAP BETWEEN RESEARCH AND APPLIED SCIENCE ENABLES FASTER, MORE FOCUSED RESEARCH AND DEVELOPMENT.

BIODURO:

MANUFACTURING CAPABILITIES

The strategic merger of BioDuro with Formex provides end-to-end solutions for integrated drug discovery and development, API synthesis and optimization, formulation and cGMP manufacture of drug products. The companies have completed 25 IND and NDA filings with 10- to 200-fold solubility enhancement on insoluble compounds performed. Using advanced and proprietary technologies, the newly merged company offers services to enhance the bioavailability of poorly soluble compounds to provide seamless translation of high-value clinical candidates developed by BioDuro's preclinical group into more efficacious clinical trial material (CTM), using gram-scale quantity of API for initial formulation, while providing scalable operations that will offer clients phase I-III clinical development as well as clinical and commercial manufacture of drug product, with purpose-built cGMP manufacturing in San Diego.

EARLY OPTIMIZATION OF A DRUG CANDIDATE

The rejection of a potential drug candidate may occur because of molecular issues, such as poor solubility or absorption, dissolution issues or the need for specialized drug delivery. A more effective approach to identify the best drug candidate is for the same development team to test and optimize the molecule first, which causes no meaningful time delay. Utilizing the same provider and an integrated approach can reduce the risk of eliminating a potentially strong candidate, which might result in bypassing a possibly valuable treatment for patients.

After a target is identified and a molecule is selected for further processing, BioDuro chemists first optimize the properties of the molecule, improving its characteristics for further testing in *in vitro* and *in vivo* assays. Utilizing advanced and proprietary technologies, the company provides services to enhance the bioavailability of poorly soluble compounds, and has the equipment, scientific tools and expertise to overcome issues quickly.

At a very early stage, BioDuro chemists utilize solubility enhancement or other technologies to provide error-free assessment of candidate pharmacological properties. Toxic and potentially interfering use of organic solvents or surfactants is replaced by approaches that not only can provide good exposure in preclinical efficacy and toxicological examination, but also suggest approaches for eventual larger scale formulation pathways. Its formulators typically utilize intermediates in milligram quantities, to enhance its characteristics for testing in *in vitro* and *in vivo* DMPK studies and for initial formulation.

BioDuro has the ability to provide solutions related to increased solubility and bioavailability from preclinical drug discovery through final dosage form development and GMP manufacture.

Solubilization has the following possible applications in Drug Discovery:

[1] To provide higher aqueous solubility in target screens, where low solubility may give false negatives, and using organic solvent or surfactants can sometimes affect the target enzymes or receptors.

[2] To give higher exposure in toxicological screens without using organic solvents or surfactants, to better establish accurate NOAELs (no observable adverse effect levels), uncomplicated by solvents or surfactants.

[3] To provide better exposure in preclinical animal models (as with toxicology), without use of solvents or surfactants.

[4] To provide insight into the "drugability" of the compound (the capability of the compound to be formulated and the formulation manufactured), one consideration for selecting a primary candidate from a panel of leads.

[5] To provide early indications of approaches and excipients that can be used in late-formulation development efforts (approach screening).

CONCLUSION

Using translational medicine to bridge the gap between research and applied science enables faster, more focused research and development and can reduce risks before making big investments in later development stages. Since the molecule selected as a candidate may have multiple therapeutic uses, formulators must determine the use that can be most effectively and efficiently developed for clinical trials. P

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Mr. Mirsaidi brings both practical and strategic senior management experience for young start-ups to Fortune 100 companies, with a proven track record in the industry. He held several senior level management positions in his ten-year career at Nichols Institute Diagnostics (a division of Quest Diagnostics). As general manager and executive director at Ontogen, a small molecule discovery company, he managed operations of a subsidiary focused on high-throughput synthesis and purification of novel chemical compounds. Mr. Mirsaidi served as Vice President at AltheaDx, a spinout from Althea Technologies, a San Diego biologics GMP manufacturing company, and most recently served as CEO and founder of Molecular Response, LLC, a CRO focused on translational oncology.

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INVESTMENT RECOVERY FOR PHARMA EQUIPMENT

→ BY **MATT HICKS**, FEDERAL EQUIPMENT COMPANY

This article is the first of a two-part article written for Pharma's Almanac discussing the unique value proposition of pharmaceutical manufacturing equipment. All manufacturing organizations need to responsibly manage assets, but pharmaceutical equipment requires unique strategies to manage and recapture the value of equipment.

Mergers and acquisitions among pharmaceutical companies, as well as an ever-changing product mix, lead to surplus capital equipment among pharmaceutical manufacturing facilities. Often these surplus inventories occupy valuable manufacturing and lab space, or are in storage facilities or "bone yards." An effective capital equipment investment recovery strategy can help turn idled equipment into money-making assets through sales that generate cash, network redeployments that save time and money, and tax deductible donations. There are multiple approaches to viable equipment investment recovery strategies. Regardless of whether equipment investment recovery is handled project-by-project, through a third party or through a formal department, there are some basic best practices for a pharmaceutical manufacturer to consider.

Investment recovery best practices, specific to the pharmaceutical manufacturing industry, can be grouped into the following topics:

[1] Inventory identification
[2] Valuation of the inventory
[3] Internal uses, or redeployment
[4] Removal
[5] Sale

INVENTORY IDENTIFICATION

Identifying surplus inventory is time consuming. If the equipment is installed in a production facility, a solid asset list for the area is the best starting point for an equipment inventory. Typically this is available from the finance department in the form of a fixed asset list, based on the cost center. Robust preventative maintenance programs are also good sources for equipment lists.

While a physical inventory will still be necessary, it can be done much more quickly with a list, as the team will be verifying rather than collecting information. If a list is not available, a physical inventory identifies basic information, including name plate info, internal asset tags and property numbers. Photos of the name tag and of the equipment are helpful in remembering and verifying the information later. Once a list is in hand, the finance department can properly identify the assets on hand.

The next step in inventory identification is determining what items are available for sale. There are three main considerations here:

+ Cleaning and decommissioning
+ Proprietary considerations
+ Approvals and documentation required to sell

Cleaning and Decommissioning. Equipment removed from production typically undergoes a cleaning protocol and decommissioning plan. Always confirm that these have been completed according to standard operating procedures. This may require a sign-off from the Environmental, Health and Safety manager to verify that the equipment has been cleaned and does not contain any residual product or residue. There may also be a sign-off from the compliance department to make sure that

the decommissioning plan has been properly executed. The decommissioning plan should remove any batch-related and proprietary information from the equipment.

Proprietary Considerations. Part of making this equipment available for sale will be considering whether the equipment is specific to a proprietary process or product. All proprietary information must be removed, including batch information and process steps. Careful consideration should be given as to whether the equipment itself is part of a proprietary process. If the equipment was designed or customized for a specific process or product, that design or customization may be confidential or a business secret. While this is often unlikely, it is definitely a factor that must be taken into consideration when deciding to sell equipment outside the company.

Approvals and Documentation Required to Sell. Most firms require some documentation of the sale for accounting and regulatory purposes. Usually fixed-asset disposal forms are available from the finance department. If not, users need to document the asset number, sale or income amount, buyer and the date. The asset-disposal report documents the sale and the decision to sell. The person assigned to sell surplus equipment will usually want to ensure the cost center owner, or other management, has approved the decision to sell; this anticipates the possibility of someone later deciding that they had been saving that particular piece of inventory. The forms are also used to document the value of the sale for accounting, finance and tax purposes.

AN EFFECTIVE **CAPITAL EQUIPMENT INVESTMENT RECOVERY STRATEGY CAN HELP TURN IDLED EQUIPMENT INTO MONEY MAKING ASSETS** THROUGH SALES THAT GENERATE CASH, NETWORK REDEPLOYMENTS THAT SAVE TIME AND MONEY, AND TAX DEDUCTIBLE DONATIONS

VALUATION

Establishing equipment value involves both internal and external research.

Every capital asset should have two values in the accounting records:

[1] Purchase price
[2] Net book value

The purchase price equates to what was paid for the equipment when it was purchased. Often the "price" or original cost used by accounting reflects a project that could have more than one equipment asset or associated construction and facilities costs. In these cases, additional research will probably be required to unravel all of the project's costs.

The net book value is the current value of the equipment according to accounting. Capital assets are generally depreciated over time. The net book value reflects the amount left to depreciate. This amount will be eliminated if the asset is sold or other-

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Matt Hicks, Chief Operating Officer at Federal Equipment Company, is a pharmaceutical industry veteran with more than 15 years of experience helping companies get the most value and utility out of its manufacturing and process equipment assets.

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wise disposed. Interestingly enough, neither the purchase price nor the net book value has any bearing on the other valuation of the equipment's fair market value.

Fair market value represents what the equipment is worth in the market. There are two levels of the market to consider, wholesale and retail.

The wholesale market represents dealers and other sellers of equipment. The pricing here is generally less than what end-users would pay. That is because they are taking on the risk of buying and holding the inventory in stock for resale.

The retail market is what an end-user would pay for that same piece of equipment in the same condition.

Both prices have some art and science behind them and are a function of the overall secondary market for such items. Formal appraisals can represent both wholesale and retail pricing in different situations.

Formal appraisals are most often associated with the due diligence required for loans or mergers and acquisitions. Most often these appraisals are based on what the equipment would sell for in an orderly liquidation, which would most commonly be an auction that was not forced due to insolvency or bankruptcy. End-user buying cycles do not always allow for opportunistic buying at auctions, which causes these valuations to trend towards wholesale pricing. The impact of the valuation, both finance and fair market value, and the ultimate sale, redeployment or donation, are primarily influenced by the company policies that control the fixed-asset disposal process.

INTERNAL REDEPLOYMENT

Many companies consider implementing redeployment programs within their manufacturing networks. Often the same makes and models of equipment are used in different facilities. This is especially true of lab equipment. Redeployment, or moving a piece of equipment from one facility to another within your network, is the most efficient use of idled or surplus assets. The equipment history is known and experiences are easily transferred. This all works in theory. In practice, the process can be quite cumbersome.

Too often, internal redeployment processes poorly represent the equipment available. The equipment list is simply a spreadsheet. The description is not enough to determine suitability, photos and information are hard to come by, and there can be financial consequences at the receiving site, which often ruins the cost savings that can be achieved. A web-based platform can usually help with descriptions and photos. However, the financial piece is the bigger obstacle to tackle.

Many companies transfer the equipment from site-to-site at net book value ("NBV"), or the depreciated purchase price, which remains on the books at the time of transfer. The shipping site often disposes of the asset financially by transferring the remaining to the receiving site at the remaining NBV. If the NBV is at zero-value, then the transfer is a win for both entities as only the expenses of moving the item and reinstallation and commissioning will occur. However, as mentioned above, entire projects are often rolled into the NBV of a given asset which includes the equipment, construction costs, installation, start-up, and so on, which are not generally transferred with the equipment itself. This overinflates the actual value of the equipment on the financial books of the receiving site. That value can be inflated enough that the receiving site will not be able to tell the difference between the costs of new equipment or receiving the used equipment. This is an unfortunate result, as the transaction is still a non-cash event for the receiving site, yet undesirable from a financial standpoint. And the equipment remains idled in a state where it is not producing income, but is only generating costs in the form of storage, utilities and so on. The solution is to adjust what value is actually being transferred.

Companies that have implemented advanced equipment redeployment policies use an "impaired value" approach to the valuation of the asset. The impaired accounting approach evaluates the loss in value of an asset that has dropped below its recorded NBV. The goal is to get an idea of the asset's true value in the market and transfer it at that impaired value rather than the NBV. Many redeployments that would be abandoned under an NBV valuation can be successfully completed using this approach. With the financial issues addressed, the other obstacles are either technical or preference.

Some companies have implemented policies requiring project engineers to consider surplus equipment prior to purchasing new equipment. If not implemented properly, these policies can become bureaucratic exercises because some project managers prefer to buy new equipment and continually write exceptions to the policy. In general, there are two considerations in regards to these policies.

The first consideration is the positioning of the mandate in the project process. The policy is more likely to be successful when the mandate is early in the capital planning process. Ideally, this occurs right after the need is identified and before any new equipment is specified.

The second consideration regarding surplus equipment is that it must be displayed in a centralized place and in a way that allows the project manager to quickly and thoroughly evaluate the equipment and associated costs, such as removal and shipping.

This completes the first of a two-part article. We have reviewed inventory identification, valuation of the inventory, internal uses versus redeployment, and the associated components involved in pursuing these elements. In the next article we will discuss the removal and sale strategies. P

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ESTABLISHING SPECIALIZED CDMO CAPABILITIES FOR THE PRODUCTION OF ADVANCED THERAPIES

→ BY **OLIVER TECHNOW, SCOTT DONCASTER** AND **HEATHER DELAGE**, BIOVECTRA

Most pharmaceutical and biopharmaceutical companies are establishing closer relationships with a few select service providers that have unique combinations of capabilities and demonstrated performance.

To be successful, contract development and manufacturing organizations (CDMOs) must be forward thinking—constantly anticipating the future needs of potential customers and investing in state-of-the-art facilities, equipment and technologies. To attract those customers, CDMOs must also have a very strong track record of performance with respect to the quality of the products and services, their ability to meet project objectives and timelines, and their regulatory compliance history – all combined with advanced and specialized capabilities. A commitment to transparency, open communication, true collaboration and a genuine respect for the needs of each client's individual projects has also become essential for CDMOs that want to participate in strategic partnerships with their customers. BioVectra Inc. does all of this and more.

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Manufacturing and development support services through every stage of drug development.

Expertise in synthetic organic chemistry, fermentation, custom MPEG production, and natural extraction, and producing both chemical and biologic molecules, including highly potent compounds

STRONG HISTORY OF PERFORMANCE

While outsourcing provides many benefits to drug manufacturers, including access to needed capacity and technical expertise, the ability to convert capital expenditures into operating expenses, and the opportunity to increase productivity and cost efficiency, it also carries a significant amount of risk. CDMOs that present minimal risk through demonstration of consistently high performance, combined with the needed technical expertise are most likely to be selected.

BioVectra has been providing a unique combination of synthetic organic chemistry and fermentation of chemical and biologic molecules – including highly potent compounds, downstream processing, methoxypolyethylene glycol (MPEG) production and conjugation chemistry services – for more than four decades to small and large pharmaceutical, biotechnology, generic, and early stage companies. R&D to commercial-scale quantities of cGMP raw materials, intermediates and active pharmaceutical ingredients are produced at three facilities on Prince Edward Island, Canada, all of which are regulatory audited by the FDA, Health Canada and the Japanese Ministry of Health.

The company has submitted 10 product filings, including ANDA, DMF, VMF and CMC section preparations for both the FDA and Health Canada. Through various partnerships, BioVectra has developed challenging new entities and generic products, including particulate injectable formulations with highly potent and cytotoxic active ingredients, controlled release products, and APIs semi-synthesized from metabolites via highly challenging fermentations. Its extensive capabilities in the handling, processing, and quantifying of APIs from natural sources have been applied to the isolation of domoic acid from mussels, adenosine deaminase from bovine sources, and taxanes from yew trees. BioVectra also offers cGMP bioprocessing reagents, such as dithiothreitol (DTT) and tris (2-carboxyethyl)phosphine hydrochloride (TCEP-HCl), and develops custom solutions for MPEG functionalization using proprietary, scalable chemistries.

SPECIALIZED YET DIVERSIFIED

Production of the advanced therapies under development today often requires a wide range of specialized capabilities. Many of today's drug candidates require both biologic and small-molecule production and purification capabilities, as well as expertise in pegylation and conjugation chemistry. Even so, most CDMOs have elected to focus either on biotechnology or small-molecule chemistry, and few can offer a combination of both.

Since its inception as a manufacturer of biological reagents, BioVectra has been evolving to meet its customers' needs. The addition of cGMP manufacturing capabilities for DTT and other reagents required the development of expertise in scaled chemical manufacturing, and the company continues to develop synthetic and analytical methods for customized bioprocessing reagents. During this period, the company

also developed expertise in the extraction, handling, and quantification of APIs (chemicals and proteins) from natural sources. By natural extension, BioVectra developed expertise in microbial fermentation for the production of metabolites, in particular using filamentous fungal and bacterial strains, native and recombinant bacteria, and salt water microbial organisms. Many of these products were highly potent, which led BioVectra to develop specialized facilities, equipment and procedures for the safe production and handling of potent compounds. Application of the company's core synthetic chemistry competencies for downstream chemical modification and purification of secondary metabolites was the next step in the company's evolution.

PRODUCTION OF THE **ADVANCED THERAPIES** UNDER DEVELOPMENT TODAY OFTEN REQUIRES A **WIDE RANGE OF SPECIALIZED CAPABILITIES**.

As a result, BioVectra has a unique combination of capabilities – it is in fact a highly diversified CDMO offering a range of very specialized technologies. With this technical profile, BioVectra can serve as a single development and manufacturing partner for pharmaceutical companies developing novel therapies that require expertise in the processing of both small and large molecules. In addition, these services are available at R&D to commercial scales, allowing customers to avoid the time and cost associated with technology transfer from one service provider to the next.

INVESTING FOR THE FUTURE

Innovation lies at the heart of the pharmaceutical industry, and CDMOs must keep pace with their customers. That requires the ability to anticipate future client needs and the willingness to invest in new capabilities. BioVectra has, throughout its history, worked closely with its customers, installing capacity and building expertise to meet their needs. More recently, the company has aggressively invested in capacity expansions around its core competencies of fermentation and downstream processing. Expenditures from 2014 through 2016 totaling more than $50 million include the following: acquisition of the former Sepracor API production facility located in Nova Scotia, Canada; installation of an additional 30,000L of fermentation capacity (for a total of 60,000L); installation of improved downstream purification equipment to support existing fermentation capacity with specialized capabilities in potent intermediate and API purification processing; investment in new preclinical fermentation and potent chemistry suites; and the addition of 13,000 square feet of laboratory, office, workstation, and meeting space for its growing workforce.

NEW LEADERSHIP TEAM FOCUSED ON GROWTH

In addition to these investments, BioVectra also recently brought Oliver Technow on board as President to guide the company through its next phase of development. With his extensive experience in commercial development and marketing, brand, and life cycle management for various global pharmaceutical companies, Mr. Technow has a unique perspective on the needs of CDMO customers. This market understanding, combined with the extensive knowledge of the company's long-serving business development and technical leaders, will help BioVectra expand its partnerships with existing customers and develop new collaborative relationships. P

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Oliver Technow President, BioVectra

With more than 20 years of global pharmaceutical industry experience, Oliver Technow, President of BioVectra, has held numerous leadership positions in commercial development, marketing and brand management and life cycle management in Europe and North America, and was appointed President of BioVectra Inc. in December 10, 2015. He holds an industry master's degree from Frankfurt Chamber of Commerce, Frankfurt Germany.

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Since joining BioVectra in 1995, Scott Doncaster, Vice President, Manufacturing Technologies and Engineering has demonstrated his leadership supervising enzyme and natural products bioextraction process operations. In 2000, Doncaster was promoted to Operations Manager, to Director of Manufacturing in 2005 and to his current role in 2014. He holds a B.Sc. in biochemistry from Mount Allison University in New Brunswick, Canada.

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

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SCALE-DOWN MODELS: AN INDISPENSABLE TOOL TO BIOPHARMACEUTICAL PROCESS DEVELOPMENT

→ BY **JOHN MOSCARIELLO**, CMC BIOLOGICS

Several advances in scale-down models have made great contributions to accelerating biopharmaceutical process development.

Therapeutic biologics have gained considerable momentum in the past three decades by delivering superior clinical performance to common disorders (e.g., rheumatoid arthritis) and disease areas for which traditional small-molecule drugs have proven ineffective. Due to their inherent structural complexity, biologics production is strictly scrutinized from early development stages by regulatory agencies. Both biopharmaceutical manufacturers and regulators heavily emphasize developing science-based, consistent and robust manufacturing process to ensure quality, safety and efficacy of final biological products.

SCALE-DOWN MODELS — INDISPENSABLE FOR PROCESS DEVELOPMENT, CHARACTERIZATION AND VALIDATION

This modern biopharmaceutical manufacturing process not only incorporates principles of quality by design (QbD), but also allows implementation of continuous improvement. Such process is built upon thorough understanding of the process and the product, which cannot be achieved without the aid of scale-down models, or small-scale models.

Scale-down models are increasingly adopted by the biopharmaceutical industry and serve as an indispensable tool for process development, characterization, optimization and validation. Due to the complexity of biological products, their manufacturing process needs to be well understood, characterized and controlled. A typical biomanufacturing process development starts as early as in the drug discovery stage (i.e., small cell culture shake flasks), when process knowledge is limited. The process is continuously developed, tested and refined through benchtop bioreactors, pilot-scale bioreactors and commercial-scale production. Throughout this journey, scale-down models are used to allow process specialists to quickly gain process knowledge and translate it into optimal operation conditions in a cost-effective and timely manner.

TYPES OF SCALE-DOWN MODELS

Scale-down models have been applied to a broad spectrum of process development, from upstream cell line selection and growth medium optimization to downstream product separation and purification. Multidimensional experimental studies can be conducted in scale-down models to test process parameters. The extent of such studies usually is not feasible or cost-prohibitive at commercial scale.

Based on the purpose of design goals, there are two types of scale-down models:

[1] Miniaturization of a full-scale unit operation

[2] Partial, or "worst-case," model of specific properties[1]

The miniaturized full-scale model is designed to mimic the whole unit operation (e.g., bioreactor cell cultures) and examine effects of input material and process parameters on process performance and product quality. This type of study is typically conducted in a reduced-size version of the full-scale equipment. The comparison of model performance to full-scale is required to qualify these scale-down models. A qualified scale-down model can, in turn, allow the ease of scaling up the operation.

Partial / worst-case scale-down models are designed to represent a specific physical and / or biochemical environment within a unit operation and test the worst-case conditions of a subset of parameters (e.g., shear force). Miniaturized equipment, or an apparatus imparting a desired force, property or environment is usually used in the study.[1] These models are particularly useful in identifying critical process parameters (CPPs), defining their acceptable ranges and understanding the impact of parameter deviations on the manufacturing process.

SCALE-DOWN MODELS ARE INCREASINGLY ADOPTED BY THE BIOPHARMACEUTICAL INDUSTRY AND SERVE AS AN INDISPENSABLE TOOL FOR **PROCESS DEVELOPMENT, CHARACTERIZATION, OPTIMIZATION AND VALIDATION**.

Regardless of type, the scale-down model needs to be qualified prior to submitting scale-down process characterization studies for Biologics License Applications (BLAs). The purpose of qualification is to demonstrate the suitability of a model in evaluating the effect of input material and parameter variation on process performance and a product's critical quality attributes (CQAs).[1] Parallel to the gradual increase of production scale, the scale-down model is continuously developed and improved during clinical development. Formal model qualification is typically carried out in Phase III runs when final scale-up is complete and full-scale data is available for comparison. A combination of qualitative and statistical assessments is then performed to determine to what degree the model represents its full-scale counterpart and reliably predicts full-scale manufacturing performance.

REGARDLESS OF TYPE, THE SCALE-DOWN MODEL NEEDS TO BE **QUALIFIED PRIOR TO SUBMITTING SCALE-DOWN PROCESS CHARACTERIZATION STUDIES** FOR BIOLOGICS LICENSE APPLICATIONS.

REGULATORY SCOPE

The main regulatory guidance for scale-down models is ICH Q11, which recognizes the importance of scientifically justified small-scale models to support process development and "the extrapolation of operating conditions across multiple scales and equipment."[2] In the process validation package for licensure, both commercial-scale process validation studies and small-scale studies are required. It is expected that the results from commercial-scale batches closely mirror results from small-scale studies. The significance of the data obtained from small-scale studies to support process validation depends on the successful demonstration that the model appropriately represents the proposed commercial-scale operation.

ICH Q11 also requires studies to demonstrate process ability to remove product-related impurities (e.g., intermediates, degradants), process-related impurities (e.g., host cell DNA and proteins), and potential contaminants (e.g., viruses). In the case of viral clearance, ICH Q5A(R1) provides specific guidance on this matter.[3] The viral clearance studies can only be performed using qualified scale-down platforms, including chromatography and nanofiltration, in a virology lab located outside the cGMP facility. The viral clearance data is required for both Investigational New Drug (IND) Applications and BLAs, though the scope of data is reduced in IND applications.[4] The difference in data requirement reflects regulatory agencies recognition of the status of biomanufacturing process at the beginning of clinical trials, when process parameter ranges are not well established.

LIMITATIONS OF SCALE-DOWN MODELS

Despite a scale-down model's ability to test various input parameters at conditions even outside normal operating ranges, it cannot fully represent a physically larger, more complicated and expensive system. It is important for biological manufacturers to understand the limitations of their scale-down models. As pointed out in the FDA's recently updated Process Validation Guidance, any differences that exist between small-scale and commercial process "may have an impact on the relevance of information derived from the models."[5]

Furthermore, scalability varies among scale-down models for different unit operations. Generally, chromatography and filtration scale well. For chromatography, it is widely accepted that operation of a smaller diameter column at the same bed height and linear velocity is an acceptable scaled-down model for larger-scale columns. For filtration, once operating parameters are normalized, filtration scales rather well. On the other hand, small-scale models for harvest/centrifugation (e.g., disk-stack centrifugation) are poorly scalable. This unit operation is best characterized at scale.

Another challenge for scale-down models is prediction of filter performance in the presence of a viral spike during viral clearance assessments. The virus and/or impurities often cause filter fouling, which does not commonly occur with protein streams. Therefore, it is difficult to predict maximum viral filter loading using a non-virus-containing feedstream. The best means to overcome these limitations is to develop processes that no longer require viral clearance from chromatography. Many well-established techniques to inactivate viruses (such as low pH, detergent, UVC) and / or to remove viruses (such as nanofiltration) can be utilized to eliminate the need for clearing viruses by chromatography.

TECHNOLOGY ADVANCEMENT IN SCALE-DOWN MODELS

Several advances in scale-down models have made great contributions to accelerating biopharmaceutical process development, including automated scale-down bioreactor systems for cell culture (e.g., ambr® 250, Sartorius Stedim Biotech), microcolumns for chromatography, and mechanistic modeling and simulations for chromatographic performance prediction. These technologies allow process scientists to better understand critical process parameters and optimize processes rapidly without the need for pilot-scale runs and extensive experimentation. Additionally, they require significantly less material than traditional scale-down models. P

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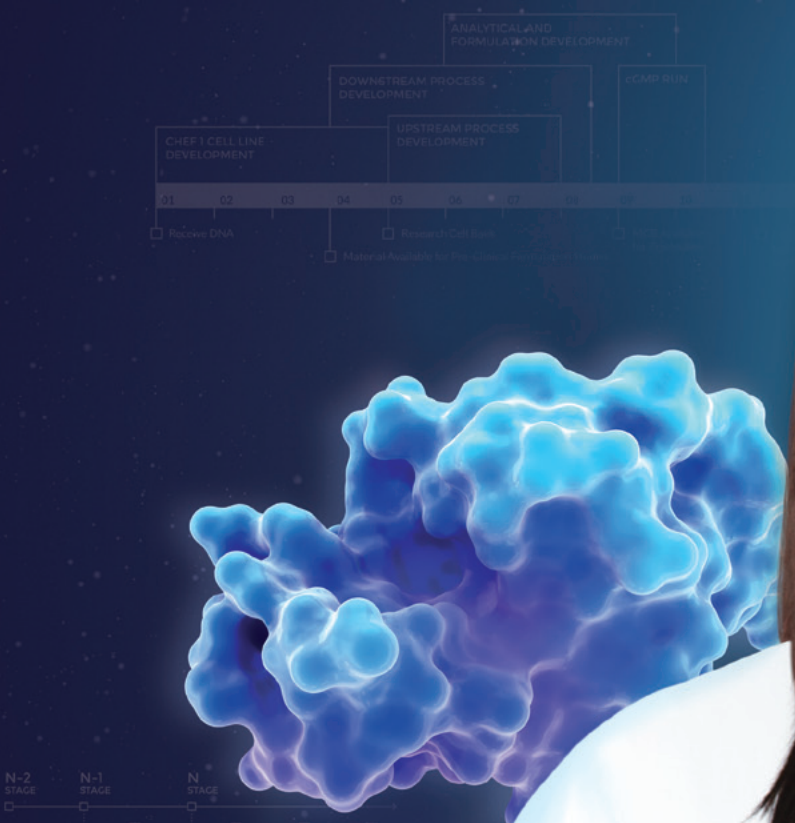

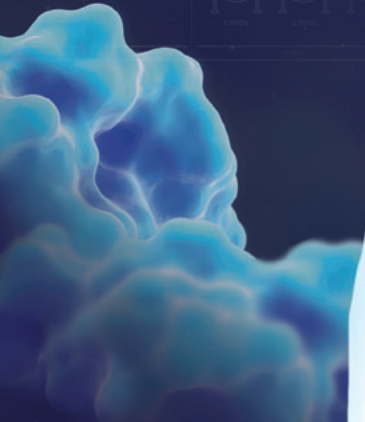

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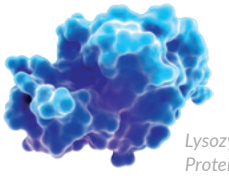

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BIOPHARMA'S ASCENDENT SUPPLY CHAIN REVEALS ITS

PRESENT POTENTIAL & FUTURE PROMISE

Is there a more exciting, dynamic sector of the pharmaceutical industry than the biologics sector? There's no need to answer, because the question is entirely rhetorical; of course there isn't. The journey that a high-potential large-molecule drug must make to attain blockbuster or biosimilar status is a long and winding one. The ecosystem that nurtures and creates these biologic therapies is as complex as the molecules they are developing.

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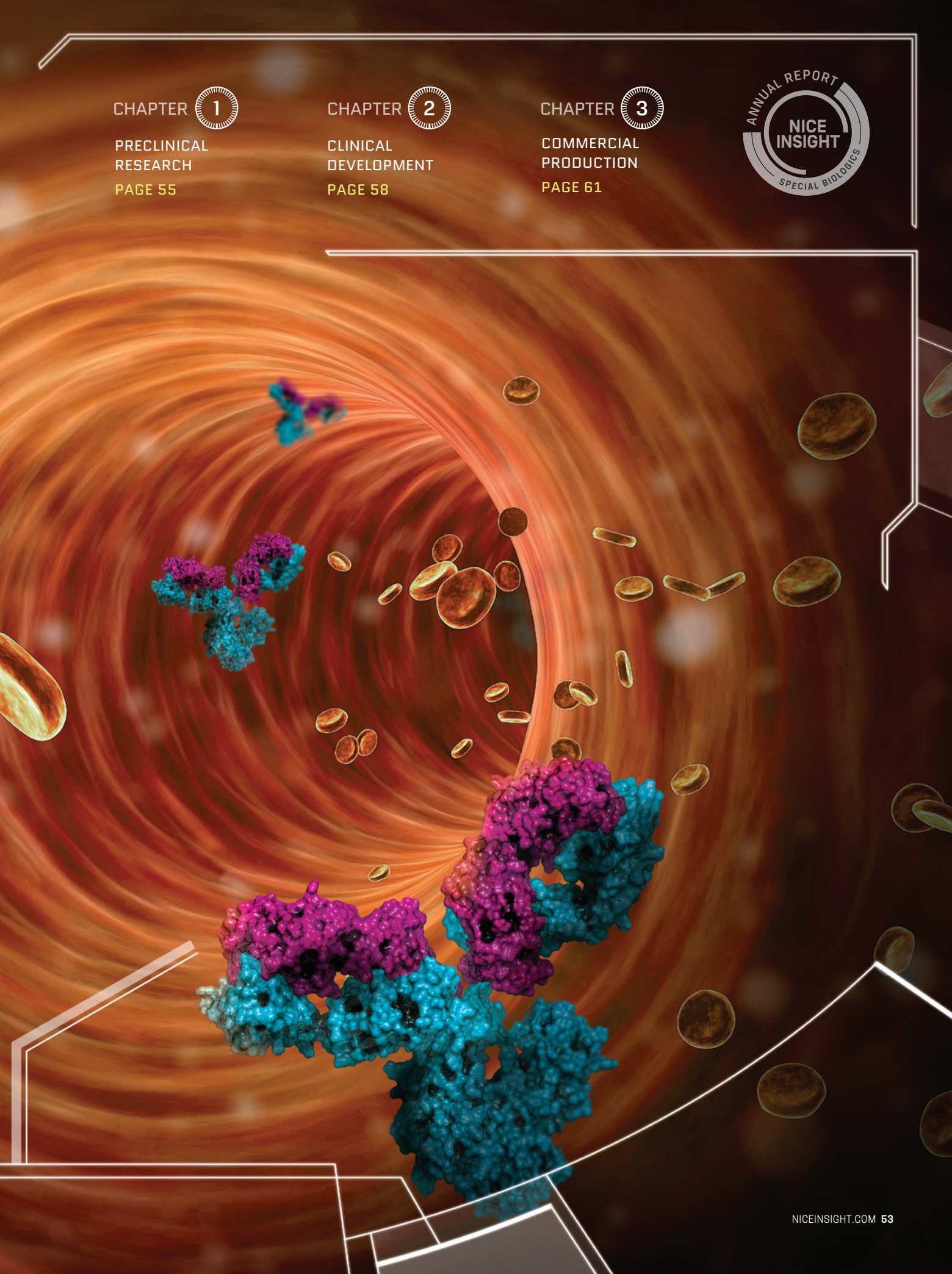
NICE INSIGHT

ANNUAL REPORT
NICE INSIGHT
SPECIAL BIOLOGICS



INTRODUCTION

According to PhRMA, (general) research and development spending by its members grew from $2 billion in 1980 to an estimated $51.6 billion in 2013. The percentage of sales that went to R&D in 2013 reached 23.4% of domestic sales. Clearly a lot of that R&D money will continue to be spent in developing pipelines in the biopharmaceutical sector.[1]

Of the billions of dollars spent on R&D each year for clinical research, roughly 90% is spent on clinical trials of medicines and devices in the U.S. In 2013, PhRMA states that the biopharmaceutical industry sponsored an impressive 6,199 clinical trials involving more than 1.1 million people. Investing in biotech R&D has yielded better returns than the pharma-industry average, note McKinsey & Co. analysts. The current biologics development pipeline supports an outlook of continued healthy growth. According to McKinsey, the number of biotech patents applied for has been growing at 25% annually since 1995 and there are currently more than 1,500 biomolecules undergoing clinical trials.[2]

IMMUNE THERAPIES ARE QUICKLY BECOMING THE FOURTH PILLAR OF CANCER TREATMENT

The success of the clinical pipeline will lead to an unprecedented number of new molecule launches, rising from a handful a few years ago to 10 to 15 annually in the coming years. A further steep increase is to be expected as multiple players begin to receive approvals to produce biosimilars after 2015.

One recently approved biologic is making headlines and offers the industry a case history of biopharmaceutical R&D success. In December 2015, the Washington Post reported that President Jimmy Carter had advanced melanoma and was beginning radiation therapy.[3] The report said Carter would also be receiving an infusion of Keytruda, Merck's first among a promising new class of immuno-oncology (I/O) drugs aimed at unleashing the human immune system to fight cancer cells. Keytruda was launched in the fourth quarter of 2014, and according to Merck, global sales in 2015 were approximately $566 million.[4] Keytruda, as well as similar I/O therapies, works by allowing the body's immune system to recognize and attack cancer cells as it would do to any other intruder.

Immune therapies are quickly becoming the fourth pillar of cancer treatment, say industry experts. These types of drugs are expensive – Keytruda is roughly $150,000 per year, but it has shown remarkable results in some patients, including Carter, who announced he was "cured" of his melanoma.

PROMISE OF IMMUNO-ONCOLOGY THERAPIES

In early March, the Tufts Center for the Study of Drug Development (CSDD) announced findings of a new report on investments in research and development for new I/O drugs.[5] Tufts says dramatic improvements in complete response rates in trials for new I/O therapies are helping to increase the number of alliances between pharmaceutical, biotech companies, universities and cancer centers. Thirteen universities and cancer centers in the U.S. have announced research alliances with pharma and biotech companies, and the number of I/O alliances between pharma/big biotech and small enterprises grew at a torrid pace, accounting for $39 billion in research commitments over three years.

Currently, more than 130 biotech and 20 pharma companies are developing I/O therapies, according to Tufts. That activity reflects – and is fueling – worldwide I/O product sales, explains Tufts, with annual revenues expected to reach $25 billion to $40 billion by 2020, up from $2.5 billion in 2015.

The biopharmaceutical industry's recent successes have been fueled by massive commitments of private and public capital, as well as billions in corporate operational budgets and other resources. Success breeds success, and it's clear that oncological therapies are going to attract even more investment. The following offers a review of the complexities of the biopharmaceutical supply chain and trends across a development ecosystem that is, by most accounts, effectively translating research dollars into highly successful treatments that save lives. To a great degree, contract service providers, including CROs and CDMOs, are becoming an integral part of the industry's success and are fast becoming key contributors in this incredibly dynamic pharma sector. P

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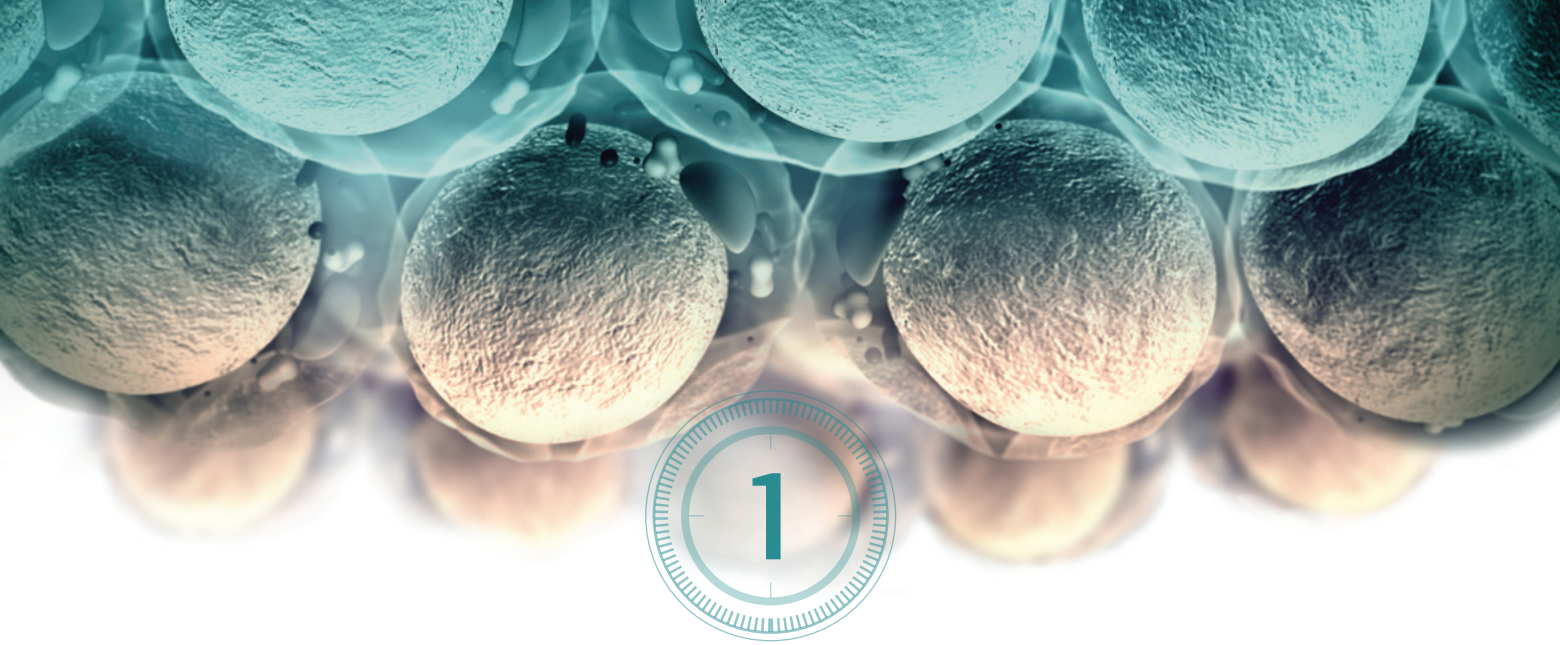

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PRECLINICAL DEVELOPMENT: THE SAFETY HURDLE PRIOR TO HUMAN TRIALS

HERE NOVEL MOLECULES FIND THEIR HUMAN POTENTIAL AND BEGIN TRANSLATING DISCOVERY INTO MEANINGFUL THERAPEUTICS

Before any new biopharmaceutical molecules reach the preclinical stage, they have to pass through a series of selections at the discovery stage: target discovery and validation, hits generation and screen, and lead selection and optimization.

Preclinical testing is the final deciding gate prior to clinical studies, and only 12% of the candidates advance to the Phase I clinical trial. From this point, the success rate for the investigational biologics increases at each clinical phase, with 17% at Phase I, 27% at Phase II, 58% at Phase III, and 82% at the registration phase.[1] On average, drug discovery and preclinical development take three to six years and account for 30.8% of costs per approved compound, approximately $788 million.[2,3]

PRECLINICAL TESTING

During preclinical development, the critical question biopharmaceutical developers seek to answer is whether the novel molecule is safe to be tested in humans – which is also the primary concern of regulatory agencies. The safety assessment starts early, in the stage of screen preparation when bioassays (used to assess biochemical and functional properties such as binding and efficacy assays) of lead molecules are initially developed.

As the candidates advance to the preclinical stage, more extensive tests have to be performed both *in vitro* and *in vivo* to gain better understanding of their pharmacodynamics (PD) and pharmacokinetics (PK) behavior and establish their pharmacologic, safety,

PRECLINICAL'S REGULATORY FRAME

The regulatory framework governing preclinical safety evaluation of biotechnology-derived pharmaceuticals is ICH S6(R1) Guideline, which is applicable in the U.S., European Union, and Japan. The S6(R1) Guideline contains two parts, original S6 Guideline (published in 1997) and S6 addendum (published in 2011). The S6 addendum is complementary to S6 with updated and clarified guidance on five topics: species selection, study design, immunogenicity, reproductive and developmental toxicity and carcinogenicity assessment. The addendum prevails when differences exist between the two guidelines.[8] In addition, the FDA requires all studies supporting safety evaluation, such as toxicology studies and animal testing, to comply with Good Laboratory Practice regulations (21 CFR Part 58).[9]

and toxicity profile. Concomitantly, biopharmaceutical developers need to assess their manufacturability and plan for GMP clinical-scale production since larger quantities of biopharmaceuticals will be needed for clinical trials.

At the end of the preclinical study, the most promising molecules are selected for human testing. Before initiating clinical trials, the sponsor is required to submit an Investigational New Drug application (IND) for any trials conducted in the U.S., which usually goes into effect 30 days after the FDA receives it. A typical IND must contain three categories of information: preclinical data on animal pharmacology and toxicology studies; chemistry, manufacturing, and control (CMC); and clinical protocols and investigator information.[4] The regulatory landscape is more complex in the EU, where clinical trials are regulated by the National Competent Authorities (NCAs) in each member state (currently 28 member states) instead of one central agency, the European Medicines Agency (EMA). Similar to an IND, a Clinical Trial Authorization (CTA) application must be submitted to the NCAs.[5] Timelines for review and approval of CTA applications vary among NCAs, ranging from less than 14 days to 90 days.[6,7]

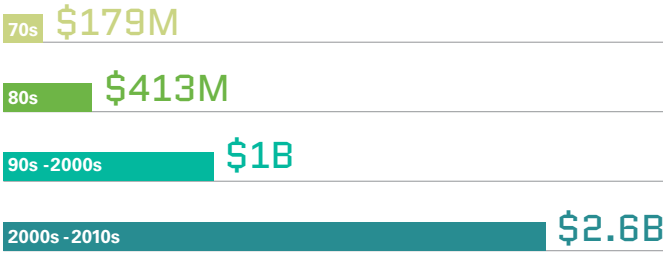
PRECLINICAL TESTING CHALLENGES

One significant challenge associated with preclinical testing of biopharmaceuticals is the selection of relevant animal species. In general, the regulation requires toxicology studies to be conducted in two relevant species. The animal toxicity data is essential to determine the safe starting dose and dose range for the first-in-human (FIH) study and identify potential adverse effects relevant to humans. However, for many biologics, there are limited choices of relevant species due to their high tissue- and/or species-specific activity. Sometimes, nonhuman primates may be the only relevant species. When relevant animal species are not available, alternate approaches are considered such as using homologous molecules or transgenic animal models.[10]

To date, protein-based biologics (i.e., monoclonal antibodies (mAbs), fusion proteins, and recombinant proteins) account for most development-stage and marketed biopharmaceuticals. One specific challenge with therapeutic proteins is immunogenicity, the generation of antidrug antibodies (ADAs). The undesired immunogenicity may affect biologic's PK and PD and induce immune reactions. The ICH S6 addendum provides specific instructions on when ADAs level should be measured. On the other hand, ICH S6 recognizes the limitation of nonclinical studies in predicting potential immunogenicity of human or humanized proteins in humans. In other words, immunogenic responses observed in animals are not indicative for humans.[10] Based on the perspective of Dr. Andrew J. McDougal, a FDA/CDER nonclinical reviewer, specific safety concerns for mAbs include cross-reactivity, slow elimination, exaggerated phar-

FIGURE 1
DRUG DEVELOPMENT COSTS HAVE INCREASED

According to a 2014 study, it costs an average $2.6 billion to develop one new drug. More recent studies estimate the cost to be even higher. Less than 12% of the candidate medicines that make it into Phase I clinical trials will be approved by the FDA.



SOURCE TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT

FIGURE 2
TRENDS IN DRUG PORTFOLIOS

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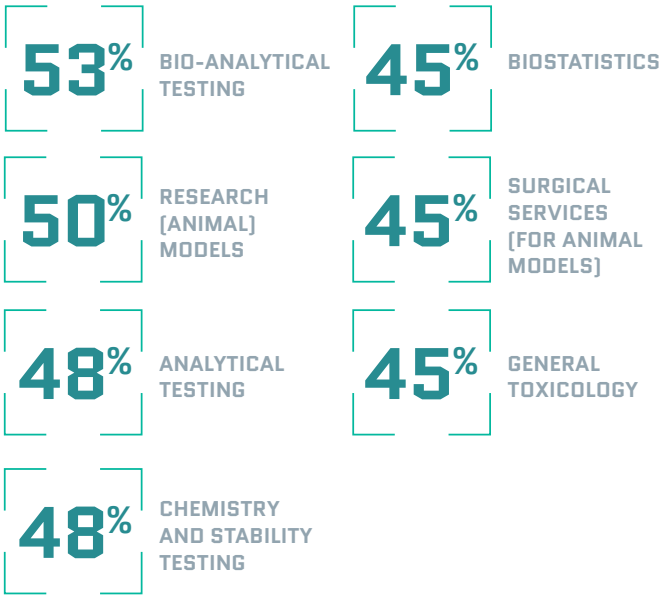
FIGURE 3

% OF RESPONDENTS WHO OUTSOURCE PRECLINICAL TRIAL SERVICES



macology, and slow recovery from toxicity. Safety concerns for cytokines and growth factors are species-specificity, interaction with host endogenous cascade, and tumor-promoting potential.[11]

COLLABORATIONS WITH CROS FOR PRECLINICAL TESTING

Bringing a novel biopharmaceutical from bench to bedside takes a broad range of collaborations across biopharmaceutical industry, academia, patient and disease groups, government, and contract research organizations (CROs). Groundbreaking discovery (i.e. a novel drug target) flourishes in academia. However, it is the industry that leads the efforts in translating the discovery into meaningful therapeutics. To improve the R&D efficiency and accelerate development, engaging with CROs has become a widely adopted strategy by the biopharmaceutical industry. According to the 2016 Nice Insight CRO Outsourcing Survey, 80% of the respondents acquire or plan to acquire preclinical trial services while 53% of them currently engage with cros for preclinical (includes discovery phase) research. Among a cluster of 16 preclinical trial services, bio-analytical testing (53%), research models (animal models) (50%), analytical testing (49%), chemistry and stability testing (48%), and biostatistics, surgical services (for animal models), and general toxicology (45% respectively) are the top 5 most needed services.[12] Midsized pharma/biotech companies demonstrate a slightly higher than average demand for all of the surveyed preclinical services while the service demand from small pharma/biotech is lower than average.

In selecting CROs for biopharmaceutical preclinical development, a CRO's development experience weighs heavily in a sponsor's decision-making process. A CRO's experience and expertise in bioanalytics, pharmacology, toxicology, and PK and PD is critical in designing appropriate studies so that valuable safety information of the molecule of interest can be collected and evaluated. Vertical integration is another desired feature often sought by biopharmaceutical clients when selecting a CRO. Drug discovery and development is a continuous coordinated process of research, production, and regulation. In the preclinical phase, CROs with expanded expertise in manufacturing, regulation, and clinical studies are more capable of synchronizing preclinical testing, production and regulatory compliance in a holistic manner, and are thus poised for a long-term partnership with biopharmaceutical manufacturers. P

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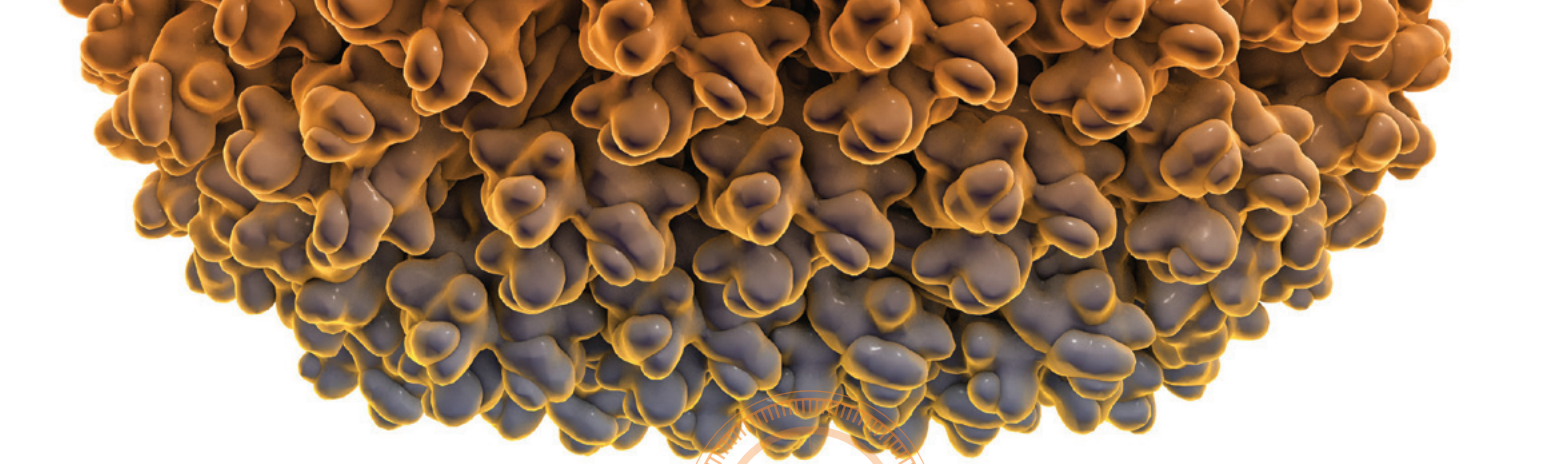


2

2016 SEES RAPID ADVANCES IN BIOTECHNOLOGY CLINICAL DEVELOPMENT

BRINGING A PROMISING MOLECULE TO COMMERCIAL, THERAPEUTIC REALITY REQUIRES INTENSIVE FOCUS ON PROCESS DEVELOPMENT AND ANALYTICAL AND CLINICAL VALIDATION

2016 looks to be another good year for the biopharmaceutical industry and its outsource service partners, as budgets and pipelines continue to escalate. Pipelines have shifted to a greater focus on biologics compared to small-molecule drugs. Currently, there are more than 250 biotechnology health care products and vaccines available to patients, many for previously untreatable diseases.[1] Of the 45 new drugs approved in 2015, 31% (15) were biologics, and the numbers are expected to grow significantly over the next few years.[2]

According to the 2016 Nice Insight CDMO Outsourcing Survey,[3] about two-thirds of companies are developing large-molecule products as new biological entities (NBEs), surpassing small-molecule products at 57%, while half focus on biosimilars – another jump from previous years. Most of these companies are developing antibody drug conjugates and vaccines, followed closely by hormones, blood factors and growth factors.

Industry analysts predict 2016 will feature the launch of as many as 12 new drugs expected to become blockbusters by 2020, including biosimilars of major blockbuster drugs that will soon be coming off patent. The predictions for top 10 drug sales in 2016 include many current biosimilar prospects.[2]

With strong growth in this market, biopharma companies are increasingly relying on outsourcing providers for technical and scientific expertise, regulatory support and operational efficiency. Contract service providers are well positioned for accelerated growth in the years ahead.

As the development of biologics becomes increasingly more complex, big biopharma companies are ac-

quiring smaller and medium-size companies and partnering with high-quality service providers to fuel new product development. The trend of small biotech partnering with large pharma for clinical development has facilitated the development of more novel molecules.

Preferring fewer, well-qualified contractors, sponsor companies are choosing outsourcing partners that offer sophisticated technology, advanced methodologies, comprehensive services, and the needed skills and expertise to develop high-quality products with optimal efficiency. The continuing trend of industry consolidation enables drug sponsors to develop their candidates under one roof, and helps ensure a continuum of quality throughout the development process.

FIGURE 1

% OF RESPONDENTS WHOSE BUSINESS IS ENGAGED IN THE DEVELOPMENT OF SMALL AND LARGE MOLECULES

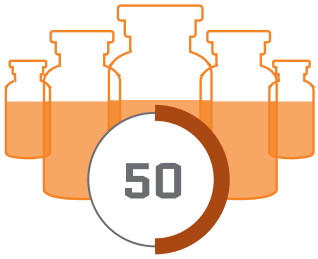
IMPROVEMENTS IN TECHNOLOGY AND PROCESSES

Many current candidate biologics – antibodies and antibody fragments, highly potent antibody-drug conjugates (ADCs), cell and gene-based therapies – are different from the first simple recombinant proteins. They require more advanced methods for characterization and the identification and removal of contaminants. Drug developers have been continuously challenged to develop analytical methods to accurately determine the chemical, physical and therapeutic properties of different actives, and potential contaminants, from raw material selection to process analysis, formulation development and release testing.[4]

Changing expectations of biologics characterization have driven improvements in analytical equipment, processes and systems. With the move toward continuous processing and other advances, more rapid and sensitive analytical techniques are required. In addition, rapid early bioprocess development is crucial to timely regulatory filing for biologics, often leaving a narrow space for early process development. It is typical to spend considerable time and resources in late-stage development to achieve a higher titer and improve the manufacturing process. A relatively high titer process in the early stage enables rapid downstream and analytical development.[5]

To meet these needs, production and analytical technologies have advanced dramatically over the past two decades. Newer methodologies have emerged, such as ultra-performance liquid chromatography (UPLC) systems, which have improved resolution and sensitivity in shorter run times. 2D high-performance liquid chromatography (HPLC), a new version of a traditional methodology, provides a convenient and accurate method for characterizing single-product peaks, side products, and excipients. High-resolution mass spectrometry (MS) allows for the analysis of samples that are incompatible with traditional MS.[6]

MS-based methods and next-generation sequencing (NGS) technologies address the need for greater sensitivity in less time.[4] NGS is also being applied to quality control testing in the lab. It is a highly sensitive, universal test to detect and identify any adventitious virus throughout the product lifecycle in a single, comprehensive analysis that minimizes false negatives without prior specification of their nucleic acid sequences. The process involves the sequencing of all nucleic acid material present and the application of algorithms, filtering steps, and taxonomic assignment to determine the presence and identity of contaminating viruses in biologic compounds.

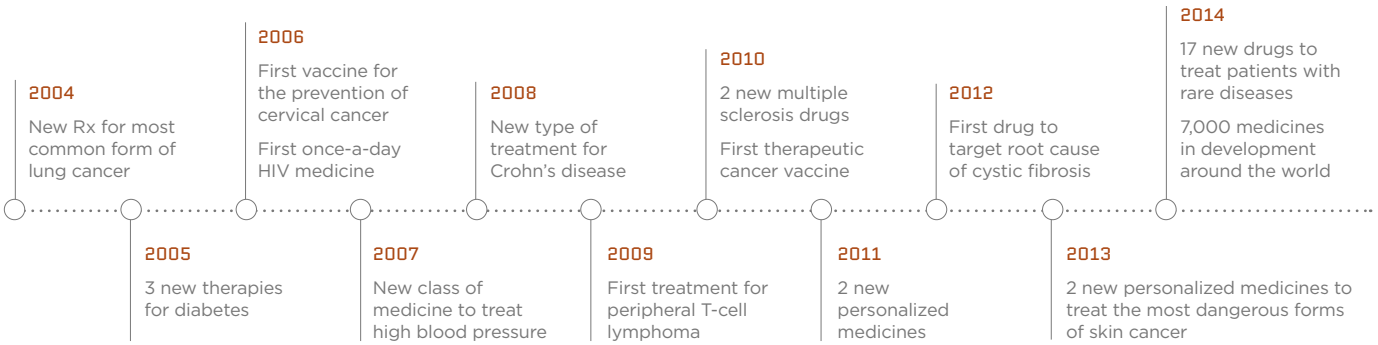


% RESPONDENTS OUTSOURCE STERILE/CONTAINED MANUFACTURING

EXPERTISE INCREASINGLY IMPORTANT

The interest in specialized technologies is underscored by the number of participants in the 2016 Nice Insight CDMO Outsourcing Survey that plan to outsource, or already outsource, specific drug product development and manufacturing activities associated with the biopharmaceuticals. For instance, 36% of respondents outsource lyophilization, 50% sterile/contained manufacturing and 44% parenteral manufacturing/packaging. In addition, 31% and 26% of survey participants look to service providers for clinical- and commercial-scale manufacturing of pre-filled syringes/injectables, respectively, 28% fill/finish operations and 22% blow/fill/seal manufacturing.[3]

FIGURE 2 A DECADE OF ADVANCES



SOURCE FDA

Advanced MS instruments with significantly increased sensitivity provide greater insights into the impurity profiles of biotherapeutics and allow the identification of previously unknown host-cell contaminants.[4] As the industry introduces more complex and increasingly potent molecular formats with novel highly potent product-related impurities, ongoing advances will be necessary.

Other improvements are rapid microbiological screening methods, more automated approaches to complex analytical problems, and improved systems for data analysis. Biopharmaceutical development and process validation have been accelerated by mini bioreactor systems, which can rapidly generate a large amount of development data, significantly reducing process development time.[6] In response to the increasing need for parallelization and miniaturization of controlled and monitored bioreactors, microbioreactors with working volume below 1L have been developed.

WHAT'S THE OUTLOOK FOR BIOSIMILARS?

Very healthy indeed, based on broad forecasts of strong market growth. With an estimated $67 billion of patents on biological products expiring by 2020, biosimilars represent a major opportunity for the industry. The FDA approved the first biosimilar, Zarxio from Novartis, in 2015.[9] Others are expected to launch in the near future, including biosimilars of mega blockbuster drugs such as Johnson & Johnson's Remicade and AbbVie's Humira.

The development of biosimilars, compared to new drugs, faces significantly condensed timelines from cell line to first-in-human trials. A biosimilar development program needs to accelerate quickly toward preclinical and Phase 1 studies. Phase 2 studies typically are not required because dose response and other patient-treatment concepts are already established by the innovator medicine. Phase 3 studies are typically limited to fewer patients, which ultimately shortens timelines and costs.[7]

Although the FDA published guidelines on biosimilar development in 2012, the need for a well-defined development process, beginning with characterization and then comparison with the attributes of the reference product, is crucial. The industry has been eager for further regulatory guidance to determine interchangeability for biosimilars. Because of the complexity of biologics, the only way to establish whether there are differences that affect the safety and effectiveness of the follow-on product is to conduct clinical trials. Critical guidance on how biosimilars should be labeled to ensure regulatory transparency and accurate prescribing has yet to be issued by the FDA. P

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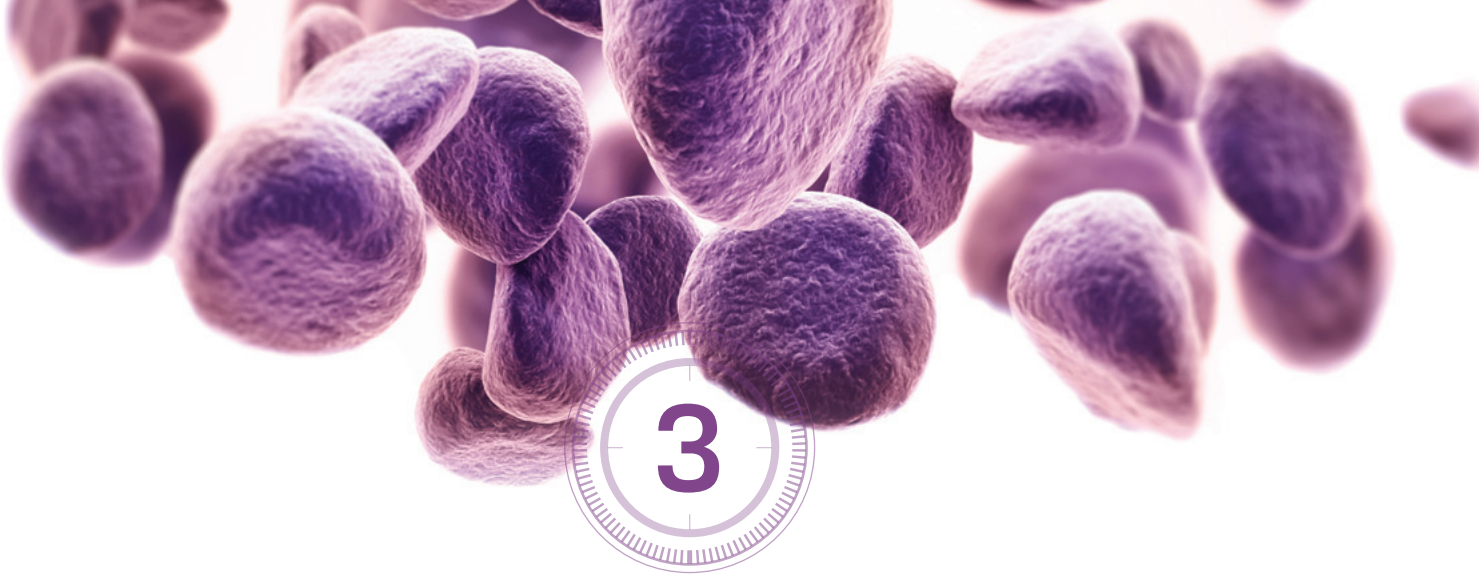


3

INCREASED INVESTMENT IN R&D DRIVING GROWTH OF OUTSOURCING TO BIOPHARMACEUTICAL COMOS

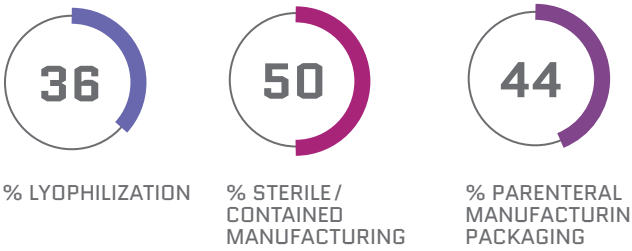
BRINGING A BIOLOGIC THERAPY TO COMMERCIAL REALITY TAKES AN ABSOLUTE DEDICATION TO OPERATIONAL, TECHNICAL EXCELLENCE; CONTRACT MANUFACTURERS ARE INCREASINGLY PROVIDING THIS CAPABILITY.

Increased investments at the discovery and early development phases are leading to robust pipelines and creating demand for greater clinical- and commercial-scale manufacturing capacity. While biologic drug manufacturers are expanding their own in-house capabilities, these companies are also increasingly turning to outsourcing partners, particularly for the production of drug substances and products that require specialized expertise.

INCREASED OUTSOURCING INDICATED

Estimates of the biopharmaceutical contract manufacturing market vary somewhat, but there is a consensus that the strong growth witnessed in recent years will continue going forward. HighTech Business Decisions (HBD) valued the market at $3 billion in 2015 with the growth of annually.[1] The company predicts that big bio/pharma companies will increase

FIGURE 1
% OF RESPONDENTS WHO OUTSOURCE SPECIALIZED SERVICES



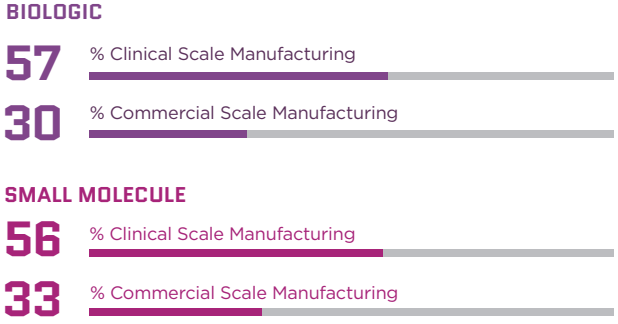
outsourcing levels from 16% to 34% from 2015 to 2019, leading to a value for the market of $4.1 billion by the end of the period.[2] In addition to the robust biopharma pipeline and greater rates of new drug commercialization, increased funding of biotech companies and a broader array of service offerings by contract manufacturing organizations (CMOs) are considered to be key contributors to this healthy growth.[1]

Six biopharma CMO/CDMO executives interviewed by HBD indicated that the number of requests for proposals that they received in 2015 was higher than that in 2014, with one company experiencing an increase of more than 10%.[1] They pointed to varied reasons for the increase, ranging from a greater number of RFPs for smaller, specific projects to growing interest in outsourcing at early stages to CDMOs with a comprehensive suite of services in order to avoid technology transfer issues and speed time to market. Biosimilar projects are also increasing in number.[1]

While outsourcing continues to be seen as an effective means of increasing cost efficiency, cost savings is no longer the primary driver. Biopharmaceutical companies are also seeking technical expertise (such as for the manufacture of antibody-drug conjugates and bispecific antibodies), operational efficiency, regulatory support and the advantage of focusing on core competencies, according to Roots Analysis[3]: "Spanning multiple operations within wider manufacturing processes, outsourcing is increasingly being viewed as a strategic imperative."

HBD identified over 500 companies that claim to be CMOs/CDMOs, but note that only approximately 90 of them have the actual capabilities needed to manufacture recombinant proteins at large scale. Roots Analysis, meanwhile, says that over 160 biopharmaceutical CMOs offer services ranging from cell line development to biologic API manufacturing to fill/finish operations. These companies include both pure contract service providers such as Lonza and CMC Biologics and large bio/pharma companies that have excess capacity available for contract manufacturing, such as GlaxoSmithKline Biopharmaceuticals and Boehringer Ingelheim BioXcellence.

FIGURE 2
% OF RESPONDENTS WHO OUTSOURCE DRUG SUBSTANCE SERVICES



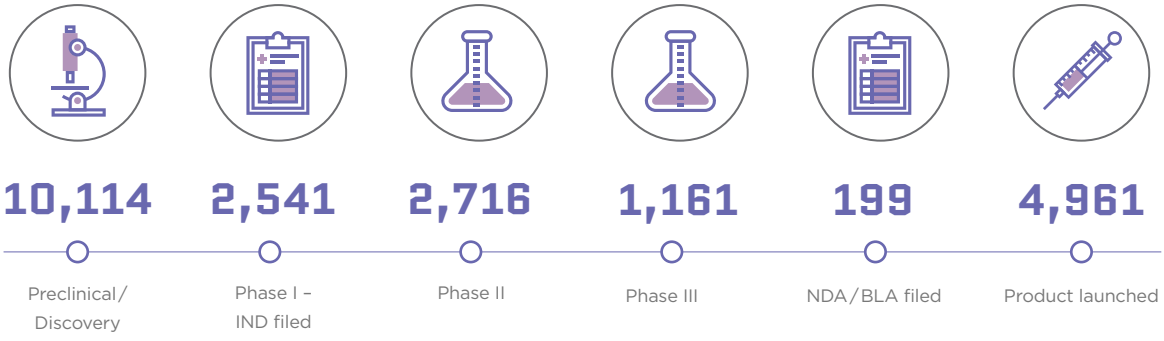
COST SAVINGS IS NO LONGER THE PRIMARY DRIVER.

The extent to which biopharmaceutical CMOs/CDMOs are benefiting from significant increases in spending by bio/pharmaceutical companies of all sizes is revealed in the results of the 2016 Nice Insight CDMO Outsourcing Survey[6] of bio/pharma professionals (n=587). Most notably, 95% of respondents indicated that they currently or intend to use biopharmaceutical manufacturing services. In addition, a similar percentage of survey participants use or plan to use CDMOs/CMOs for clinical- and commercial-scale biologic API manufacturing (57% and 30%, respectively) as do for small-molecule API manufacturing (56% and 33%, respectively). With respect to the spending levels for the survey participants using biomanufacturing services, 73% and 26%, respectively, spend over and less than $50 million annually on all outsourcing activities.

HEIGHTENED M&A ACTIVITY

The strong growth in the contract biopharmaceutical market has attracted the interest of new entrants. One notable example is Samsung Biologics, whose success, according to CEO Tae Han Kim, is based on the company's extensive manufacturing and engineering expertise which was gained in the semiconductor industry. This is coupled with Samsung Biologics' ability to attract highly skilled industry experts with direct experience in biologics plant design and

FIGURE 3 CURRENT WORLDWIDE PIPELINE & LAUNCHED PRODUCTS, LARGE MOLECULES



SOURCE BIOPHARM INSIGHT, JAN 2015

construction, validation and cGMP operations.[4]

Merger and acquisition (M&A) activity has also been fairly intense in the contract biopharma sector. The market is fairly fragmented with a large number of players (*vide infra*), so it is not surprising that consolidation is occurring. There are additional drivers, however – the largest perhaps, being the desire of CMOs to transform themselves into international CDMOs. Such service providers can meet client needs for global partners with small- to large-scale capabilities, expanded service offerings and advanced technologies.

CAPACITY CONSIDERATIONS

Results of two different industry surveys of biopharmaceutical contract manufacturers suggest that CMOs/CDMOs will be expanding capacity in the coming years. Capacities for mammalian cell culture and microbial fermentation in 2015 were reported by BioPlan Associates to be nearly 82% and 68%, respectively, with mammalian capacity utilization in the U.S. (72%) higher than that in Europe (51%), and vice versa for microbial capacity utilization (55% and 66%, respectively).[5] In addition, the surveyed CMOs expected on average 5-year planned increases of 49% and 25% for mammalian and microbial bioreactor capacity, respectively. Companies adding notable capacity include Patheon Biologics, AbbVie (for pipeline support and CMO services), KBI Biopharma and Fujifilm Diosynth Biotechnologies. P

NOTABLE BIOPHARMA CMO M&A

- Merck KGaA acquisition of Sigma Aldrich
- Pfizer acquisition of Hospira, including its contract parenteral drug manufacturing operations
- Albany Molecular Research acquisitions of Cedarburg Laboratories and Oso Biopharmaceuticals
- Merger of Patheon and DSM and the subsequent acquisition by the newly formed DPX Holdings of Gallus Biopharmaceuticals
- Par Pharmaceuticals acquisition of JHP Pharmaceuticals
- Merger of Cambridge Major Laboratories with AAIPharma

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CDMO INDUSTRY LEADERS

How are contract development and manufacturing organizations (CDMOs) perceived in the biologics marketplace by their customers?

To measure more objectively the perception companies have of the industry's leading CDMOs, Nice Insight study respondents were asked to compare and rate 123 respective companies on their perception of the following attributes: Quality, Reliability, Innovation, Affordability, Productivity, and Regulatory Compliance. These key outsourcing drivers, once individually rated, tabulated and averaged, create a Customer Perception (CP) Score. CDMOs with the highest Nice Insight CP scores rank among the industry's finest and are perceived to be the best among their peers when it comes to overall operational excellence.

Mammalian Biopharmaceuticals

1 Samsung BioLogics 94.33% CP Score Mean

2	GSK Contract Manufacturing	90.67%
3	Pfizer CentreSource	90.33%
4	Sanofi CEPiA	89.00%
5	Boehringer Ingelheim	88.67%
6	AbbVie Contract Manufacturing	88.50%
6	Kemwell	88.50%
8	Cytovance Biologics	88.33%
8	WuXi	88.33%
10	Cobra Biologics	88.00%

Microbial Biopharmaceuticals

1 Samsung BioLogics 92.33%

2	Pfizer CentreSource	90.00%
3	Catalent	88.50%
4	Boehringer Ingelheim	87.83%
5	BioVectra	87.67%
6	Cytovance Biologics	87.50%
6	Paragon Bioservices	87.50%
8	AbbVie Contract Manufacturing	87.17%
9	Hisun Pharmaceuticals USA	86.83%
10	Sanofi CEPiA	86.67%

Vaccines

1 Sanofi CEPiA 89.83%

2	Cobra	89.17%
3	Catalent	89.00%
4	Corden	88.83%
5	Paragon	87.00%
6	AMRI	86.83%
7	Cook	86.67%
7	IDT	86.67%
9	Lonza	86.17%
10	FujiFilm Diosynth	85.83%
10	KBI Biopharma	85.83%

Large Molecule API Clinical Scale Manufacturing

1 Samsung BioLogics 92.00%

2	Pfizer CentreSource	89.00%
3	Cook Pharma	88.50%
4	Dishman Pharmaceuticals	87.83%
5	Cytovance Biologics	87.67%
6	AbbVie Contract Manufacturing	87.17%
7	Corden Pharma	87.00%
7	Hisun Pharmaceuticals USA	87.00%
9	Fareva	86.83%
9	Paragon Bioservices	86.83%

Large Molecule API Commercial Scale Manufacturing

1 Samsung BioLogics 95.50%

2	Pfizer CentreSource	92.17%
3	Avid Bioservices	89.67%
4	Dr. Reddys CPS	89.17%
4	GSK Contract Manufacturing	89.17%
6	Dishman Pharmaceuticals	89.00%
7	AbbVie Contract Manufacturing	88.67%
8	Cobra Biologics	88.17%
9	Corden Pharma	87.83%
9	Sanofi CEPiA	87.83%

2016 SURVEY DATA

587 **SURVEY RESPONDENTS**

123 **CDMOs IN THE SURVEY**

6 **KEY DRIVERS OF OUTSOURCING** Quality, Reliability, Productivity, Affordability, Innovation & Regulatory Compliance

CP **CUSTOMER PERCEPTION SCORE** Average of six individual key driver scores

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CRO INDUSTRY LEADERS

How are contract research organizations (CROs) perceived in the biologics marketplace by their customers?

To measure more objectively the perception companies have of the industry's leading CROs, Nice Insight study respondents were asked to compare and rate 74 respective companies on their perception of the following attributes: Quality, Reliability, Innovation, Affordability, Productivity, and Regulatory Compliance. These key outsourcing drivers, once individually rated, tabulated and averaged, create a Customer Perception (CP) Score. CDMOs with the highest Nice Insight CP scores rank among the industry's finest and are perceived to be the best among their peers when it comes to overall operational excellence.

Biostatistics

1	BioSkin GmbH	88.83% CP Score Mean
2	InnoPharma S.r.l.	87.83%
3	InVentiv Health	87.17%
4	Clintex Research	86.67%
5	ICON	86.33%
6	Worldwide Clinical Trials	86.17%
7	MPI Research	85.83%
7	PRA Health Sciences	85.83%
7	WCCT Global	85.83%
10	Spaulding Clinical	85.50%

In vivo Pharmacology

1	BRI Biopharmaceutical Research Inc.	89.50%
2	InVentiv Health	87.50%
3	MedPace Inc.	87.33%
4	American Preclinical Services	86.83%
5	ICON	86.50%
6	GenScript	86.33%
7	Parexel	85.67%
8	PRA Health Sciences	85.50%
9	Seventh Wave Laboratories	85.33%
10	Evotec	84.83%
10	Quintiles	84.83%

Bioequivalence

1	CNS Network	89.50%
2	Novum Pharmaceutical Research Sciences	87.83%
3	Worldwide Clinical Trials	87.17%
4	MPI Research	87.00%
5	PRA Health Sciences	86.50%
6	Premier Research	86.17%
7	Spaulding Clinical	85.83%
8	Product Safety Labs	85.67%
9	BRI Biopharmaceutical Research Inc.	85.50%
9	Sannova Analytical	85.50%

Bioavailiblity

1	CNS Network	89.50%
2	Novum Pharmaceutical Research Sciences	89.00%
3	Worldwide Clinical Trials	88.50%
4	MPI Research	87.83%
5	PRA Health Sciences	87.67%
6	Spaulding Clinical	87.17%
7	Product Safety Labs	87.00%
7	BRI Biopharmaceutical Research Inc.	87.00%
9	ICON	86.83%
9	INC Research	86.83%

Bio-analytical Testing

1	Blue Sky BioServices	87.33%
2	Novotech	87.00%
3	Quest Diagnostics Clinical Trials	86.83%
4	ICON	86.00%
4	Toxikon Corporation	86.00%
6	Evotec	85.83%
6	Smithers Avanza	85.83%
8	PRA Health Sciences	85.67%
8	CNS Network	85.67%
10	Surpass	85.50%

2016 SURVEY DATA

586 **SURVEY RESPONDENTS**

74 **CDMOs IN THE SURVEY**

6 **KEY DRIVERS OF OUTSOURCING** Quality, Reliability, Productivity, Affordability, Innovation & Regulatory Compliance

CP **CUSTOMER PERCEPTION SCORE** Average of six individual key driver scores

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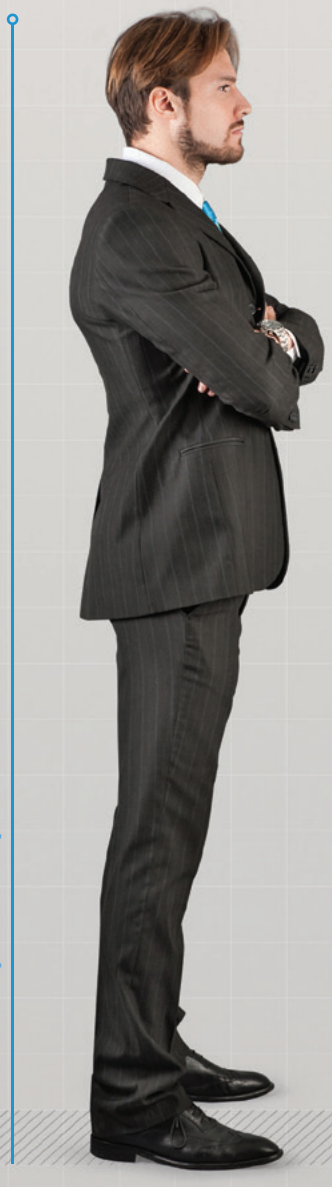

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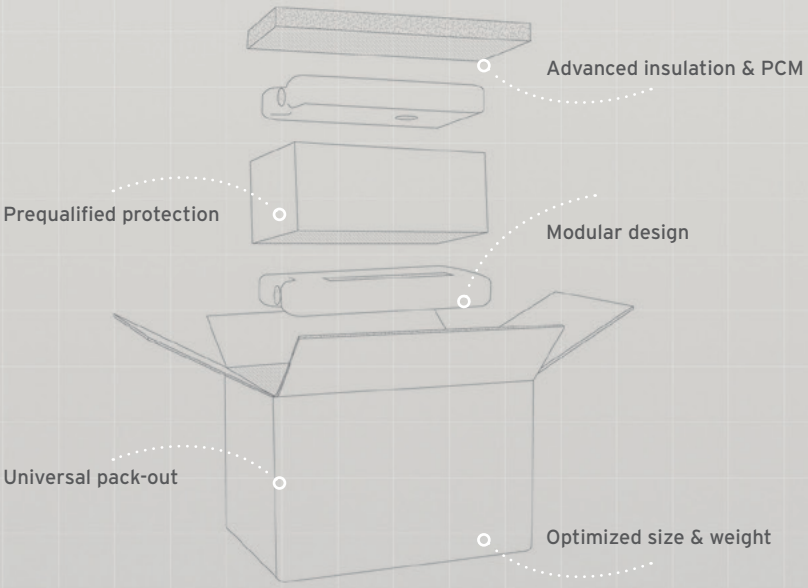

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NICE INSIGHT REPORT
PHARMA EQUIP

SINGLE-USE TECHNOLOGIES IMPROVE FLEXIBILITY AND ARE INTRODUCING A NEW ERA IN OPERATIONAL ECONOMY FOR BIO PROCESSORS

Biopharmaceuticals continue to grow in importance and number as pharmaceutical research uncovers new treatment options for new and existing conditions. Growth in emerging economies with improved living standards and a rapidly growing middle class is also helping to fuel this transition. Although the overall pharmaceuticals market is expected to grow at a compounded annual growth rate (CAGR) of 4%-7% to reach $1.3 trillion in 2018,[1] significant challenges still exist in the market, including patent cliffs that are already impacting legacy products, mounting and changing regulations, increasingly complicated development and manufacturing processes for in-demand drugs (mainly biologics), and instability in the emerging markets.

Due to the unique aseptic requirements for biopharmaceutical drugs – requirements further compounded by most biologic drugs currently requiring parenteral administration – the manufacturing process is complex, challenging and inexorably linked to the therapeutic and commercial success of biologic products. For the biopharmaceutical industry, both outsourcing partners and technological advancements are proving valuable in overcoming these challenges.

Most notably, single-use systems (SUSs) are offering flexible options for producers looking to drive efficiencies into the biopharmaceutical process. With options for both upstream and downstream processes, the flexible factory concept is becoming the model for cost-effective, aseptic production, whether companies are pursuing major or emerging markets and improved agility with both small- and large-scale production.

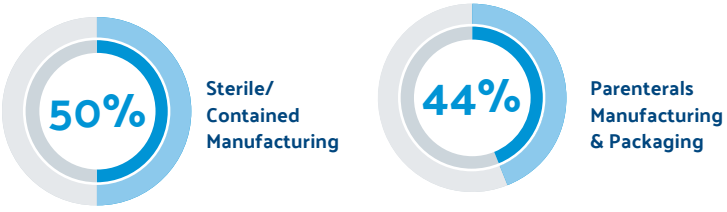
Flexibility from Start to Fill-Finish

In the 2015 Nice Insight Equipment Survey (overall n=560, biotechnology n=208), 91% of respondents claimed to be using bioprocessing equipment. The same survey also indicated that quality and performance were by far the most important factors considered when selecting an equipment supplier.[2] Though many biopharmaceutical manufacturers have implemented SUSs at various phases of the

production cycle, the decision to transition away from more traditional multi-use/stainless steel systems is significant at every level of implementation.

Nice Insight's 2016 CDMO Outsourcing Survey showed that 50% of those responding outsourced services for sterile/contained manufacturing and 44% outsourced for parenteral manufacturing/packaging, both key to bioprocessing. With that, 55% of respondents outsource to CDMOs for mammalian cell line-based development and biomanufacturing.[3] As many current SUSs are designed primarily for mammalian cell cultivation, CDMOs are often some of the earliest adopters of technologies like SUSs. Single-use technology development continues to improve, and solutions now exist for nearly all upstream and downstream processes at most production volumes. These specific benefits include ease of use, increased capacity and an overall reduction in downtime; however, manufacturers with large production volumes of one specific drug may not experience these benefits.

% RESPONDENTS WHO OUTSOURCED SPECIALIZED SERVICES



SOURCE NICE INSIGHT'S 2016 CDMO OUTSOURCING SURVEY

When in place, SUSs can greatly reduce the need for and frequency of sterilize-in-place (SIP) and clean-in-place (CIP) processes, as well as on-site facilities/equipment associated with these operations, allowing for rapid changeovers of small- and medium-scale production operations without an increased risk of contamination or a large equipment footprint.[5]

Without the need for fixed equipment or hard piping, the footprint of SUS-based bioprocessing shrinks, and is made mobile and flexible. Similarly, with consumable components (tubing, bags, etc.), single pieces of equipment can perform multiple operations. Despite the category's many advancements over the decades, there are still risks and limitations associated with the implementation and use of single-use technology.[5]

Quality Materials, Vendors

Vendor reliability and material quality are critical to the successful implementation and maintenance of an SUS. Though many upstream processes are lower risk in general, due to most liquids being recoverable media or buffer solutions, quality concerns magnify with downstream processes, such as protein purification, one of the final steps in biomanufacturing. SUS equipment failure at these stages presents a greater risk.[4] Components are often delivered sterile/ready-to-use and the integrity of items such as bags may be verified at delivery, but the fragility of plastic items greatly increases the risk of damage between delivery and use. Point-of-use testing – via helium integrity or pressure decay – can often help minimize these risks/failures, but vendor selection and material quality are also critical.[4]

Lower Risk for Global Operations

Emerging markets (Brazil, Russia, India, China, Mexico and Turkey) are growing more rapidly than developed markets and will account for nearly 50% of absolute growth by 2018,[1] but the risks involved with penetrating this space are great. These markets often favor local investment over imports, meaning partnership with a local CDMO may be a more reliable option, but SUSs also make the flexible factory, or single-use facility, concept[5] a possibility for companies looking to pursue emerging markets and answer demand for generic versions of biopharmaceuticals. Rapid entry and low financial risk are key to providing competitively priced options. Single-use operations provide the flexibility and mobility required to meet these demands.

As single-use technology continues to improve, offering greater capacity, more durable materials and even greater flexibility, their appeal will only grow for biopharmaceutical processors. To speed entry into new markets, manage supply chain risk and take advantage of advanced processes, CDMOs will remain a viable option to access the advantages of single-use technology production. P

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PROCESS SAFETY EVALUATIONS CRUCIAL TO SUCCESSFUL CDMO OPERATIONS

→ BY **VINCE AMMOSCATO** AND **SEAN LAPEKAS**, ASH STEVENS

To ensure contract service providers have the capabilities to safely perform all processes for a given project, it is essential that contract development and manufacturing organizations conduct comprehensive process safety evaluations.

While much of the emphasis on safety in the pharmaceutical industry relates to ensuring patient safety, as should be the case, often other crucial aspects of safety – in particular process safety – receive less attention than is appropriate. With increasing pressure to deliver faster turnaround times and lower cost, the performance of comprehensive process safety evaluations, which are time consuming and expensive, can be glossed over by contract development and manufacturing organizations (CDMOs), most often due to a lack of awareness and understanding of their importance. Inattention to process safety can, however, lead to devastating consequences.

It is essential that CDMOs conduct all pharmaceutical manufacturing processes in a safe manner. To do so requires

an effective process safety management system and strategy within a culture that emphasizes safety. Prior to acceptance, proposed projects must be evaluated to determine whether the capabilities of the CDMO are adequate, and only those projects for which suitable facilities, equipment and skilled personnel are available should be accepted. Once a project is underway, both theoretical and physical analyses must be conducted to determine the thermodynamic and kinetic properties of all materials involved in the process and the process itself, both under normal and worst case scenario conditions. Only with access to this information can the behavior of a process be fully understood with appropriate engineering, safety controls and procedures implemented. The failure to establish an effective basis of safety can lead to inadequate process design and protection of operators and, in the most severe cases, the surrounding community and environment.

RULE #1

KNOW YOUR CAPABILITIES

The types of processes conducted by CDMOs range widely, and consequently so do the potential hazards and risks they pose. Some processes, such as those that involve the use of unstable raw materials, exothermic reactions and / or the production of non-condensable gases, are more hazardous than others. In addition, as reactions are scaled from the lab to the pilot plant and then commercial volumes, the risk they pose increases.

Not all CDMOs are equipped to safely manage every possible process required for the production of pharmaceuticals. Therefore, the first step in establishing an effective process safety strategy is determination of the company's capabilities – and limitations – with respect to handling process hazards. In general, a paper assessment of the hazards presented by a potential new project, including the potency of the compounds and the potential for highly energetic chemistry / highly hazardous reactivity, should be suitable for determining whether the process presents hazards beyond what the CDMO is equipped to safely manage. A willingness to reject potential projects based on such a safety evaluation is the foundation of an effective safety management strategy.

If a project is deemed within the bounds of the CDMO's capabilities, the proposal / quote submitted to the client should include an outline of all anticipated process safety testing (and associated costs) needed to establish an appropriate basis of safety and potential safety measures.

RULE #2

START EARLY

Comprehensive safety evaluations should begin immediately once a project is accepted and run parallel to process development activities. The benefits of this approach are numerous – not only is the identification of any potential risks / hazards achieved prior to scale-up; any necessary changes to the process can be completed prior to process scale-up.

The comprehensive hazard evaluation should identify both desired and undesired potential material and reaction hazards. Thermal stability testing of the materials and mixtures used in the process is completed using instruments such as a differential scanning calorimeter (DSC), a thermal screening unit (TSu) and / or accelerating rate calorimeter (ARC). The enthalpies of the intended synthetic reactions can be obtained by either estimation techniques using available thermodynamic data, or measured with a reaction calorimeter. The generated data is then used to identify any process hazards and establish a defined basis of safety for each that will minimize the likelihood of adverse events and, where necessary, provide protection to operators and the environment from any potential event that may occur.

RULE #3

DON'T SETTLE FOR JUST DSC DATA

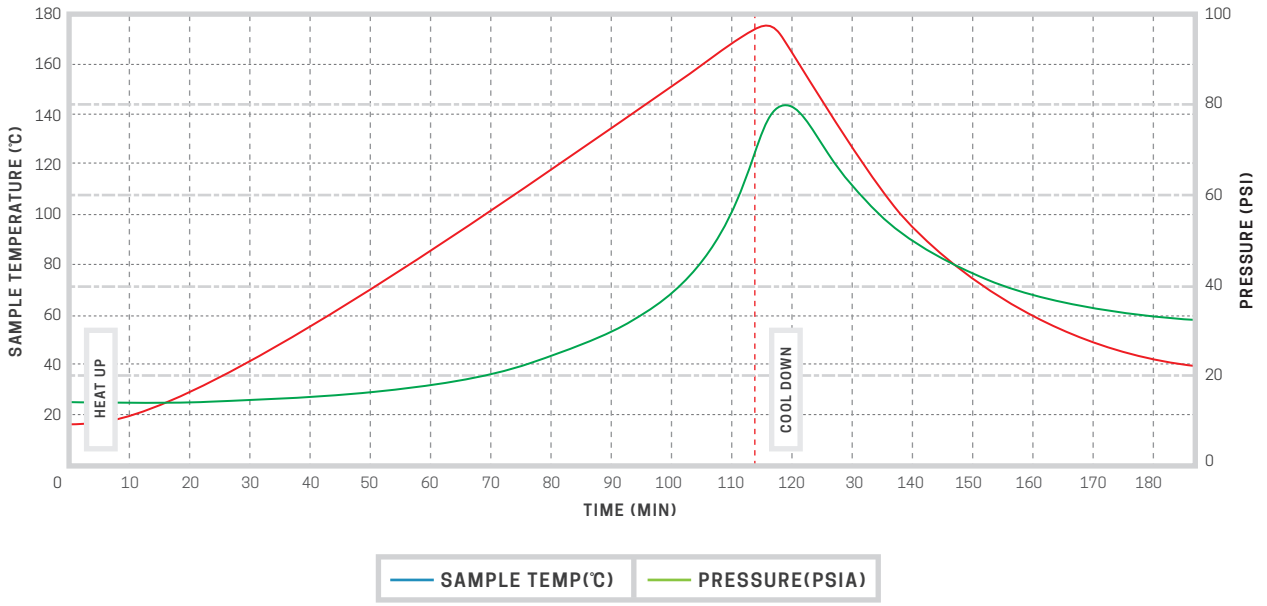
Once a project is accepted, the CDMO should conduct a more thorough paper assessment, considering all of the functional groups of the molecules involved and the process conditions. If the reaction is sufficiently simple, this phase may include estimation of the heat of reaction using heat of formation data for analogous reactants and products taken from the literature.[1] If no concerns are raised, then reaction calorimetry testing may be deferred until later in process development, so the testing will reflect the process as it will be scaled-up.

If there is any question about the potential stability of the materials in a process, DSC is performed on individual starting materials / reagents / products and / or reaction mixtures. The sample is heated at a constant rate, and the heat flows to (endothermic change) and from (exothermic change) the sample are recorded as a function of temperature and time. A DSC scan provides information about phase changes, decomposition or other self-reactivity behavior of the sample and whether these events occur exothermically or endothermically. For reliable results in safety testing, it is crucial that closed pressure rated crucibles be used for these types of DSC experiments.

There are limitations to DSC methods, however. First, the "onset" temperature can vary depending on the instrument sensitivity and the conditions under which the test was conducted.[2] Second, DSC does not provide any information on changes in pressure, and it is pressure buildup after an energy release due to solvent vaporization or the release of gases that often leads to undesired consequences.

→ **FIGURE 1 WHY PRESSURE IS IMPORTANT**
TSU scan showing no detectable thermal event in the sample temperature profile, but generation of non-condensable gases when comparing P_{Final} to $P_{Initial}$.

TEST CONDITIONS:
20°C-170°C at 1.5°C/min heating rate.



COMPREHENSIVE SAFETY EVALUATIONS SHOULD BEGIN IMMEDIATELY ONCE A PROJECT IS ACCEPTED AND **RUN PARALLEL TO PROCESS DEVELOPMENT ACTIVITIES.**

Therefore, analysis using a TSu or other similar pressure recording screening tool is imperative for evaluating both temperature and pressure responses, which can be studied under either isothermal or ramped temperature conditions. There are cases, in fact, where only slight exotherms or even endotherms are observed in DSC scans, but measurable pressure events are detected during a TSU analysis (SEE FIGURE 1).

Kinetic data and the heat of reaction of the desired process chemistry are then obtained using a reaction calorimeter. Traditionally, the Mettler Toledo RC1 has been the industry workhorse used for reaction calorimetry. A disadvantage of this system is that many users have it equipped with a 500-mL or larger reactor, and requires substantial quantities of material. Microreaction calorimeters have been recently developed, however, that utilize 1.5-mL to 20-mL vials and require minimal material, making the test quicker and more feasible for regular testing of all processes, regardless of development phase. It is important to note, however, that while a properly designed and executed microcalorimeter experiment will provide a reliable heat-of-reaction value, it may be difficult to determine the heat-release profile that will be observed during a slow addition that is typically employed on scale-up. If the microcalorimeter uncovers a large exotherm that will require strict temperature control via addition rate, further testing in larger equipment may be appropriate.

ASH STEVENS:

OTHER ISSUES TO CONSIDER

- Whenever possible, process safety testing should be conducted in ventilated fume hoods.
- All oncology compounds should be treated as highly potent if occupational exposure level (OEL) data is not available.
- Because large quantities of sample are required for dust hazard testing, which is generally conducted at an outside testing lab, it may be preferable to establish handling and transfer procedures designed to minimize dust generation and use a risk management approach to determine if dust hazard testing is needed.
- OSHA Process Safety Standard.

RULE #4

DATA INTERPRETATION IS KEY

To establish the most appropriate basis of safety therefore requires the ability to know which tests to conduct and how to effectively interpret the obtained data. The experience and expertise of the CDMO's process safety personnel are thus crucial to successful evaluations. Both an understanding of the potential reactivities of molecules based on their structures, and extensive experience conducting safety evaluations of many different processes, are needed to be able to identify the best series of tests that will fully elucidate the reaction behavior for a given process.

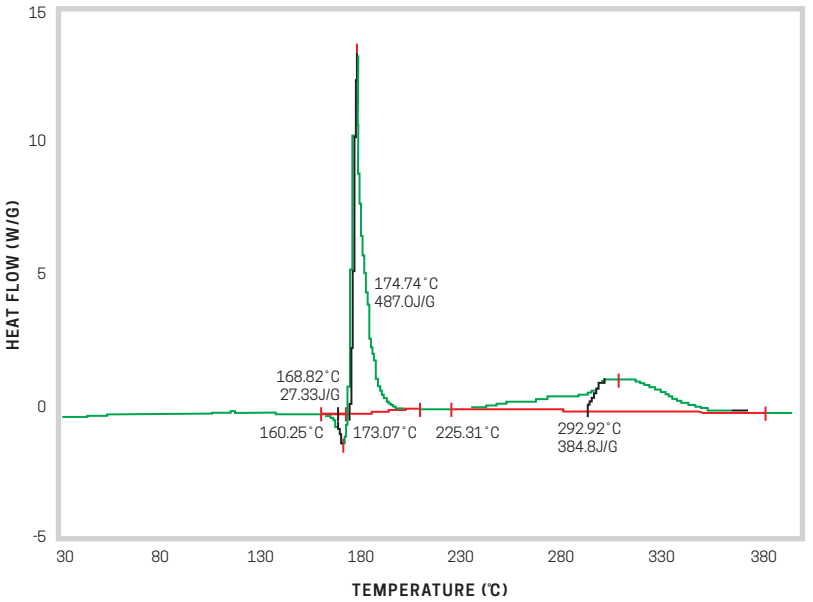
For instance, if a screening test conducted on a reaction mixture uncovers a decomposition event, quite often the practice is to assign a default safety margin, below which the reaction must be executed. However, one must remember that the screening test is performed in a sealed system, in which vaporization of the solvent is suppressed. If the "onset" of the decomposition event is above the atmospheric boiling point of the solvent, then to reach that secondary decomposition event, all of the solvent would first need to be vaporized. Before simply adding a 100°C safety margin (a common practice) that would require cooling of the reaction further than necessary, leading to excessive energy consumption, carbon emissions and additional expense, it would be prudent to first evaluate the rate of decomposition at the atmospheric boiling point, and determine the modes of failure that could lead to evaporation of solvent (i.e., the adiabatic temperature rise of the desired reaction, equipment failures, etc.), and base a safety margin on these findings.

The rate at which energy is released, and not just the amount of energy, should also be considered. Information on the time to

→ FIGURE 2 DSC INTERPRETATION

DSC scan of solid with melting temp followed immediately by decomposition.

TEST CONDITIONS:
30°C-400°C at 10°C/min scan rate.



The above DSC scan reveals that the sample melted and then immediately decomposed in the range of 160°C-180°C. The actual reaction is run in solvent, however. When in solution, the solid would not undergo melting; the energetic decomposition could therefore potentially shift to a lower temperature. Additional testing should be conducted to observe the behavior of the compound in the reaction solvent.

maximum rate can be gleaned from DSC scans. From a pure qualitative perspective, a broad decomposition peak suggests that energy may be released following *n*th order kinetics, while a sharp peak indicates a rapid release and possible autocatalytic decomposition. In the latter case once the initiating event is triggered, there is much less time to correct the situation before a full-blown runaway occurs. If ARC testing is not readily available, conservative Time to Maximum Rate information can often be estimated by conducting DSC analyses at multiple isothermal temperatures or scan rates and applying advanced software to develop scalable models of reactions that can be used to predict stability under different heating conditions.[2]

If the results of such an analysis raise any flags, more accurate data can be obtained using an accelerating rate calorimeter. Given the large instrument footprint and expense, ARCs are not typically owned by smaller CDMOs. Samples must therefore be sent to an external testing laboratory for ARC analysis. The test provides information about the relationships between time, temperature, pressure and kinetics for exothermic reactions under adiabatic conditions, such as those generally experienced in process equipment during loss of cooling.

Finally, it is not sufficient to consider only the desired reaction conditions. The behavior of the process under various undesirable conditions – worst-case scenarios such as loss of cooling or other equipment failure (i.e., stirring, feed pumps, etc.) – must also be evaluated in order to determine the most effective basis of safety. P

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Moving Science To Commercialization

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NICE CONSULTING REPORT
MERGERS AND ACQUISITIONS

M&A

PROTECTING THE CORE AND MAXIMIZING VALUE

With a number of mergers and acquisitions taking place in the CRO and CMO/CDMO space, this article highlights several areas driving the success of those new organizations, including: acquisition target criteria, fit with acquiring entity, building management consensus and performance expectations, onboarding new sites and teams, inclusive employee communications and projecting a new brand internally and externally.

→ BY **BRUCE MILES,** NICE CONSULTING

In October 2015, **Haig Barrett, Inc**. Management Consultants (Los Angeles) and **That's Nice LLC** (New York) a science agency announced the launch of **Nice Consulting**, a partnership designed to offer strategic and specialized consulting tailored to the marketing needs of life science companies, to help them to drive value in their brands, pricing, competitive positioning and capacity utilization.

Acquisition potential is predetermined by your criteria

Successful acquirers know what they are looking for before they begin. They have developed insights driven by thorough analyses of markets, customers, competitors, regulators and internal capabilities that lead them to identify a handful of very specific acquisition criteria. Moreover, these criteria enable a dispassionate evaluation of the target's fit from a strategic, financial and cultural perspective.

Capturing the full potential – mining for Silver and Gold

Most research indicates that only 40% to 60% of mergers succeed – and just 30% are cross-border mergers (Association for Corporate Growth). What exactly is a successful merger, and why aren't there more success stories? Generally, a merger is considered to be successful if the company achieves both the strategic imperative behind the merger and the merger synergies and operating results promised when a deal is announced.

Regardless of the strategic imperative, it has been our experience that the most successful mergers recognize that true long-term value is found in the white spaces within and between key value-creation functions (Product Development, Sales & Marketing and Supply Chain), while less successful mergers tend to focus too much attention on back-office integration and systems consolidation.

This is often immediately reinforced by the creation of a single Merger Integration team, with functional departments each addressing issues related to their functional scope. Instead, we recommend a two-pronged approach, reporting to an Integration Team Leader.

MOST RESEARCH INDICATES THAT ONLY 40% TO 60% OF MERGERS SUCCEED – AND JUST 30% ARE CROSS-BORDER MERGERS (ASSOCIATION FOR CORPORATE GROWTH).

SILVER TEAM This team takes the internal perspective, and is responsible for day one execution and synergy capture (cost reduction) related to Human Resources, Legal, Finance & Accounting and Information Technology. A key role of this team is avoiding employee defections and managing employee communications.

GOLD TEAM This team takes the external / customer-focused perspective, and is responsible for maximizing the value contribution (revenue and profit) of the Product Development, Sales & Marketing and Supply Chain organizations. A key role of this team is avoiding customer defections and managing external customer communications.

Capturing Value in the White Spaces

The Gold Team should be formed to specifically focus on leveraging the synergies within and between the value-creation assets entrusted to the newly combined organizations. Revenue increase during a merger is always more difficult to achieve, and takes longer than expected.

Don't underestimate the degree to which competitors will seek to poach your best customers and your best sales people, as your team develops strategies to address the following:

PRODUCT PORTFOLIO

To what degree do we need to rationalize the existing portfolio of development projects? Can we establish common platforms for existing products?

INNOVATION AGENDA

How do we best combine our teams to increase efficiency, fully leverage new capabilities and improve innovation?

SALES CHANNELS

How can we consolidate our sales force to remove overlap yet improve customer retention and sales?

MARKETING & BRANDING

How do we enhance and project our brand(s)? To what extent, and when, do we combine or shift our brands? What messages do we want our customers to hear during the merger integration?

SUPPLY CHAIN

When and how do we introduce new capabilities? To what degree can we consolidate, and how do we make this seamless for our customers?

Noteworthy mergers and acquisitions over the past few years:

Feb. 2014
Par Pharmaceuticals' acquisition of JHP Pharmaceutical

Mar./Sept. 2014
Merger of Patheon and DSM and the subsequent acquisition by the newly formed DPX Holdings of Gallus Biopharmaceuticals

Apr./Jul. 2014
Albany Molecular Research's acquisitions of Cedarburg Laboratories and Oso Biopharmaceuticals

Oct. 2014
Recipharm's acquisition of Corvette Pharmaceutical Services Group, a Flamel Technologies facility

WuXi PharmaTech's acquisition of XenoBiotic Laboratories

Nov. 2014
Consort Medical's acquisition of Aesica Pharmaceuticals Limited

Siegfried Group's acquisition of Hameln Pharma

Jan. 2015
Piramal Enterprises' purchase of Coldstream Laboratories

Sept. 2015
Pfizer's acquisition of Hospira, including its contract parenteral drug manufacturing operations

Mar. 2016
Renaming of AAIPharma and Cambridge Major Laboratories as Alcami

Clearly Defined Integration Strategy

To successfully integrate two companies, the approach must be consistent with the strategic intent. Guiding principles, priorities and governance must reflect the logic behind the merger. A well-defined integration strategy should clearly articulate both financial and non-financial goals, as well as risk mitigation strategies.

The following areas of focus are foundational to the ultimate success of an acquisition.

1

SOLID CORPORATE GOVERNANCE PROCESS

Comprehensively linking strategic intent to principles, processes, people, measurements and communications is challenging at the level of one company. Introducing a second company and stakeholder group to the mix multiplies these complexities. Decision-making authorities and approaches must be well defined. Cross-functional coordination, not only in the timing and execution of merger tasks, but also in the timing and consistency of communications to customers, employees and suppliers, is absolutely critical.

2

CULTURAL FIT

Bringing disparate groups of people together from different companies may be more difficult than it sounds. Subtle differences in language, decision-making, performance measurements, incentives – "culture" – can translate into major differences in expectations and behavior. Addressing these differences takes real work on the front-end of any merger, and throughout the integration period. Allowing differences to "resolve themselves over time" is a recipe for failure.

3

APPROPRIATELY RESOURCED INTEGRATION TEAM

Selecting the right individuals to lead the integration effort is essential. Those you choose will need to move quickly and make tough decisions based on limited information, yet remain sensitive to the needs and concerns of customers and employees from both companies. Although most of the organization should remain focused on running the existing business, full-time resources must be dedicated to the merger integration effort. Furthermore, incentives, for the integration team and adjacent leaders critical to the integration, should be implemented and equitably aligned across the organization.

4

INTERNAL OWNERSHIP VS. EXTERNAL ASSISTANCE

A central issue in the integration process is to find the right balance between internal and external resources to ensure success.

We believe it is imperative to have your people take ownership and responsibility for the success of the merger. A consultant's role is to help your people succeed. They should provide objectivity and practical experience in aligning the integration strategy with the merger's strategic intent and an organization's capabilities, honest evaluation and guidance regarding cultural and leadership challenges, cross-functional orchestration, continuous review of risk and risk mitigation strategies, and a persistent focus on maximizing merger synergies.

Fewer, more senior-level consultants can provide the coaching and guidance needed (and address management bandwidth issues), whereas a small army of more junior-level consultants can overwhelm your team with endless task lists, stretching them thin, distracting them from running the day-to-day business and increasing the risk that bigger-picture issues go unaddressed.

SUCCESSFUL MERGERS & ACQUISITIONS THRIVE ON INTENTIONAL, MEASURABLE AND ADAPTIVE PLANS WITH DEDICATED RESOURCES INCENTIVIZED TO DELIVER RESULTS

5

APPROPRIATE & ALIGNED PERFORMANCE EXPECTATIONS

Setting and aligning performance expectations begins well before the acquisition transaction even closes. As the acquirer builds its valuation model and identifies both revenue and cost synergies, expectations are being quantified and bought-in-to by leadership. Successful acquirers evaluate the financials both from an acquisition justification perspective and how they will operate the business once acquired. Performance expectations developed and established in this process enhance the likelihood of a successful acquisition.

In conclusion, successful mergers and acquisitions thrive on intentional, measurable and adaptive plans with dedicated resources incentivized to deliver results – capturing both the silver and the gold. P

M&A has been ongoing for both sponsors and contract service providers, continuing consolidation on both sides of the industry

The strategy for some contract manufacturers to achieve integrated services for large portions – or all – of the pharmaceutical development lifecycle from discovery to commercialization has been one large driver in M&A. Contract manufacturing organizations (CMOs) turning themselves into contract development and manufacturing organizations (CDMOs) continues. There is also a rise in the number of 'primary' (drug substance) contract manufacturers that have expanded into 'secondary' (drug product) manufacturing — and vice versa.

2015 Banner Year for Pharma M&A

For many in pharma, 2014 was seen as a peak year for M&A activity. Some $200 billion in deals came into play, even with failed bids like Pfizer's attempt to acquire AstraZeneca and Abbvie's efforts to acquire Shire. With 2015 in the rear-view mirror, industry observers and journalists alike were heralding the robustness and amazing acceleration of this past year's M&A action. Top of mind for many was Pfizer's now-thwarted acquisition of Allergan. This $160 billion deal was to be the largest M&A deal in the industry's history. Earlier in 2015 Abbvie announced its intentions to acquire Pharmacyclics for $20 billion, a deal that was identified as the largest global M&A deal of 2015 — now that the Pfizer/Allergen deal is void, Teva's $40 billion acquisition of Allergan's Activis operations takes the top spot. Even with Pfizer/Allergan off the table, 2015 M&A activity was relatively robust, sustaining a trend that is likely to carry on throughout 2016.

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Bruce Miles has 30+ years of experience in business strategy, operational excellence and corporate development. His clients have included several of the world's leading life sciences, retail, consumer and industrial companies. Prior roles Bruce has held include COO of a Philips Healthcare division, Consulting Partner with Ernst & Young, Managing Director at AlixPartners and Distribution Sector Executive at IBM.

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ACHIEVING LARGE-SCALE CELL AND GENE THERAPY MANUFACTURING

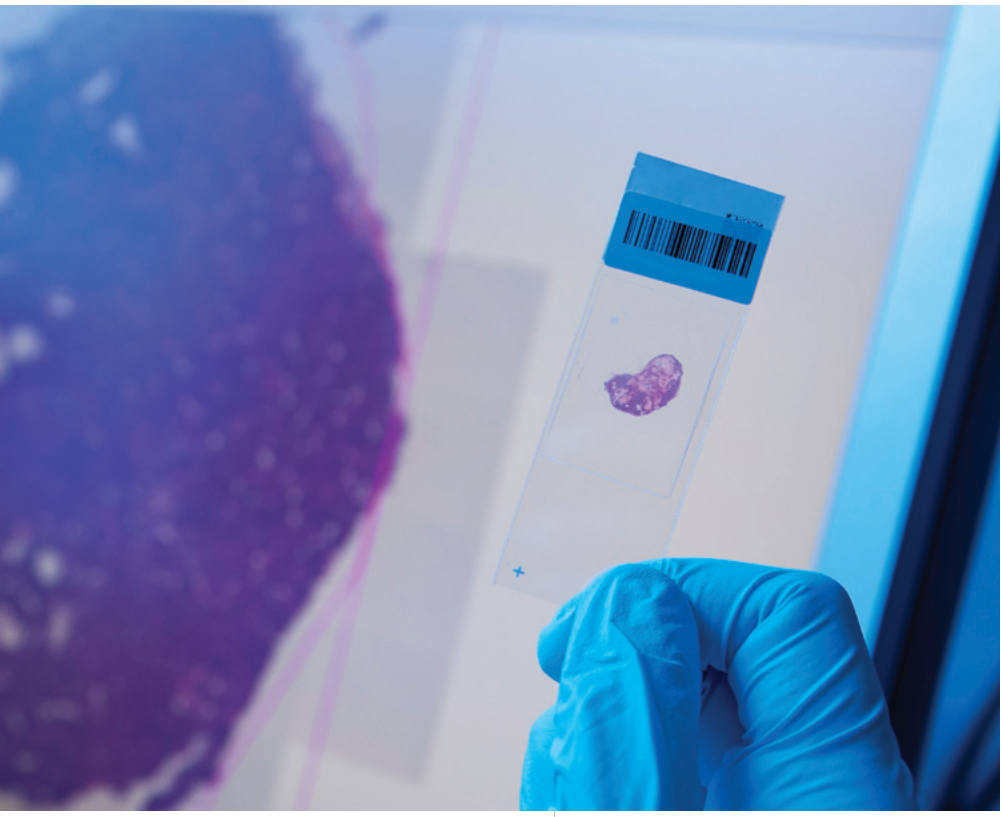
→ BY **MARK BAMFORTH, MBA, STEVE KASOK, MBA,** AND **RICHARD SNYDER, Ph.D.**, BRAMMER BIO

Initial clinical successes with cell and gene therapies have driven significant investment in these next-generation technologies by both large bio / pharma companies and start-up specialist firms backed by venture capital dollars. Many of these companies are eager to advance beyond early clinical trials to phase III and commercial products, but lack the manufacturing capability.

There is a significant need for contract manufacturing partners with the specialized expertise necessary to innovate and implement novel manufacturing solutions that will help accelerate the commercialization of these advanced treatments that have tremendous potential to improve patient lives.

The cell and gene therapy industry is in the growth phase of its economic life cycle. Significant research and development expenditure by large pharma / biotechs and cell and gene therapy-focused biotechs is driving new product development. More than 500 companies have been identified by Jain PharmaBiotech to be involved in cell therapy alone,[1] and the gene therapy market is estimated by Roots Analysis to be growing at 48.8% per year to reach $11 billion by 2025.[2] There is a rich pipeline of over 500 cell and gene therapy products in the clinic, which will drive significant capacity needs as the pipeline matures and progresses to commercial supply.[3]

The early clinical successes that have been achieved are driving significant investment in cell and gene therapy technologies. Larger bio / pharma companies are either developing in-house expertise or



partnering with smaller, specialized companies focused on cell and gene therapies, many of which have been established with funding from venture capital groups and some of which have already completed successful initial public offerings (IPOs). As a result, there are numerous companies facing mounting pressure from investors to move into late-stage clinical trials and on to commercial launch. Most, however, do not have the capabilities required to manufacture cell and gene therapy products on the commercial scale.

Successful realization of commercial cell and gene therapies is thus predicated on the ability of these innovators to establish partnerships with contract development and manufacturing organizations (CDMOs) with the specialized expertise required to facilitate the progression of their products from the clinic to the market. At present, however, the contract development and manufacturing capacity dedicated to supporting the cell and gene therapy market is limited, and most capabilities can be described as immature.

ENTIRELY NEW TECHNOLOGY

Cell and gene therapies, while biopharmaceuticals, are quite different from existing biologic drugs, such as blood factors, interferons, recombinant proteins and monoclonal antibodies. Because these products comprise whole viruses or living cells, manufacturing processes are designed to maintain their potency. Product characterization (strength, identity, viability, purity, potency, viral safety) and release testing are particularly challenging, and require the use of novel analytical methods. Process development and validation, establishment of process reproducibility and alignment with current Good Manufacturing Practices (cGMP) also require innovative solutions for large-scale production. As with any new treatment platform, both safety concerns and regulatory uncertainties must be addressed. For example, with large patient populations, the logistics of extracting cells from patients, sending them to a site for processing and then delivering them back to the same patient, while feasible, does add additional layers of complexity.

Successful growth and maturation of the gene and cell therapy sector requires the application of existing process optimization and commercial manufacturing expertise to these emerging technology platforms, as well as the development of novel processing and analytical solutions. Consequently, scientists highly experienced in current state-of-the-art technologies for small-scale gene and cell therapy production and who are capable of innovative problem-solving, must be united with a leadership team that brings deep manufacturing and commercial expertise combined with knowledge of facility design, quality and regulatory systems.

APPLYING EXPERIENCE TO EMERGING TECHNOLOGIES TO MEET A SIGNIFICANT MARKET NEED

Recognizing the critical need for contract manufacturing organizations with this unique set of capabilities, Brammer Bio was founded with the goal of establishing a best-in-class CDMO dedicated to supporting the development of cell and gene therapies from early phase clinical studies to phase III and beyond. The company has

SUCCESSFUL REALIZATION OF COMMERCIAL CELL AND GENE THERAPIES IS THUS **PREDICATED ON THE ABILITY OF THESE INNOVATORS TO ESTABLISH PARTNERSHIPS** WITH CONTRACT DEVELOPMENT AND MANUFACTURING ORGANIZATIONS (CDMOS)...

been designed from the start to enable accelerated process development, and clinical and commercial manufacturing, as well as guide the industry in maturing to a robust supply base.

Brammer Bio brings together the wealth of industry experience in biologics development and clinical / commercial manufacturing of its cofounders – and previously cofounders of Gallus Biopharmaceuticals – with a 10-year track record in cell and gene therapy development, early-phase manufacturing and analytical testing services of Florida Biologix. An additional cell and gene therapy manufacturing facility in Massachusetts enables the company to provide support from discovery through commercial launch to customers, in accordance with global standards.

THE OPPORTUNITY: FOUR TECHNOLOGY PLATFORMS

The CDMO opportunity can be divided into four technology platforms:

[1] Autologous cell therapy
[2] Allogeneic cell therapy
[3] *Ex vivo* gene therapy
[4] *In vivo* gene therapy

[1] Autologous cell therapies are based on cells that are harvested from the patient. The cells are shipped to a manufacturing site where the cells with the desired properties are isolated and then expanded. The cells are then shipped back to the patient for reintroduction. Such patient-specific therapies have a low risk of adverse immune reactions, but are expensive due to the inability to scale the process.

[2] Allogeneic cell therapies have the advantage of being derived from universal donor cells, which allows for greater scale. The cells are harvested from the donors and shipped to the processing facility for isolation, expansion and banking of multiple doses. Cell types that do not elicit immune responses upon implantation are used for these treatments, and therefore a single product has the potential to treat hundreds or thousands of patients.

[3] *Ex vivo* gene therapies are autologous cell therapies in which the cells harvested from the patient are genetically modified, typically using a viral vector to introduce new genetic information, and then reintroduced into the patient. The greatest focus is on chimeric antigen receptor T-cell (CAR-T) therapies, which contain special cell-surface receptors that recognize specific proteins on tumor cells. After infusion into the patient, the T cells multiply, recognize the cancer cells containing the antigen and kill them, and also reactivate components of the immune system that are suppressed by cancer cells.

[4] *In vivo* gene therapies involve the direct delivery of genetic information into patients using viral vectors with the goal of enabling patient cells to effectively express missing or deficient proteins.

CONCLUSION

Cell and gene therapies are showing success in the clinic for the treatment of cancer, nervous system disorders, cardiovascular diseases and many rare disorders. The challenge faced by the industry today is the scale-up of manufacturing to achieve robust production of high-quality, safe and efficacious medicines that will have a significant impact on patient lives. CDMOs dedicated to supporting the commercialization of these promising treatments must have the ability to translate existing expertise in small-scale gene and cell therapy production and in large-scale biologic drug manufacturing into novel, efficient and reliable processes suitable for commercialization. Brammer Bio has been designed with this unique set of capabilities in order to support cell and gene therapy companies to rapidly move their autologous and allogeneic cell therapies and ex vivo and in vivo gene therapies into the clinic and to the marketplace. P

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brammer bio

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BEST-IN-CLASS CONTRACT MANUFACTURING

Brammer Bio is a CDMO focused on providing process development, clinical, and commercial supply of viral vector and cell and gene therapy products, enabling the delivery of novel medicines and improving patient health. We have a highly skilled team of scientists with the development, manufacturing and analytical expertise from 100 client projects that is required to tackle the challenges posed by these novel technologies and help accelerate their transition from the clinic to patients in need while focusing on meeting cGMP standards. Brammer Bio has the expertise to support your gene and cell therapy projects to Phase III and beyond.

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→ **REVIEWED**

NEW BRAND IDENTITY FOR **BRAMMER BIO**

Brammer's vision was to build a best-in-class cell and gene therapy CDMO.

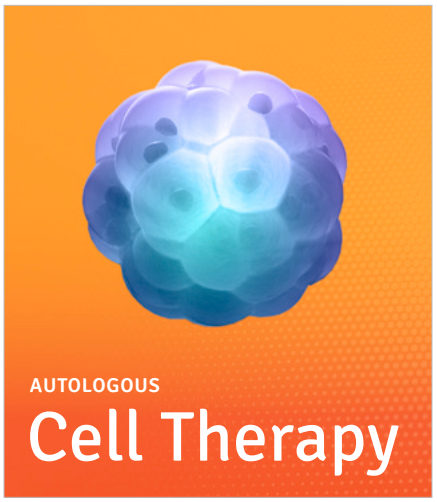
The challenge was to develop a tagline that supports the new identity and brand in the cell and gene therapy CMO marketplace. We had the option to go with either a descriptive tagline that immediately helps establish some fast equity in the brand tied to the services and market, or something that is more evocative and memorable.

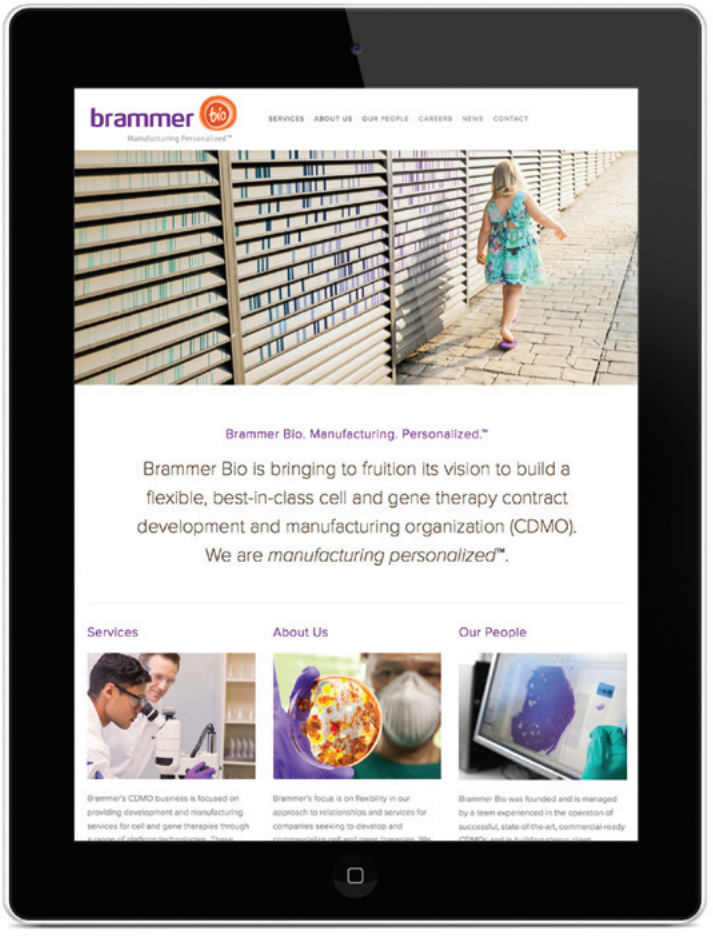
THE RESULT IS "MANUFACTURING PERSONALIZED."

It is derived from contract manufacturing and personalized medicine. It also alludes to the flexible, personalized nature of Brammer Bio's customer pitch. Logo and brand identity were created employing a direction that is striking and energetic, with a visual allusion to cells.

→ **LOGO PROCESS**

Logo and brand identity were created employing a direction that is striking and energetic, with a visual allusion to cells.





→ WWW.BRAMMERBIO.COM

The name “Brammer” is a west of Scotland colloquialism meaning “Best in Class” and “Excellence.”

BRAND COLORS

The orange and purple color palette provided by the client offers a pleasing, colorful aesthetic and contributes to the attention-grabbing aesthetic that’s found throughout Brammer’s graphics, illustrations and modified images.

BRAND IMAGERY

Lifestyle images are used on the website and in publications to help visitors connect the fact that Brammer Bio’s science touches real lives, and is in fact derived from real lives. It is consistently positive yet deliberately grounded in tone. Our aim was to bring elements of the science and corporate colors, with embedded cells and DNA markers into lifestyle imagery.

Technology images are used along with striking three-dimensional illustrations of cells and viral vectors. We integrated the corporate color palette into this imagery to reinforce the brand aesthetic. Advertising shows the cells in an environment of woven textures alluding to flexibility and collaboration.

RIGOROUS INTEGRATION IN A SCALABLE DEVELOPMENT & MANUFACTURING ENTERPRISE TO SUPPORT CONTINUED GROWTH OF BIOPHARMACEUTICALS

→ BY **SYED T. HUSAIN**, ALCAMI

The pharmaceutical and biopharmaceutical development and manufacturing market continue to experience significant expansion as the development of small molecule drugs and more complex large-molecule biologics rival for attention. Small and midsize pharma/biotech companies are leading drug discovery and the engagement of contract development and manufacturing organizations (CDMOs) helps them to improve capabilities and enable companies to compete in this dynamic market.

To attract and keep customers, competitive CDMOs are bolstering their offerings by expanding areas of expertise. In recent years, some of these expanded capabilities have been organic, while others have been achieved through strategic partnerships and mergers with strong, capable partners.

One example is "Alcami", the alliance of AAIPharma Services and Cambridge Major Laboratories, which through rigorous integration and improvements formed a full-service CDMO offering drug substance and drug product development, manufacturing, testing and packaging services. The development of biopharmaceuticals – often in the form of parenteral or injectable medications – requires unique expertise, facility specialization, and an understanding of the entire development process. Current outsourcing trends in this market are prompting companies like Alcami to increase recognition of how significant aseptic processing is to customers' success – and how important it is to engage contract partners with the best capabilities, finishing parenteral medications aseptically.

A REASON TO RELY ON OUTSOURCING

According to the 2016 Nice Insight CDMO Outsourcing Survey of over 500 outsourcing-facing pharmaceutical and biotechnology executives, outsourcing partners are being engaged for every phase of development, with over 50% of all respondents outsourcing every phase with the exception of phase IV / Post-Launch.[1] Additionally, overall engagement increased for phase II, III, and IV by as much as 25 percentage points (phase III) since 2015.[2] However, some of the newest numbers are even more significant in specific segments.

Phase IV / Post-Launch services, for example, are outsourced to CDMOs by nearly half of all big pharma respondents (47%) while 69% of emerging pharma / biotech companies engage CDMOs as outsourcing partners for preclinical services. Overall, the annual outsourcing expenditure on CDMOs was $51M or greater for 71% of survey respondents with 28% exceeding $100M. With that, 75% of total respondents expect that number to grow over the next five years[1], indicating a steadily increasing reliance on outsourcing partners.

Even more noteworthy, however, is the percentage of services outsourced for biopharmaceutical drugs and associated manufacturing processes. As the world's population ages, the middle class continues to swell and treating chronic conditions becomes more prevalent in developing countries, the demand for biopharmaceuticals rises; this increase is clearly visible in outsourcing practices.

Large molecule new biologic entities (NBEs) and biosimilars accounted for 26-50% of all outsourced services for 16% and 13% of all respondents, respectively. Additionally, microbial cell line and mammalian cell line based development and biomanufacturing were outsourced or will be outsourced by 62% and 55% of survey respondents.[1] Some of this outsourcing is due to traditional pharmaceutical companies increasing their focus on biologic drug development and seeking cost effective ways to make this investment.

EXPERTISE FOR BIOPHARMACEUTICALS

Biopharmaceuticals and parenteral drugs in general require aseptic processing at nearly every stage of the production process. These processes require advanced controls and optimal packaging materials to meet regulations and guarantee patient safety. Like many pharma/biotech companies, contract service providers are beginning to form scalable enterprises to reduce costs while bolstering their services to offer a more complete suite of options to support the drug development and manufacturing cycle.

Most of today's biologic drug products – including monoclonal antibody drug products that have been on the market for over 20 years – are designed for parenteral

WHEN **THE PRODUCT IS THE PROCESS**, THE PROCESS IS EVERYTHING, AND THAT PROCESS DOES NOT END WITH DRUG DEVELOPMENT OR PRODUCTION, **IT ENDS WITH THE PATIENT**.

CURRENT OUTSOURCING TRENDS IN THIS MARKET ARE PROMPTING COMPANIES LIKE ALCAMI **TO INCREASE RECOGNITION OF HOW SIGNIFICANT ASEPTIC PROCESSING IS** TO CUSTOMERS' SUCCESS.

administration[3] but considerable challenges exist in liquid drug development, including quality concerns and close regulation. These drugs also require advanced primary and secondary packaging materials and technology due to the complexities associated with administration, high development costs and increasing patient demand.[4] Protecting the sterility of the product as it moves through each phase of formulation, filtering, filling, and packaging is mission critical. Full-service CDMOs have been investing in advanced containment and process technologies to mitigate these risks at all stages. With the right CDMO partner, it's even possible to follow the processes as far as distribution services.

Alcami is leading by example. In 2014 Cambridge Major Laboratories, a full-service CDMO providing active pharmaceutical ingredient (API) development and manufacturing, combined with AAIPharma, an experienced, long-term provider of pharmaceutical analytical testing, drug product development and drug product manufacturing and packaging services. The result? Alcami, a supplier of integrated chemistry, manufacturing, and controls (CMC) services with centers of excellence in solid-state chemistry and formulation development services and a U.S.-based drug product sterile manufacturing facility. In fact, they recently announced the completion of clinical trial material from API manufacture to Drug Product (sterile) release in 79 days which is a 65% reduction in timeline in comparison to a non-integrated approach.

Over the last several years, Alcami has produced millions of parenteral fills in its small- and large-molecule sterile parenteral product manufacturing facilities that also support lyophilized products, suspensions, emulsions and terminal vial sterilization. The combined operational matrix allows seamless integration of services covering development, testing and manufacturing from API, and on to finished packaging.

THE PACKAGING IS THE PRODUCT

While the outsourcing of biopharmaceuticals is noteworthy in all four respondent segments in the 2016 Nice Insight CDMO Outsourcing Survey – Emerging, Small, Mid-Size, and Big Pharma/Biotech – the outsourcing of packaging materials is also significant, with over half of all respondents outsourcing both commercial (58%) and clinical (60%) scale primary packaging.[1] Though packaging has not typically be considered in the early stages of drug development, packaging materials can significantly impact a biopharmaceutical drug product and the growth in biopharmaceuticals is heightening the need for unique containment and delivery systems.[5]

Most understand the fill-finish process of aseptically prepared drug products requires sophisticated equipment in a highly controlled cGMP environment to ensure product quality and patient safety. The complexity of most biopharmaceuticals also prevents easy identification or characterization with many products being heat sensitive and susceptible to microbial contamination. These conditions necessitate the use of aseptic principles at every step, potentially illustrating why controlled room temperature (CRT) packaging and cold-chain packaging services were outsourced to 47% and 36% of respondents, respectively.[1]

Single-unit dosing is reducing medication non adherence and helping assure the promised therapeutic benefits of biopharmaceutical drug products; however, for these benefits to carry through from the manufacturing process, fill-finish processes have to meet stringent requirements to ensure flow path sterility and integrity, operational safety, and fill-volume accuracy. Additionally, all the requirements of a drug, including shipping, storage, and the dose form, as well as ease of administration, should be considered during drug development. The expertise of an experienced and integrated CDMO partner will help speed the evaluation of options and the execution of final packaging processes.

When the product is the process, the process is everything, and that process does not end with drug development or production, it ends with the patient. When the process can be contained and monitored by one company with expertise at every stage, all production processes can remain consistent, aseptic, reliable, and cost effective for all parties involved. P

→ ABOUT THE AUTHOR

Syed T. Husain Chief Commercial Officer, Alcami

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

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NEW BRAND LAUNCH EVENT
RAINBOW ROOM NEW YORK
MARCH 2016

→ **REVIEWED**

NEW NAME, LOGO FOR **ALCAMI**

ALCAMI represents a rebranding of AAI Pharma Services and Cambridge Major Laboratories (CML), creating a world-class supplier of comprehensive pharmaceutical development and manufacturing services.

NEW NAME

The Alcami name is an anagram of AAI-CML, so it pays homage to the legacy. It also serves as a reference to "Alchemy," the forerunner of modern chemistry, based on the transformation of matter, particularly converting base metals into gold, and also refers to a process of transformation, creation or combination.

AAI-CML
ALCAMI.

→ **ANAGRAM**

TAGLINE

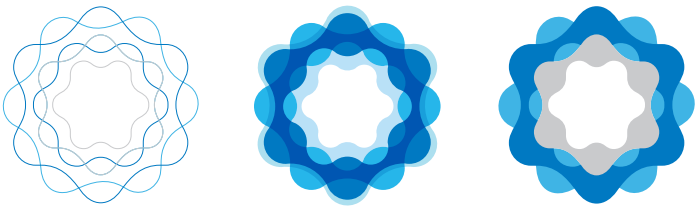
The aim for the tagline was to communicate a message of seamless transition with reference to the additional capacities and capabilities that would support the clinical progression and commercialization of medicines for their customers.

THE RESULT IS "CONNECTED AT EVERY LEVEL."

This communicates the integration and the connection between a CDMO and customer, and AAI/CML's strategy to be focused on end-to-end service for the right audience.

The tagline establishes a connection from drug substance to drug product and the multi-layering of relationships between the new entity and the marketplace. It is a connection through science and philosophy – a true partnership.

→ LOGO MARK PROCESS



→ EXPLORATION OF TYPEFACE

ALCAMI All caps / Curved strokes

alcamiii Hand-drawn / Optical kerning

alcami Lower case / Increased height

→ BEFORE

AAIPHARMA | CAMBRIDGE MAJOR LABORATORIES

→ AFTER

alcami™

LOGO

The direction is further progressed in the logo. The connection of the multi-layered hexagonal shapes alludes to elements of processing complexity and relationships that are sophisticated.

The symmetry of the logo suggests a connected relationship between Alcami and its customers; it brings their personality forward.

The primary color palette meets industry expectations and brings continuity from the legacy organizations.

There is a delicacy and refinement to the visual, which conveys continuous partnership. The concept can be used in multiple forms, adapted and evolved. Derivative messaging keeps the "connected" theme fresh and relevant.

→ WWW.ALCAMINOW.COM

A HOLISTIC INTERPRETATION OF COMMITMENT TO QUALITY

→ BY **ORIOL PRAT**, GRIFOLS PARTNERSHIP

Quality is the first concern of any pharmaceutical manufacturer. Translating that concern into a quality strategy comprising effective procedures and practices is another matter, and can be particularly challenging for injectable drug products. Outsourcing of fill/finish activities adds an additional layer of concern because it introduces the risk of losing control over manufacturing quality. Therefore, selection of a contract service provider with a holistic approach to quality and a clear track record of quality performance in all aspects of injectables manufacturing is essential.

Demand for injectable drug products is increasing at a healthy rate, due in part to growth of the biologics market and because injectable formulations offer a mechanism for increasing the efficacy, while reducing the side effects, of many small-molecule drugs. In some cases, fewer doses of injectable drugs are required, which can increase patient adherence (particularly for self-injected therapies). *Markets and Markets* predicts that the injectable drug delivery market will increase at a CAGR of 12% from $326.1 billion in 2015 to $574.8 billion by 2020.[1]

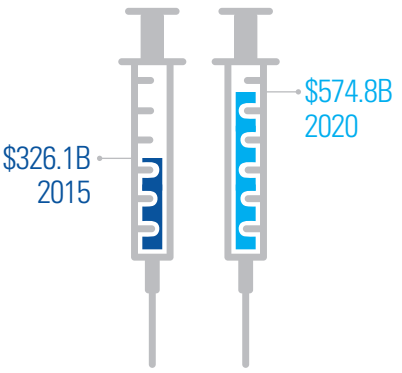
Quality issues have plagued the injectable drug market in recent years. Numerous recalls due to product quality issues have contributed to shortages of many injectable products in the United States. This troubling situation underscores how the lack of appropriate quality strategies,

and a quality culture, can directly impact patients.

A key indicator of the quality of injectable drug products is the extent of foreign particulate matter. One of the leading reasons for recent recalls of injectable drug products is the presence of visible particles.[2] During the period of 2008-2012, 22% of FDA recalls of sterile injectable drugs were attributed to the presence of visible particles.[3] Examples of recalls in 2015-2016 have included the injectable anticancer drugs gemcitabine, carboplatin, cytarabine, fluorouracil and methotrexate; saline injection products have also been the object of several recalls.

Various pharmacopeias include standards for the production of injectable products, but meeting requirements for the manufacture of products that are "essentially free" of particles is very challenging.[4,5] Materials found in recalled drug products have included metal particles, fiber and glass particles, silicone fragments and insect parts.

While several practical measures can be taken to prevent contamination of injectable drugs with particulate matter, from the use of appropriate cleanroom and vial/stopper designs to the use of isolators and sterile filtration, doing so will achieve only limited success without an overall culture of quality.



12% INCREASE

INJECTABLE DRUG DELIVERY MARKET CAGR FROM 2015 TO 2020

BENEFITING FROM BLOOD PLASMA INDUSTRY EXPERIENCE

The plasma-derived proteins market, in which Grifols is one of three top players, is particularly sensitive to quality issues, largely due to significant quality problems that occurred during the 1980s-1990s, related to virus contamination. Unlike most other companies in the sector, Grifols has never experienced any quality problems due to virus contamination, and this track record of performance has placed the company in a prestigious position in the plasma-derived proteins market.

This commitment to quality and our culture of continuously striving for the highest quality levels are also applied across all of the company's activities, from non-biological injectable products to reagents and instrumentation for clinical diagnosis.

PARTICULATE CONCERNS

In addition to being a crucial indicator of quality for injectable products, the presence of particulates in finished pharmaceutical sterile products can have significant consequences for patients. Clinical effects can range from minor problems to serious complications and even death.[6] In the U.S. alone, approximately 190 million liters of intravenous fluids are administered to patients each year, and thus particulate matter contamination is a real concern for the pharmaceutical industry.[6]

Given the increasing number of recalls due to contamination by visible particulates in parenteral drugs and the heightened concern of the FDA and other regulatory agencies, Grifols is actively working to improve its manufacturing operations and enhance its existing quality programs. In addition to adopting a vertical integration model for control of the entire manufacturing process, Grifols has introduced automation technologies (robotics) and implemented

ONE OF THE **KEY OPPORTUNITIES** FOR PARTICLE GENERATION OCCURS DURING THE **BAG MOLDING PROCESS.**

advanced process controls, such as artificial vision, to reduce human interactions with injectable products and thus further minimize the potential for contamination.

GREATER CONTROL WITH VERTICAL INTEGRATION

The use of Form-Fill-Seal technology at Grifols Partnership provides a good example of how vertical integration results in the highest quality performance. The process involves the formation, filling and sealing of plastic (polypropylene) containers (bags) in one step and in a fully automated manner without any human interaction. To ensure complete control of the process, Grifols manufactures components, including ports and stoppers, employed in the Form-Fill-Seal process and uses equipment developed and manufactured by Grifols Engineering.

One of the key opportunities for particle generation occurs during the bag molding process. For this reason, Grifols has integrated this process into its filling operations through the adoption of Form-Fill-Seal technology in order to maintain control over this critical aspect of injectable solution manufacturing.

Grifols Engineering is a Grifols company devoted to the design of pharmaceutical production plants, processes and machinery for both Grifols and other pharmaceutical manufacturers. Because it is part of a pharmaceutical company, Grifols Engineering is particularly knowledgeable about the quality and compliance requirements for pharmaceutical production processes and the design of manufacturing facilities.

With this vertical integration approach, Grifols has control of the entire process from start to finish, ensuring that all parts of the manufacturing process are performed following the same high-quality standards.

AUTOMATION ADVANTAGES

At the Grifols Partnership plants in Spain, where non-biological injectable drugs are manufactured, high levels of automation are employed to reduce human interactions with drug products and thus minimize the risk of contamination. No further operator intervention is required on the Murcia plant "Form-Fill-Seal" production lines for injectable solutions once the plastic rolls are loaded; bag production and printing, filling, capping, over-wrapping, sterilization and packaging are fully automated, and the final product is not touched by anyone until the point of use. Fully automated glass vial production lines at the Barcelona plant also minimize human interactions with products.

ADVANCED INSPECTION TECHNOLOGY

The Barcelona plant has also pioneered the implementation of artificial vision systems in Europe. Developed in collaboration with Diagnostic Grifols, another Grifols company that has extensive knowledge of artificial vision technology, the systems enable the automatic inspection of injectable products for particulates, avoiding the potential for human error.

PARAMETRIC RELEASE

Parametric release is a system of release that gives assurance that the product is of the intended quality and is based on evidence of successful validation of the manufacturing process. The information collected on process monitoring carried out during the manufacturing process, and the compliance with the Good Manufacturing Practices, provides the desired assurance of the quality of the product. Companies that have shown high consistency in their overall quality systems can be approved for parametric release for sterility. In 2007, Grifols was one of the first companies in Europe to obtain this authorization.

CONCLUSION

Products manufactured by the Grifols Partnership CDMO are of vital importance to patient health and quality of life. Safety is therefore more than just a regulatory requirement; at Grifols it is a philosophy that goes hand-in-hand with quality, and both apply not only to our products, but our internal manufacturing, communication and operational processes. Our holistic approach to quality has resulted in a robust and reliable quality system and positioned Grifols Partnership as an ideal strategic partner. P

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ABOUT THE AUTHOR

Oriol Prat Director Contract Manufacturing, Grifols Partnership

Oriol has been working in pharmaceutical marketing and sales, with a focus on the hospital business both domestic and internationally, for 30+ years. He has spent the last 15 years devoted to the strategic business growth of products and markets. In the past 10 years, he has concentrated on the development of the contract manufacturing business unit at Grifols, designing the strategy of positioning and communication, as well as driving the company towards necessities of the market.

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NICE INSIGHT PHARMACEUTICAL EQUIPMENT 2016 ANNUAL STUDY

NICE INSIGHT

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Nice Insight recently completed the 2016 Pharmaceutical Equipment Survey, which profiles 40 of the industry's leading pharmaceutical equipment companies. Companies were selected based on their size, sales, regions covered, equipment manufactured and marketing practices, as well as customer awareness and perception. Phamaceutical equipment subject matter experts vetted these parameters and companies for relevance within the industry.

DEMOGRAPHICS

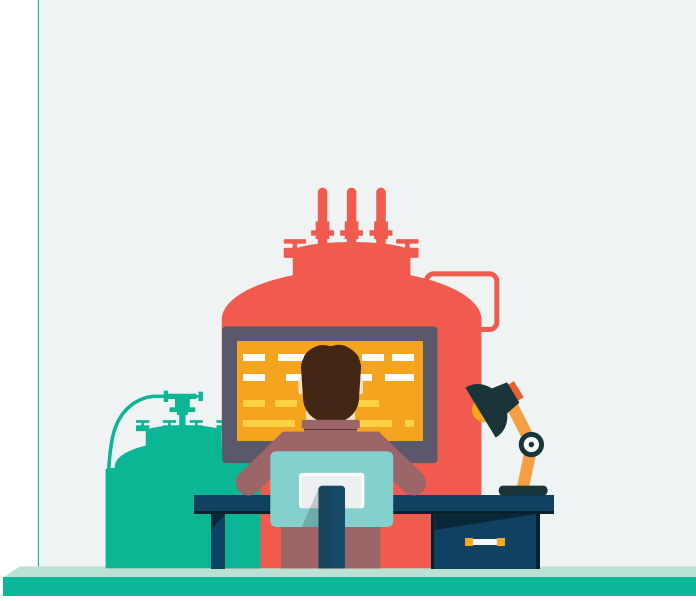
The 2016 Pharmaceutical Equipment Survey was deployed to an international audience. Responses were collected from a total of 489 industry professionals worldwide, including those in Asia, Europe and North America.

All respondents are currently employed in pharmaceuticals or biopharmaceuticals. Many are involved in the production of generics, OTC medications, nutraceuticals and contract development and manufacturing organizations (CDMOs). The companies represented vary widely in size, from emerging, defined as under 100 employees, to large, with over 2,500 employees.

In order to ensure the 2016 Pharmaceutical Equipment Survey provides the most accurate picture of the current equipment market, Nice Insight established strong criteria to determine respondent validity. Respondents are screened for [a] industry, [b] range and depth of pharmaceutical equipment knowledge, [c] company interest level in purchasing new systems and technology and [d] level of direct involvement in equipment purchasing decisions.

The majority of respondents currently hold managerial or executive positions in their respective departments and organizations. There was an even mix of respondents from various departments: manufacturing, purchasing, engineering, operations and corporate / executive. Of the qualified respondents, random sampling was used to create a pool of responses from which the results of the survey were analyzed.

From the entire pharmaceutical equipment spectrum, Nice Insight focused on three major segments for 2016 – Processing, Bioprocessing and Packaging.



PROCESSING

Processing equipment focused on equipment for formulation and manufacturing of mainly small-molecule pharmaceuticals. Processing equipment was further subdivided into three categories based on the type of dosage for which they were designed: solid dosage, semi-solid dosage and liquid dosage.

BELOW IS A LIST OF EQUIPMENT COVERED UNDER EACH OF THE THREE SUB-CATEGORIES

SOLID DOSE:

Tableting
Encapsulation
Conveyors / Transfer
Blenders
Conical Mills
High Shear Mixers / Granulators
Agglomeration / Compaction
Blade / Hammer Mills
Counting Equipment
Form / Fill / Seal
Fluid Bed Processors / Dryers

SEMI-SOLID DOSE:

Mixers / Stirrers / Blenders
Homogenizing Equipment
Heating / Cooling Equipment
Size Reduction Equipment
Milling
Form / Fill / Seal

LIQUID DOSE:

Spraying Equipment
Homogenizing
Conveyors
Filtration
Milling
Freeze Drying

BIOPROCESSING

Bioprocessing equipment covers the equipment needed for the development and manufacturing of biologics. Bioprocessing equipment is further subdivided into two categories based on the stage of development/manufacturing: upstream and downstream.

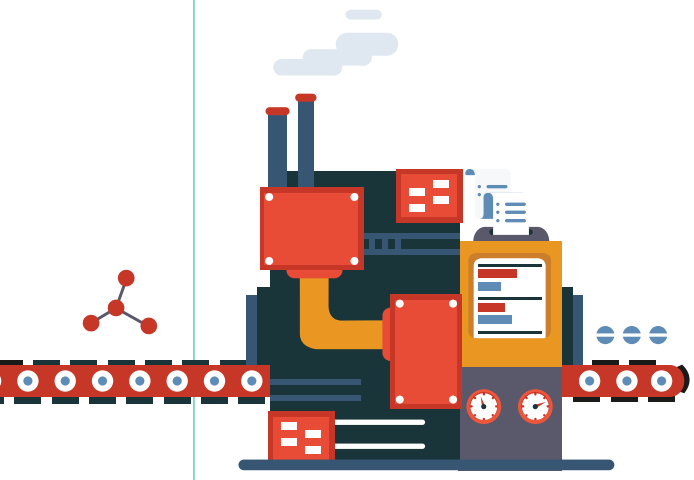
BELOW IS A LIST OF EQUIPMENT COVERED UNDER EACH OF THE TWO SUB-CATEGORIES

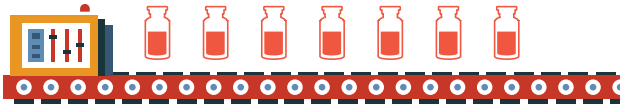
UPSTREAM:

Bioreactors
Fermenters
Incubators
Cell Culture Biological Shakers
Disposable Bioprocessing Equipment
Mixing/Blending/Milling Equipment

DOWNSTREAM:

Filtration Equipment
Purification Equipment
Chromatography Systems and Equipment
Separation Equipment
Disposable Equipment





PACKAGING

As the name suggests, the packaging equipment category covers equipment used in primary and secondary packaging of (bio) pharmaceutical products.

BELOW ARE THE PACKAGING EQUIPMENT LISTED UNDER THE PRIMARY AND SECONDARY CATEGORIES

PRIMARY PACKAGING:

Aseptic Fill-Finish and Capping Equipment
Non-Aseptic Fill-Finish and Capping Equipment
Unit Dose Fill-Seal
Blow/Fill/Seal
Inspection Systems
Containment Solutions
Product Assembly Lines

SECONDARY PACKAGING:

Cartoning Equipment
Overwrappers and Stretch Banders
Bulk Packaging Equipment
Checkweighers
Serialization Equipment
Tamper-Evident Solutions
End Packaging

Participants were queried on their interest level in purchasing new equipment, thus mapping out the market for these three categories. The collected responses determine the drivers for evaluating equipment providers and the influence of purchasing exploration. The survey also illustrates the main sources of dissatisfaction when working with an existing equipment supplier.

KEY PERCEPTION DRIVERS

PROCESS INTEGRITY

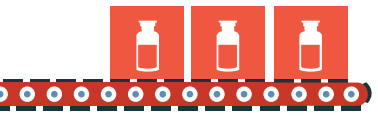
Equipment ensures that the product is manufactured and packed in line with stringent compliance rules

RELIABILITY

Business gives the impression that the company is stable, reliable and dependable

TOTAL COST OF OWNERSHIP (TOC)

Business provides the most ideal asset purchase price with an efficient cost of operation



THE COLLECTED RESPONSES DETERMINE THE DRIVERS FOR EVALUATING EQUIPMENT PROVIDERS AND THE **INFLUENCE OF PURCHASING EXPLORATION**.

2016 SURVEY DATA SEGMENTS

BUYER GROUP
- Branded Pharmaceutical
- Biopharmaceuticals
- Generic / Over the Counter

BUYER SIZE
- Large
- Mid-sized
- Small / Emerging

REGION
- North America
- Europe
- Asia

DEPARTMENT
- Corporate / Management
- Operations
- Technical

PRODUCT DOSAGE FORM
- Oral solid
- Semi-solid
- Liquid
- Specialty

EQUIPMENT CATEGORY
Processing Equipment
- Solid Dose
- Semi-solid Dose
- Liquid Dose

Bioprocessing Equipment
- Upstream
- Downstream

Packaging
- Primary
- Secondary

EFFECTIVE EVALUATION

Accurately and effectively evaluating the market can be a challenge. The 2016 Pharmaceutical Equipment Survey seeks to provide awareness and perception standing within the competitive market. Awareness and Perception are the two key measures for a company's performance from a marketing perspective. Awareness is measured on a four-point scale: [1] Never heard of, [2] Familiar with name/logo, [3] Somewhat known and [4] Well known. This perception measure helps companies identify their gaps in awareness, allowing for the identification of market needs and opportunities. The tool can also be used to inform equipment-purchasing decisions from a buyer perspective.

Company perception is measured on six key decision drivers – Reliability, Customer Service, Process Integrity, Total Cost of Ownership, Post-Sales Support and Overall Equipment Efficiency.

Each driver is ranked on a 5-point scale, from Unsatisfactory to Excellent, which serves as a measure of respondent perception. These perception scores are weighted, aggregated and tallied to provide a unique total that allows each supplier to be compared against each other both per driver and on an aggregate level. Buyer perception, based on personal experience or information accrued through industry knowledge, is thus quantified.

The proprietary Nice Insight comparison tool segments the awareness and perception scores of equipment companies rated on various criteria. These scores elucidate the crucial marketing benchmarks of awareness and perception from multiple perspectives, allowing purchasers, providers and market players to better grasp this ever-evolving space.

Overall, the Nice Insight 2016 Pharmaceutical Equipment Survey provides a comprehensive awareness / perception score of a pharmaceutical equipment provider. Nice Insight is very excited with the 2016 findings and looks forward to sharing the results with the industry. P

CUSTOMER SERVICE

Business gives the impression that they are easy to do business with and provide excellent customer attention and service

OVERALL EQUIPMENT EFFICIENCY (OEE)

Business gives the impression that the products and services offered help achieve key performance indication and lean manufacturing levels

POST-SALES SUPPORT

Business gives the impression that the products come with comprehensive after-sales support and service agreements

COMPANY PROFILE

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, which 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

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

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

Ash Stevens

Ash Stevens Inc. is a fully integrated CDMO, offering comprehensive drug substance development and API manufacturing services to clients developing innovative small-molecule drugs. To date, the company has received 13 U.S. FDA approvals, including four with FDA Fast Track designations. Ash Stevens supports all aspects of drug development and cGMP manufacturing from de novo process development to commercial API production. The company's state-of-the-art manufacturing facility, located in Riverview, Michigan, is FDA-registered and has the capacity to develop and manufacture APIs from grams to batch sizes up to 250 kilograms.

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

BIODURO

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

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

BioVectra

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

@ www.biovectra.com
+1 866 883 2872
11 Aviation Avenue, Charlottetown
PE C1E 0A1, Canada

brammer bio

Manufacturing Personalized™

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.

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ROUNDTABLE

BIOAVAILABILITY

Q: WHAT ARE YOUR THOUGHTS ON ENHANCING **BIOAVAILABILITY** WITH NOVEL TECHNOLOGIES?

(CONTROLLED RELEASE, EXCIPIENT SELECTION, SOLID STATE SOLUTIONS)

I think controlled release is one of the most interesting opportunities for life science companies.

Bioavailability is of concern not only to pharma but also to other industries very close to pharma. I think [controlled release is] one of the most interesting opportunities for life science companies because you can leverage a combination of drug substances with specialty products. I have in mind some natural polymers that play a role in slowing the release of the drug into the tissues, so that's an extremely normative and interesting opportunity. Also, there's a lot of work on particles engineering and solubilization of products to enhance bioavailability. All in all I think the industry is making good progress.

Luca Mantovani
CEO, INFA Group

Franck Pavan
CDMO Department Manager, Injection products, Pierre Fabre

From my perspective, new enhancing bioavailability technologies will move forward in the future. Most of the new active ingredients that are discovered have physical and chemical characteristics that are not compliant with, let's say, a clear solubility in water and that's why it's more and more difficult to maintain the bioavailability of those active ingredients. I'm quite confident that new technologies like the ones you're asking about will be improved in the future, but the technology will be highly expensive and will then be used for high-added-value products. **This is the purpose of the new generation of products: to have a better bioavailability and to be more specific for the pathologies they need to treat.**

IT'S CLEAR THAT REFORMULATION KNOW-HOW IS A CRITICAL SKILL FOR CONTRACT SERVICE PROVIDERS.

Advanced API chemistries, for example, are requiring sophisticated processing capabilities to overcome solubility and bioavailability issues. The market is evolving, and many of pharma's global players are exploring ways in which to leverage reformulation and advanced API processing skills to create new opportunities and markets for their products. That is, opportunities that can exploit and enhance the market reach of newer compounds losing patent protection, or leveraging advanced development and manufacturing capabilities in an effort to breathe new life, efficacy and market appeal into common medicines. Demand for high-quality pharmaceuticals for the Chinese population is growing as fast as China's consumer-oriented middle class and China FDA is working to regulate the industry to meet global quality standards. BioDuro's experience in China is telling. We are working with some 20 Chinese firms, many pursuing the development and manufacture of New Abbreviated New Drug Application candidates. What's interesting is that many of these compounds are being reformulated, designed to more closely match the particular physiological and societal needs of China's sprawling, diverse population.

Cyrus Mirsaidi
President and CEO, BioDuro

Solubility and subsequent issues of bioavailability have long been an issue for Pharma, especially for poorly water-soluble compounds. For both branded Pharma and contract manufacturing organizations alike, "solving" a compound's solubility issues is often the key to unlocking either its full therapeutic benefits, processing efficiency or its market potential – but more likely, all of the above. Contract manufacturers in particular are seeking market success improving their technical acumen and operations to assist drug innovators in developing formulations and other oral solid-dose and delivery technologies to overcome issues related to solubility and enhancing bioavailability. One strategy for success Pharma is adopting has to do with extending the patent protection and market life of an approved drug via the FDA's 505(b)(2) regulatory pathway, which for many is a strategic response to the pending loss of patent protection. Manipulating the formulation and bioavailability aspects of existing drugs to prepare them for new patient classes or disease categories is a major aspect of this trend. Drugs approved under 505(b)(2) rely on data from existing reference drugs and require only a fraction of the number of clinical trials for approval compared to a brand-new candidate. Ultimately this means a "new" and patent-protected drug can achieve FDA approval in as little as two and a half years. Ultimately, these market dynamics will continue to energize the industry's supply chain and that includes the need for well-managed, secure clinical supply logistics to assure clinical trial success.

Wes Wheeler CEO, Marken

Many of the new chemical molecules under consideration are very difficult to formulate from a solubility standpoint. Innovators with new molecules are looking for their supply chain partners to deliver the technologies and different types of capabilities to make chemicals more soluble. There are certainly a number of things that can make a product more bioavailable; technologies like nano-crystallization that create smaller, more soluble particle sizes is just one of several effective methods. Increasing the time a compound spends in the body and controlling release can be accomplished through different coatings technologies and techniques that manipulate dissolution profiles. Avara's fielding some interesting technology. One is a drilling technology that allows two different APIs in one tablet. We also have a polymer-coating technology that allows the product to stay in the body longer and dissolve over a specified rate over a longer period of time, and an enteric coating technology that only releases once it's in the intestine. One of the most important things to remember is there are a significant number of molecules in development that could potentially be more effective therapeutically if the industry can apply the research and development it's going to take to innovate and make medicines more bioavailable. In the near term I think we'll see a significant increase in the amount of time and effort that the industry spends towards developing technologies to make products more bioavailable.

Tim Tyson Chairman, CEO, Avara Pharmaceutical Services

Marianne Spaene
Executive Vice President Global Business Development, Marketing & Sales, Siegfried USA

One of the most promising strategies for enhancing bioavailability is to apply the API in an amorphous form that is more soluble than crystalline forms. Spray drying – a novel, flexible bridging technology that can be applied to most poorly soluble drugs – allows the API to first be dissolved with tailor-made polymers in an organic solvent so that it can be isolated and stabilized in the amorphous form. With the API encapsulated in the polymer matrix, crystallization cannot occur and the final product becomes more soluble and, ultimately, more bioavailable. Essentially, by improving bioavailability, new drugs can be made available for patients and the daily dose per patient can be effectively decreased, thereby reducing probable side effects. Siegfried as an integrated drug substance and drug product partner offers spray drying from lab development to large-scale manufacturing.

DEFINITELY, YES.

Imagine that 10 years ago, even 5 years ago, there was a lot of discussion about biosimilars but there was not really a successful breakthrough. I expect that now biosimilars will gain, in the next 5-10 years, strong traction and I see several companies which are jumping into biosimilar development. Government bodies will also play a role by subsidizing these developments, [and] having biosimilars is definitely an opportunity to [also] reduce the costs in this area.

Luca Mantovani
CEO, INFA Group

When it comes to labeling biologic copies of patented large molecule drugs, perhaps 'Biosimilars' is the wrong term. In reality, under the current regulatory frame, creating a biosimilar and getting it approved requires nearly the same expense and effort it takes to take a new biologic NDA from lab to patient. Much of biosimilars' market potential will depend on insurers' willingness to accept and pay for these medications. Another big question is whether or not prescribing doctors will trust and recommend biosimilar medications to their patients. Will there be enough competition is another question; the current generics economy sees several companies competing over the sales of a single compound, and that generates pressure that helps keep prices low — the main reason for generic equivalents. Even the rosiest predictions project only a few major players will participate in the near term. Because of that, and other factors, it's likely that pricing will be 'similar' to current biologics pricing, and we won't experience the price differential that made small-molecule generics so popular.

Stephan Kutzer CEO, Alcami

ROUNDTABLE

BIOSIMILAR

Q: ARE WE ON THE EDGE OF A NEW ERA OF BIOLOGICS? WHAT WILL THE **BIOSIMILARS' LANDSCAPE** LOOK LIKE IN THE NEXT 10 YEARS?

'gold rush' isn't as easy as what some thought it may have been early on in the process...

I think, with respect to biosimilars, we've sort of already seen some of this play out with the initial approvals in the biosimilar space. If I think back [to] 3-4 years ago, we saw what I'll call a flurry of activity from a lot of smaller companies that were attempting to participate in this space, [but] over the last 1-2 years, I've seen that drop off and [become] more focused on the more prominent players both in the pharma and the biopharm space. So I think what people are seeing is that the 'gold rush' isn't as easy as what some thought it may have been early on in the process and that getting a biosimilar approved is just as difficult and maybe, in a lot of instances, more difficult than an innovative product approval. The answer to the question is [also] a little bit different if you're talking about the U.S. versus Europe, given that [Europe has] had biosimilars on the market for 10+ years, but the US is just coming to the forefront now. Government pricing pressures, the regulatory and legal landscape, and global, large-scale capacity constraints are all significant factors that will influence the impact of biosimilar penetration in US markets.

Greg Flyte
Head of CMO Alliance & Program Management; GlaxoSmithKline

Yes, I think so, but this is exactly the beginning. There are currently big players which are not known to be players in the pharmaceutical industry but which have invested a lot in the manufacturing of the monoclonal antibodies, which are needed for biosimilar products. I think it's the beginning of great success because there is a big market for biosimilars. The companies that own the patented registered products have moved to these technologies in the 1980s and 1990s, and have made a lot of big improvements in the way they are manufacturing; nowadays, they are moving to the next steps with the new entities that they want to use for new treatments to maintain their profits. I think that the price for biosimilars won't be as cheap as it would be for standard generics because of the technology and the clinical studies that need to be implemented in order to support market introduction. There are a lot of patents which are moving out of licensed environments, and the technologies to manufacture the antibodies and the biosimilars are already available; they just need to be transferred from their production areas once the patent has expired. I think we are moving to another generation of biosimilars, which will be manufactured in highly regulated countries to support the new regulatory environment for market entry.

Franck Pavan
CDMO Department Manager,
Injection products,
Pierre FABRE

BIOSIMILARS? IT'S A BOOMING INDUSTRY, AND INCREASINGLY ATTRACTIVE TO BOTH DRUG INNOVATORS AND GENERICS COMPANIES.

But the large-molecule market space will likely not ever be as crowded as it is in the small-molecule space. For one, barriers to entry can be quite high, and it's well-known that it takes a much different set of technical and operational skills to be successful. Even though there are a number of innovative therapeutic large molecule pharmaceuticals that could potentially be replicated, not all of them are feasible as biosimilar candidates. A biosimilar developer can spend as much as £300 million to develop a large molecule drug; the choice of what molecule to develop is highly dependent on the drug's market potential, as well as opportunities to duplicate it more economically and without effecting the therapeutic effectiveness of the originally patented molecule. The bottom line is some formulations are quite advanced, and for anyone pursuing a biosimilar strategy, it takes advanced knowledge to get it right. GSK's contract manufacturing arm helps companies to develop and manufacture their biosimilar products.

Kristof Szent-Ivanyi
Business Development Head,
GSK Biopharmaceuticals

Bill Marth President and
Chief Executive Officer
Albany Molecular Research

There's going to be great opportunity in the biosimilar market; however, that potential is predicated on how well the FDA and its international peers frame law and policy to guide the industry. The pathway has been defined; but now it's time to refine the pathway such that we unleash innovation and competition in this area. We believe this a segment that will grow exponentially over the next decade and that growth is guiding AMRI's strategic planning in very distinct ways. Developers and manufacturers, like AMRI, will need to be able to field the science, services and operations to support this coming demand and we plan to be right there.

The economics of biosimilars is not at all similar to current small-molecule generic drugs – which are often steeply discounted from the innovator. Frankly, what biosimilars represent to the marketplace is not a "generic" per se; they really are a "new" branded product. Because of that, we see an increased number of larger biotech companies entering the biosimilar arena and working to leverage their considerable resources to produce formerly patent-protected large molecule biopharmaceuticals. What will the biosimilars' landscape look like in the next 10 years? It's likely that there will only be a handful of 'expert' producers manufacturing biosimilar drugs, and while economies of scale and operational expertise will likely help cut manufacturing costs, these economics will likely not translate into the savings that have been generated over the years for consumers of small-molecule medicines. The depth of penetration of biosimilars can be transformed if regulators accept the substitutability of biosimilars – that will ultimately drive the kind of prescription momentum to open the doors of the category wide open.

Mark Bamforth
President and CEO,
Brammer Bio

> [ADCs are a] huge challenge in terms of manufacturing and capital investment because you have to build both biologic and chemical synthesis capabilities.

Luca Mantovani
CEO, INFA Group

In my view, it might be understood because you need two sets of skills for ADC development. [ADCs are a] huge challenge in terms of manufacturing and capital investment because you have to build both biologic and chemical synthesis capabilities. Setting up organizations which have both skills is definitely a huge investment for a company. I would say that most of the people who are evaluating [ADCs] are probably hesitating entering this market because of this huge barrier.

ROUNDTABLE

ANTIBODY-DRUG CONJUGATE

Q: DO WE UNDERSTAND THE **CAPITAL INVESTMENT** IN OUR STAFF?

Franck Pavan
CDMO Department Manager, Injection products, Pierre Fabre

I think that ADCs made a breakthrough since 2010. This is a tremendous outcome for the pharmaceuticals laboratories for the treatment of cancers, and these therapy-targeted products will be aiming to treat specific needs, small pathologies, not wide treatments with a wide spectrum. I've been involved in several ADCs' projects, and the results on the patients which have been treated initially by those types of technologies and products were amazing. The initial ADC on the market was not strongly binded to the toxic agents, and the side effects were too powerful. Today, the new technologies which have been implemented by the laboratories prevent the toxic agent from being released until it reaches its target. That's a real improvement to the technology, which accelerates marketing of the products and will quickly move the products to the market in the future. The corollary to that is the price of such technologies, which is very high. For highly regulated countries, this is a small hurdle as the market can support it, so the ADCs will move forward for sure. The landscape is crowded as there are a lot of new companies which are trying to be involved in such new technologies by providing new linkers technologies and other companies trying to find new payloads for ADCs as this last technology is very active due to lack of candidates.

I THINK THE JURY'S STILL OUT ON ADC'S POTENTIAL FOR MARKET AND MEDICAL SUCCESS.

Yes, most agree that overall the concept of ADCs is brilliant, but after all this time, we have not seen the breakthroughs the industry needs to support ADCs' medical potential and commercial success. Further, it's not clear if the investment community will continue to finance development and capacity. Where's the 'Wow' factor? It takes a huge investment to launch new capacity, and already, as many might argue, there is enough capacity and volume to meet the market's near-term demand for ADCs. Regardless, time will tell if investors will continue to fund R&D and additional capacity to support further ADC development until we see it meet its potential. In the meantime, Alcami, like others, will continue to invest in the aseptic filling technologies and the HPAPI handling infrastructure that underpins the sophisticated biologics processing capabilities the industry is demanding.

Stephan Kutzer CEO, Alcami

I think it's expected but not fully quantified. There's really a lot of uncertainty around what it would really take to manage that kind of growth. And certainly if you're a traditional pharma person, it would be much more of a square start than upgrading or backing into by adding small pieces of equipment. It would be more of a holistic view that would be needed, so that adds a different kind of capital. There's a reasonable amount of capital just for the development piece. I'm specifically talking about the lab-based development work and that alone certainly already has a significantly higher [investment].

Nagraj Bokinkere
Technical Director, Business Development, Eastman Kodak

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