PHARMA & BIOTECH
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Markets & Companies
Pharma M&A Rush, Current Challenges for Pharma CDMOs, Expert Opinions, Market Reports, Company News

Strategy & Management
Pharma CDMO Business Strategies, Digitalization in Pharmaceutical Development, Managing of Complex GMP Processes

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Tailor-made Complex Peptides, Production of Monoclonal Antibodies, Supply of Non-cGMP Materials, Drug Research

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[1] Bode L (2012) Human milk oligosaccharides: Every baby needs a sugar mama. Glycobiology 22, 1147-1162.

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Markets & Companies 4–15

Strategy & Management 16–33

Manufacturing & Supply Chain 34–41

East or West? East and West!

What Changes Can We Expect to See in the Global CDMO Market in the Year Ahead?

Outsourcing is about the efficiencies of globalization, expense, people, and the challenge of drug discovery. Big Pharma has consolidated and faltered over the past 15 to 20 years. Though drug discovery and chemical synthesis really are "rocket science," the continued commercial viability of the industry hinges on constant breakthrough innovation. It is evident that it is going to take the whole world to discover the next generation of blockbuster drugs. The connections forged through outsourcing are the way new ideas are being hatched. Contract Development and Manufacturing Organizations (CDMOs) are playing a critical role in the pharma innovation process.

In the CDMO industry, we have witnessed a spate of new M&A activity over the past 12 months as key players are buying both capacity and new capabilities. Ten years ago, we first saw a rush to "One-Stop-Shops" or "End-to-End Services" followed by a period of relative quiescence. Beginning in 2017 we again saw the market come to life with heavyweights muscling their way into a better position to provide the full gamut of drug development services. Avista's acquisition of Solid Form Solutions, Novacap's purchase of PCI, PCAS, and Uetikon, and Thermo Fisher's integration of Patheon come to mind. There have been others, and certainly there will be more to come.

Mark Alexay, ChemOutsourcing

Trend and Growth Drivers

What is driving this trend is a bit speculative, but one suspect is the increasing number of compounds green-lighted to market by the FDA. There is nothing like success to set off feeding frenzy among the firms that compete to bring new small and large molecule therapeutics to market. According to Fortune magazine, US drug approvals hit a 21-year high in 2017. Additionally, we have seen a 10-year demographic shift in new therapeutics (new molecular entities, NME) coming from small companies rather than Large Pharma. This is significant.

Continued Page 6 ▶

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For CDMOs, we see greater opportunity as the larger companies have fewer suppliers (and now fewer drugs) than before. The blockbuster era ended in the early 2000's. Now, hundreds of "emerging", "virtual" and other small pharmaceutical companies are driving the discovery and development of new drugs. This has expanded the supplier base — they outsource everything and work quickly, unlike Big Pharma. Coupled with a spike in new generic approvals and a strong overall economy, the industry is very healthy.

Additionally, we are seeing biologic therapeutics reaching the market in greater numbers as well as the first bio-equivalents gaining approval. All in all, a great time to be a pharmaceutical executive scientist!

"China and India remain important players as long as they offer lower costs."

The China Effect

Next, there is the China Effect. China has very quickly become a key player in the pharmaceutical supply chain engine. Just 25 years ago, the first manufacturing plants were being built in economically ascendant China. Western companies quickly saw the attraction of lower-cost alternatives and legions of well-educated and hard-working scientists. Though the emergence of China has resulted in displacement of Western pharmaceutical scientists, most have adapted, imperfectly perhaps, to the new environment. The exact nature of the ever-evolving West-East pharmaceutical business is enormously complex, but main points include a new, longer supply chain extending to China and India, with most raw materials and intermediates coming out of China and most API's being made in India.

Reshoring of Manufacturing

The West typically formulates and finishes the final product, but mostly for innovator drugs. Though only 13% of US medication prescriptions, they generate the lion's share of revenue and profits. This is where CDMOs thrive and bring their greatest value. Generics are low margin and made abroad. Will manufacturing practices change? Yes they will. Many Western CDMOs have shifted their operations back to the USA and Europe (Reshoring) as intensive business activity in China has driven up labor costs. Western pharmaceutical companies prefer this arrangement, all things being equal, as cost is the main driver. This is a significant development that has spurred new growth of CDMOs in Western Europe and the USA. Still, China and India remain important players as long as they offer lower costs.

Future Global Situation

But there is more — China is now suddenly exporting API's and doing proprietary drug discovery. Surely this will bear fruit. How will India's business niche fare? No one knows. On the other hand, there have been problems in China (and India) with quality and clinical data violations resulting in large numbers of FDA Warning Letters, suspension of some imported products, and IP worries. On top of these challenges, the Chinese Government in 2016 enacted new environmental laws to protect her citizenry and waterways against widespread pollution. The legislation also made it illegal to manufacture drugs in urban areas after at least one major urban factory explosion left many dead.

The Chinese government shuttered hundreds, maybe thousands, of plants. This caused Western CDMOs to react and start re-building facilities outside China. Hovione, for example, just built a new pilot plant in New Jersey. Lastly, one doesn't hear much about the strategic risk of over-reliance on Chinese manufacturers of pharma chemicals, but in some cases, they remain the sole worldwide producers. This is risky — any production or geo-political problems could cause shortages. We hope Western governments may eventually help defray the cost of building new CDMO plants in the West to protect supply, like China does for its own people, but so no such thing has yet occurred. Reshoring represents an important and growing strategic advantage for CDMOs.

"The West leads the way in innovation."

Positive Business Conditions in the US

Lastly, it appears that the US government will maintain re-imbursement policies that drive drug discovery and development — this recurrent worry besets the industry every four or eight years. Private insurance companies follow suit. Clearly, this policy favors the CDMO business. To remain profitable, payors must compensate the brilliant discoveries that drive the industry and keep new ones coming. The West leads the way in innovation. We enjoy rule of law, patent protection, and monopoly pricing during the patent period. This all makes business possible and helps recover cost while driving shareholder value. We also have well-functioning capital markets to invest in promising research.

"Reshoring represents a growing strategic advantage for CDMOs."

We expect continued strong growth for CDMOs in the coming year and beyond. This may be the best year ever!

Mark Alexay, President & CEO, ChemOutsourcing, Teaneck, NJ/USA

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www.chemoutsourcing.com

ChemOutsourcing is the largest annual US-based API show attracting 700+ chemists, business development personnel and buyers from the pharmaceutical, biotech, chemical, and chemistry services industries. It focuses on API development spanning early drug discovery through chemical development and commercial supply. ChemOutsourcing 2018 takes place September 17-19 at the Ocean Place Resort, Long Branch, NJ/USA.

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A Promising Perspective

Geopolitical Risks and Mechanistic Changes in Pharma Supply Create Positive CDMO Outlook

Despite the favorable economic environment, the global economic risk factors have intensified against the background of record global debt and a rise in geopolitical risk. Amid growing uncertainty and regionalization, values such as trust, reliability, consistency, and cultural and regional proximity continue to gain importance.

The demographic developments continue to ensure further long-term volume growth in the pharma market. An increase in the number of older people with higher life expectancy in industrialized countries, environmental pollution, and an increase in wealth in emerging markets result in an increase in acute and chronic diseases as well as the respective demand for effective medicines. Due to state-imposed efforts to boost generics and cut health care costs, generics now make up around 80% of the prescription drug market volume, but only account for 28% of global sales.

Number of Approved Generics and Biosimilars Increases

Due to the accelerated market approval process, the number of approved generics in the United States has grown by around 40% since 2015. A similar development is expected for biosimilars, the generic versions of biologics affected by patent expiries. In the United States, biosimilars sales and their market penetration remain modest for the time being. In an effort to reduce health care costs, however, the FDA has its mind set on changing this situation: It intends to simplify and accelerate the approval process for biosimilars. 61% of the 46 approved drugs in 2017 were subject to expedited development and review methods for accelerated market approval.

Small and medium-sized biotech companies account for a significant percentage of innovation, and they increasingly introduce their products into the market by themselves. In 2017, they made up 51% of FDA market approvals. In only 28% of FDA approvals, the large pharma companies were the originators, while inlicensing and acquisitions accounted for the remaining 21%.

New Supply Chains and Additional Services

The trend to repatriate drug substance and drug product manufacturing from Asia to the West has gained more momentum amid supply, quality, and intellectual property concerns, intensified regulatory pressure from US and European authorities, and rising costs. More than two-thirds of the drug GMP warning letters the FDA issued outside the United States over the last 5 years concerned Asian producers. The Chinese enforcement of environmental protection set to high priority by President Xi Jinping are expected to cause a reduction by half of today's chemical manufacturing plants in China. First effects of the effort are being seen along the Yangtze River causing shortages in basic chemicals and intermediates resulting in interruptions of business supply chains.

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Markus Blocher, Dottikon

At the same time, many large pharma companies no longer regard API production as a core business area as long as it does not require proprietary technology. Small and medium-sized biotech companies are not interested in owning and tying up capital in expensive cGMP production facilities. Yet given the more stringent regulatory requirements, additional services and documentation are necessary in API development and manufacturing. This explains the growing demand for process development, process and API analytical methods, API manufacturing and documentation, as well as further-reaching services at custom development and manufacturing organizations (CDMO). CDMO also play an important role in the diversification of approval risks and quantity requirement volatility related to intensifying competitive pressure. In addition, they can support biotechs thanks to their experience in the compilation of chemical manufacturing control (CMC) documents required for the application for approval. If the required quality is delivered at the first attempt, painful opportunity costs and intense delays can be avoided in the market approval process. Reliability, an impeccable quality track record, and profound experience are the key criteria in selecting a CDMO.

> *„Quality requirements and regulations continue to increase."*

CDMO Strategy Models

Currently, three basic CDMO strategy models can be observed: (i) speciali-

Continued Page 10 ▶

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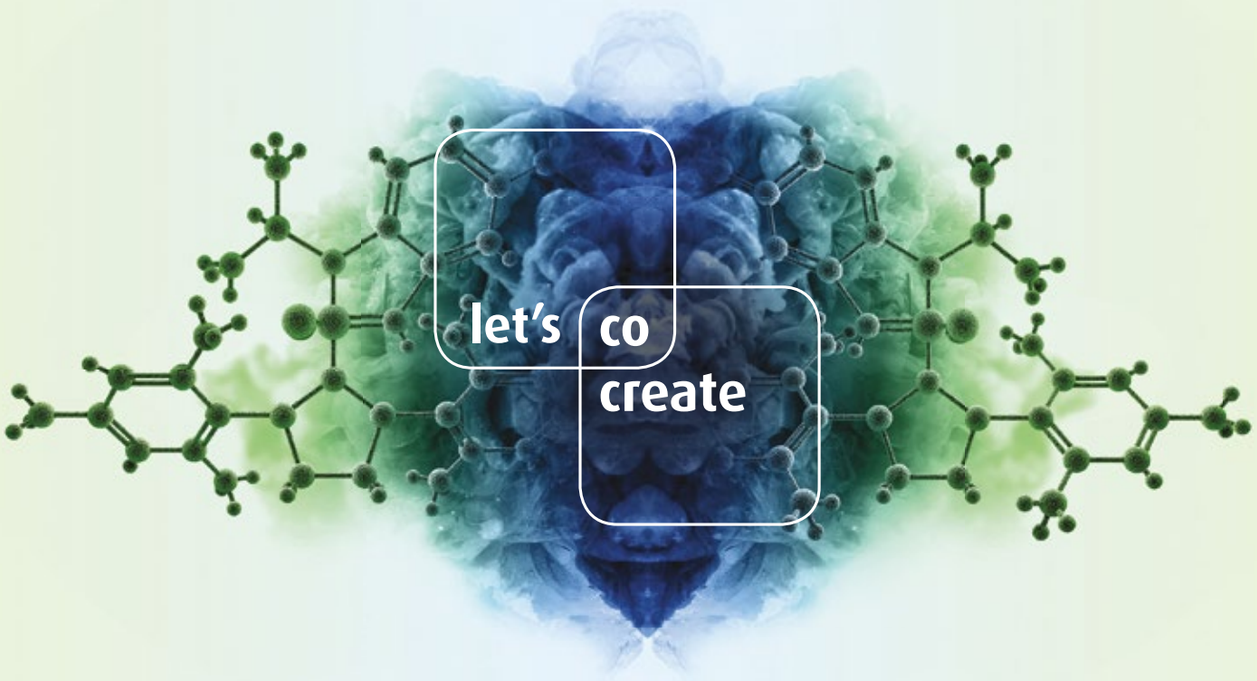

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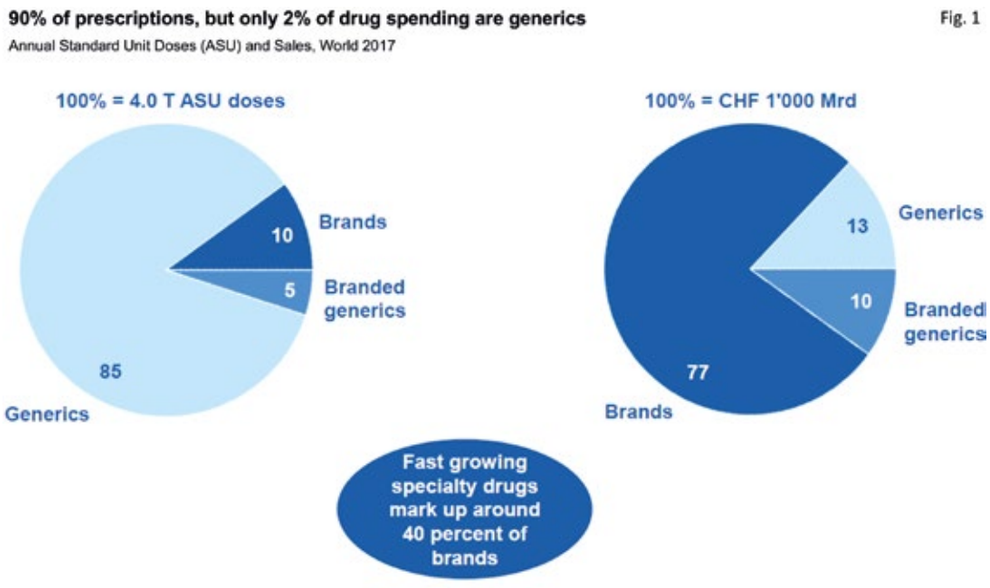
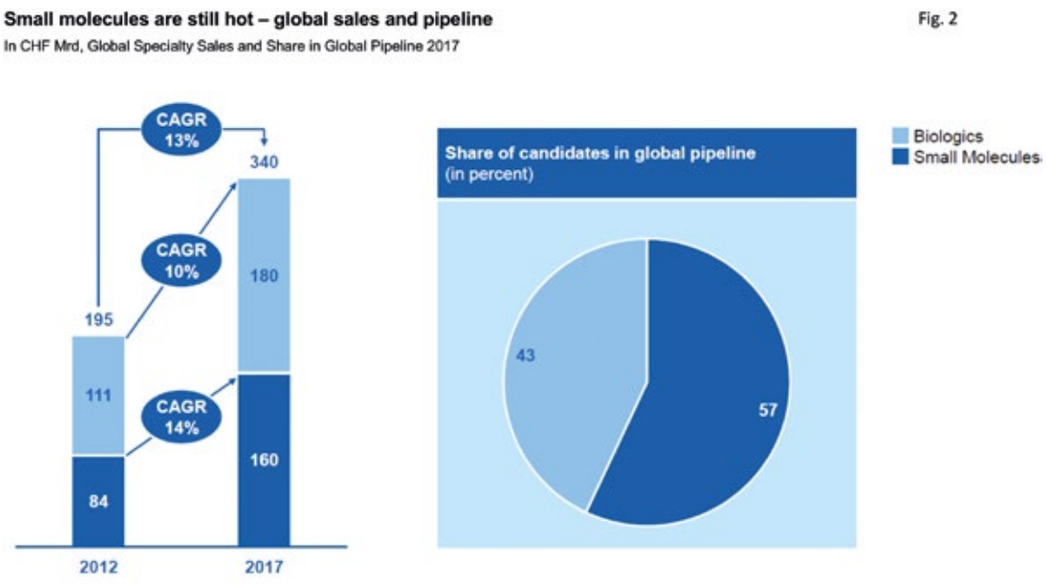


zation with a strong focus on a few value chain segments and niche technologies; (ii) horizontal consolidation, external growth based on capacity acquisition in the same value chain segment; and (iii) vertical integration, backward or forward integration in adjacent value chain segments, usually by acquisition. Many large CDMO with a global footprint currently execute a hybrid strategy between horizontal consolidation and vertical integration, while smaller and medium-sized CDMO tend to focus on technology and performance leadership. The real art lies in offering the entire range of development, manufacturing, and respective services for one or several value chain segments — with competent, high-quality execution and without dissipating energy. Time will tell whether (i) process and analytical development and drug substance manufacturing; (ii) drug product formulation and finishing; and (iii) the respective filling, packaging and distribution create sufficient synergistic value if they are offered, in total or partially combined, by the same company. It is clear that these three main value chain segments require completely different competences, facilities, and skills, both technologically and functionally. Offering these services from different operationally independent sites solely under the same CDMO brand does not add enough value for customers.



Quality requirements and regulations continue to increase, resulting in longer cGMP sequences in chemical API synthesis and higher cGMP manufacturing volume requirements. The increasing repatriation and outsourcing of small molecule APIs, along with the shortage of process development and manufacturing experience and capacities among biotech and pharmaceutical companies, have already created first bottlenecks in high-quality, technologically proficient chemical process development and API manufacturing capacities. This trend is set to become even more apparent over the coming few years, as many CDMO have been rattled by several changes of ownership and the subsequent restructuring or are, based on the crucial experiences over the last two decades, still unwilling to make capital-intensive investments in high-quality development and manufacturing capacities.

The topline pharma market development together with the mechanistic changes in the pharma value chain results in a promising perspective for high-quality, technologically experienced, and specialized providers of exclusive synthesis, especially in API manufacturing. In outsourcing APIs that are still under patent protection, pharmaceutical companies prefer partners that are able to provide the full range of services from chemical synthesis route-finding, chemical process and analytical development, and multi-step manufacturing to the API, including validation and stability studies. On the one hand, the partners should possess a cutting-edge development and manufacturing infrastructure, an impeccable quality track record, and a broad technology platform, while on the other hand offer profound experience in the development of chemical processes and the manufacturing of APIs. In addition, pharmaceutical companies cooperate with a select group of strategic partners throughout all stages from development up to market introduction and supply.

Markus Blocher, CEO, Dottikon Exclusive Synthesis AG, Dottikon, Switzerland

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Adapting to an Ever Changing Environment

How the Pharma M&A Rush is Shaking Up the CMO Industry

At Chemoutsourcing conference 2017, Jean-Jacques (John) Mondoloni, Managing Partner at Wombat Capital, chaired and moderated a round table on the topic "How Is The M&A Rush Shaking Up the CMO Industry?" This open question sparked a lively discussion about the trends and results of such consolidation. For CHEManager, he summarizes the key findings from shareholder and customer perspective. Michael Reubold also asked him to provide an outlook on how the industry consolidation may change the CMO landscape in the future.

CHEManager: Mr. Mondoloni, for more than a decade, M&A activity in the pharmaceutical industry has been at a high level. What are the major drivers of this industry consolidation? Have these drivers changed over time?

John Mondoloni: M&A activity in Pharma and the drivers of industry consolidation have evolved as companies have grown and adapted to an ever-changing environment. The cost of drug development, the length of time to get a product to approval, and stricter regulatory requirements have pushed pharma companies to pick their battles, with a focus on core expertise and acquisition — or divestiture — in complementary areas.

The drivers are diverse and vary based on the size of the company and its sector but include gaining access to critical size rapidly and reducing competition; accessing foreign markets, including emerging markets with exponential growth; entering new therapeutic areas and bringing next-generation technologies in-house. These drivers are the source of "horizontal" consolidation.

On the other hand, the need for efficient capital allocation has created a tremendous boost to the pharmaceutical outsourcing sector. Pharma companies are selling facilities to private equity firms or up-and-coming contract manufacturing organizations along with supply agreements. This results in the formation of new entrants and players becoming larger through consolidation. New segments of the pharma industry have flourished thanks to the reorganization of pharma companies.

Jean-Jacques (John) Mondoloni, Wombat Capital

M&A are one element of pharma companies to strengthen their position in the changing markets and create value. From a shareholder point of view, have most of the M&A transactions met the expectations?

"CMOs have to consolidate to stay relevant to the large pharma and specialty pharma companies."

J. Mondoloni: It is difficult to generalize or draw statistics and conclusions, as all transactions are different like all shareholders are, with different

objectives, time horizon and expectations. A buyer acquires a target company to respond to a specific need at the time of the transaction. Responding to this need could potentially create value to shareholders over the long term or short term, could enable the company to maintain its competitiveness and not destroy value, or could result in a failed merger. In all situations, it is not the M&A transaction on its own, which creates or destroys value but rather it is the vision, the implementation of a strategy by a board or management, the understanding of the other side and the sharing of aligned objectives which leads to a successful or unsuccessful outcome.

Will the consolidation in the pharmaceutical industry level off or will it even intensify?

J. Mondoloni: With favorable economic conditions, strong capital markets, solid corporate profits, and low interest rates, the M&A sector is expected to continue to flourish. Consolidation in the pharmaceutical industry from a volume-of-deals point of view could slow down in certain sectors while continuing to grow in others. From a value point of view, I expect it to grow as players are becoming bigger. In pharma outsourcing for example, looking at the API sector, with all of the recent consolidations, there are fewer and fewer independent API manufacturers available, but the ones that have been acquired in the last few years could be part of another wave of consolidation of larger entities. The final-dosage-form manufacturing segment, which was, for a long time, part of the internal capabilities of pharmaceutical companies, is becoming a strong opportunity for growth in the CMO segment where we should see an uptick in terms of transactions.

For better/faster results in R&D, collaborative product development can be essential. And outsourcing of chemical syntheses is common practice. How can pharma companies and their CDMO/CMO partners make sure that collaboration remains effective during a merger or acquisition?

J. Mondoloni: As part of a merger and acquisition process it is critical to maintain confidentiality at every level, as all parties are concerned: the pharma client, who does not want its program to be revealed to any third party, and the seller, who wants to make sure that it remains protected against any market rumors which could affect its relationship with present and future customers, the dedication of its employees and the overall performance of the company. It is a sensitive subject where discussions should happen with the client to safeguard information, but where the seller is also looking to have the smallest number of parties gain knowledge of an impending transaction. Since the relationship with the pharma client was initiated based upon communication and trust, these are the bases to funnel collaborative efforts, avoid any disruptions and maintain confidentiality. The type of buyer could also influ-

Continued Page 14 ▶

ence the CMO-client relationship. A generic buyer acquiring a CMO to get additional capacity, particularly for its own pipeline, could create concerns of continuity of services, and confidentiality if the buyer is a competitor of the pharma client. Close communication is the source of success.

Does the consolidation in the pharma industry create a necessity for CDMOs/CMOs to consolidate? Do CDMOs/CMOs have to consolidate in order to stay in the game?

J. Mondoloni: Each industry or in this case segment of industry has its own drivers for consolidation. I don't believe that the consolidation in the pharma industry will drive the consolidation of CDMOs/CMOs. In the highly fragmented contract services market, CMOs have to consolidate to stay relevant to the large pharma and specialty pharma companies. CMOs have already set themselves apart by becoming more integrated, offering unique technologies, efficiency, superior customer service and expertise on complex synthesis and manufacturing. They have also demonstrated that they have extended their geographic reach taking into account the global nature of the pharma industry but also to benefit from lower manufacturing costs, skills and specific know-how. Being larger enables the CMO to also apply more dedicated resources to quality, project management, capital expenditure, etc. to be able to remain competitive in a highly regulated environment.

In recent years, the top CMOs have been on an M&A splurge. What are the drivers and the predominant trends regarding the underlying geographical or technological strategies?

J. Mondoloni: CDMOs/CMOs have to consolidate to remain competitive. Consolidations in the CMO segment could lead to the set-up of a "one-stop-shop" model, being able to serve the client as the product goes through the various clinical trials, from discovery to commercial, while having complementary manufacturing capabilities from APIs to final dosage form. From a geographic point of view, CMOs from around the world are looking at the US market for acquisition, as it is the largest pharmaceutical market in the world. When a majority of foreign CMO customers are Americans, a foreign CMO needs to go beyond having just a sales office in the US by having its own R&D and manufacturing platform to reinforce its presence and its image. Extremely low interest rates in Europe have fueled recent cross-border transactions involving European players.

Which trends do you see changing the CMO industry in general?

J. Mondoloni: The growing focus on orphan drugs and targeted therapies has created a need for more nimble, responsive manufacturing capabilities and specialized expertise. This has led to the growing focus on high-value, low-volume APIs, leaving the manufacturing of more commoditized and large-volume APIs to manufacturers in India and China. Likewise, on the formulation front, with the development of a large number of oncology drugs and potent compounds, sterile manufacturing capabilities are expected to become one of the fastest growing segments. The smaller CMOs have to become more specialized, while the larger ones have to be more integrated, all driven by the substantial growth of the pharmaceutical sector as a whole as well as an increase in the amount of manufacturing work to be outsourced.

How can CDMOs/CMOs turn the challenges caused by consolidation into new business opportunities?

J. Mondoloni: While M&A can create challenges, it can also bring opportunities for the seller, the buyer as well as the client. Sellers' employees often welcome a larger, more established company as a potential buyer, creating strong dynamism and energy. A buyer and seller combining their respective businesses enable the client to benefit from complementary expertise, additional capabilities and sometimes additional capacity as well. Business development professionals can cross-sell services or propose delocalization of manufacturing by marketing the facility of the parent company in other countries.

Today's client is seeking more and more to forge strong and long-term partnerships with a very limited number of efficient, full-service providers. A larger entity could much more easily respond to such need and create a more sustainable, long-term, business opportunity.

www.wombatcapital.com

People

Graham Brearley is the new general manager of US drugmaker Catalent's Madison, Wisconsin biomanufacturing facility. Brearley has over 25 years' technical, operations and business experience in the biopharmaceutical industry. In his most recent position, he served as senior director, Technical Operations with Shire. Prior to that, Brearley held leadership positions at Sigma-Aldrich and Baxter. He has a bachelor's degree in applied biology from Thames Polytechnic, UK and a doctorate in biochemistry from the Council of National Academic Awards.

Paul Bradley has been appointed by CatSci, a UK-based process research and development contract research organization, as its new head of business development. Bradley joins the team with nearly 3 decades of experience in drug discovery and development, covering both scientific and commercial roles. He previously held senior positions with Pfizer, Charnwood Molecular and Concept Life Sciences.

Charlotte Leife took over as CEO of Immuneed, a Swedish biotech service company, as the company's new CEO. She succeeded **Gunilla Ekström**, who assumes a CEO position at TET Pharma, a wholly owned subsidiary of Immuneed. Before joining Immuneed, Leife has held positions at Baxter and Biogen as well served as chair of the board at the Swedish American Chamber of Commerce in Boston, MA, USA.

Anderson Gaweco has been appointed by Apeiron Biologics as chief medical and scientific officer (CMSO) and will lead the company's immuno-oncology programs. Gaweco joins Apeiron from Innovimmune Biotherapeutics, New York, USA, as founder & CEO/CSO. Previously, he was CMO at Lifecycle Pharma in Denmark, USA, held positions at Roche, Pfizer, and AstraZeneca.

A Wide Spectrum of Contract Services

Is the End-to-End Service Model the Way of the Future for CDMOs?

With its pending $425-million acquisition of Halo Pharmaceuticals, Cambrex joins other contract providers that have used acquisitions in recent years to build end-to-to end service models that provide both active pharmaceutical ingredient (API) and drug-product development and manufacturing, including Lonza, Catalent, Patheon, and Alcami among others.

By inking the acquisition of Halo Pharma, a Whippany, New Jersey-headquartered contract development and manufacturing organization (CDMO), Cambrex, a contract manufacturing organization (CMO) of small-molecule APIs and intermediates, will enter the finished-dosage form CDMO market. Halo Pharma provides drug-product development and commercial manufacturing services, specializing in oral solids, liquids, creams, sterile, and non-sterile ointments.

"This acquisition opens a completely new segment of the market for Cambrex in finished dose development and manufacturing," said Steve Klosk, president and chief executive officer of Cambrex in a July 23, 2018 statement, in commenting on the acquisition. "Halo's expertise in oral solids, liquids, creams and ointments fits well with our small-molecule API business and brings a substantial new customer base and pipeline of small-molecule products."

Halo Pharma operates two GMP-compliant facilities in Whippany, New Jersey, USA, and Montreal, Québec, Canada. Completion of the transaction is subject to customary closing conditions and is expected to occur during the third quarter of 2018.

Company on the Move

The pending addition of Halo follows a series of investments by Cambrex in its small-molecule API capacity and capabilities. In June, the company announced plans to expand research and development (R&D) capabilities at its site in Paullo, Milan, Italy. The company is investing to construct a new R&D laboratory and recruit additional scientists to increase the number of generic APIs in the company's development portfolio. Cambrex currently manufactures over 70 generic APIs. The company also installed a pilot plant at the Milan site in 2017.

In May, the company announced plans to begin a $5-million expansion of laboratory facilities at its site in Karlskoga, Sweden. In 2017, Cambrex upgraded its continuous-flow capabilities in Karlskoga with a dedicated commercial-scale unit that is capable of producing multiple metric tons of high-purity API intermediates per year, and it installed new, large-scale manufacturing capacity at Karlskoga.

Cambrex is also making other investments as part of its strategic plan to increase its development capacity and resources in North America. The company is progressing a new $24-million facility for manufacturing highly potent APIs at its site in Charles City, Iowa. The project will also see the reconfiguration of an existing small-scale manufacturing area to provide a single high-containment building to support early-stage development and manufacturing. In January, Cambrex announced an investment to expand chemical and analytical development capabilities at its Charles City site. In 2017, Cambrex completed expansions of cGMP small-scale capacity and large-scale manufacturing capabilities at its Charles City site, which followed the opening of a $50-million multi-purpose manufacturing facility there in 2016.

Earlier in 2018, the company completed a pilot-plant expansion at its facility in High Point, North Carolina with the installation and commissioning of a fourth reactor suite, upgraded the site's analytical chromatography data systems for quality control and analytical R&D, and completed the installation of multiple continuous flow reactor platforms. Cambrex gained the High Point site,

Patricia Van Arnum, DCAT

"Both pure-play CDMOs/CMOs and the contract manufacturing arms of pharmaceutical companies have end-to-end service models."

through its acquisition of PharmaCore in 2016. At the facility, Cambrex produces APIs and intermediates in batch sizes from milligrams to 100 kg to support clinical trials from Phase I to Phase III.

Building End-to-End Service Models through Acquisitions

Cambrex joins other contract providers building their capabilities through acquisition and organically to become end-to-end service providers.

Lonza, a CMO of small-molecule and biologic-based APIs, built an end-to-end service model in small molecules through its $5.5-billion acquisition of Capsugel in 2017. With the largest acquisition in the company's history, Lonza positions itself in the drug-product services sector by gaining formulation and oral dosage delivery technologies, including a position in hard-capsule technologies.

In addition to Capsugel, Lonza acquired in 2017, Micro-Macinazione, a Monteggio, Switzerland-based provider of micronization services. The addition of Capsugel and Micro-Macinazione provided Lonza an integrated offering in small-molecule technologies by adding capabilities in dosage form and drug-delivery systems to complement Lonza's existing custom API development and manufacturing services.

Lonza also has made internal investments to build capabilities for drug-product development and manufacturing to complement its API capabilities in small molecules and biologics. In November 2016, the company opened drug-product services laboratories in Basel, Switzerland, which included a new facility focused on formulation development, drug-product analytical development, and quality control. Lonza first announced plans to expand its pharmaceutical and biotechnology segment by offering development and manufacturing services for clinical outsourcing of drug products in February 2016 with a focus on parenteral dosage forms, including products for injection and infusion for intravenous, subcutaneous, intraocular and other routes of parenteral administration. Services include options for monoclonal antibodies, other biologics, drug conjugates, peptides and small molecules that require a parenteral dosage form.

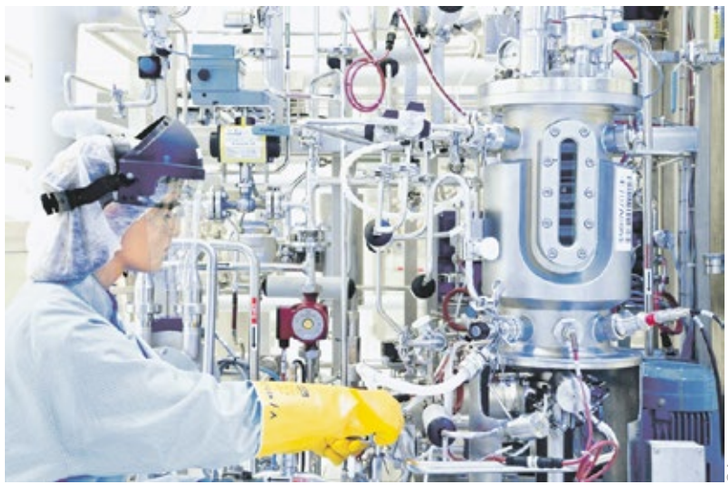
Catalent, a CDMO of drug products and biomanufacturing services, made a large play in becoming an end-to-end provider with its $950-million acquisition in 2017 of Cook Pharmica, a Bloomington, Indiana CDMO of biologic drug substances and parenteral drug products. The acquisition of Cook Pharmica provides Catalent capabilities in biologics development, clinical and commercial cell-culture manufacturing, formulation, finished-dose manufacturing, and packaging. The acquisition complemented Catalent's existing capabilities in cell-line engineering, bioconjugate development, analytical services, biomanufacturing, prefilled syringes, and blow/fill/seal technologies. With the Cook acquisition, Catalent gained a development and manufacturing facility in Bloomington, Indiana, as well as additional expertise in liquid and lyophilized sterile formulation, fill/finish across vials, prefilled syringes, auto-injectors, cartridges and safety devices, and biomanufacturing capacity to augment the company's biologics business.

Continued Page 18 ▶

Catalent operates a biologics manufacturing facility in Madison, Wisconsin and has proprietary cell-line technology, GPEx. Its operations also include fill/finish services in Brussels, Belgium and Limoges, France; conjugation technology in Emeryville, California; and a network of biologics analytical locations. Following the acquisition, Catalent created a new, dedicated business unit focused on Biologics and Specialty Drug Delivery, which spans biologics development, analytical services, and drug-substance and drug-product manufacturing, in addition to Catalent's respiratory and ophthalmic platforms.

Patheon, which was acquired by Thermo Fisher Scientific for $7.2 billion in 2017, started its strategy of becoming an end-to-end provider in 2014 with the formation of DPx Holdings, privately owned by the private-equity firm JLL Partners (51%) and Royal DSM (49%), which was the result of a $2.65-billion deal between Patheon and DSM, completed in March 2014. The move provided Patheon with small-molecule API development and manufacturing capabilities as well as the biosolutions and biologic businesses of the former DSM Pharmaceutical Products. It added the API piece to Patheon's historical core competency in formulation development and drug-product manufacturing.

Since then, Patheon has further built the API side of its end-to-end business with additional acquisitions. In 2017, Patheon added to its small-molecule development and manufacturing capabilities by acquiring Roche's API manufacturing facility in Florence, South Carolina. The site is Patheon's flagship US API operation for commercial-scale and mid-scale API production.



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Sampling of the 15L pressed fermenter at Lonza BioPharma in Visp, Switzerland.

In 2015, Patheon acquired Irix Pharmaceuticals, a Florence, South Carolina-headquartered company, specializing in making difficult-to-manufacture APIs. With the acquisition, Patheon secured additional API development and manufacturing services in the US, including high-potency and controlled substances and commercial API manufacturing at sites in Greenville and Florence, South Carolina.

The acquisition of Gallus BioPharmaceuticals, a biologics CMO, completed in 2014, provided Patheon with US-based biologic drug substance sites in the US and complemented Patheon's two existing biopharmaceutical production sites in Groningen, the Netherlands and Brisbane, Australia, which the company secured through the DSM transaction

Another end-to-end provider is **Alcami**, which became so through the combination in 2013 of AAIPharma Services Corporation (AAI), a CDMO of drug products, and Cambridge Major Laboratories, a contract small-molecule API manufacturer. Alcami, which became the name of the combined company in 2016, is headquartered within Research Triangle Park in Durham, North Carolina, with 10 locations globally. Alcami's services include: API development and manufacturing, solid-state chemistry, formulation development, analytical development and testing services, drug-product manufacturing (oral solid dose and parenteral), packaging, and stability services.

AMRI, historically a contract small-molecule API producer, built its capabilities on the drug-product side through several key acquisitions in parenteral drug development and manufacturing. AMRI entered the parenteral drug-product space with its 2010 acquisition of Hyaluron, which provided AMRI capabilities for manufacturing and sterile filling of parenteral drugs. In 2014, it acquired Oso Biopharmaceuticals (OsoBio), an Albuquerque, New Mexico-based contract manufacturer of injectable drug products with large-scale commercial production. In 2015, AMRI acquired Aptuit's aseptic clinical manufacturing site in Glasgow, UK. The addition of the Glasgow operation strengthened the company's front-end formulation expertise in its sterile injectable business to provide a single source for sterile fill/finish needs from formulation to commercial supply. AMRI now has four business segments: drug-discovery services, APIs, drug products, and fine chemicals.

© Siegfried

Siegfried's Evionnaz facility is specialized in the synthesis of APIs and intermediates.

Joining Established End-to-End Providers

Other companies also have end-to-end service models, both pure-play CDMOs/CMOs and the contract manufacturing arms of pharmaceutical companies. **Almac**, for example, a Craigavon, UK-headquartered company, offers small-molecule and peptide API development and manufacturing as well solid-dosage development and manufacturing. **Recipharm**, a Jordbro, Sweden-based CDMO, also offers API development and manufacturing through its Paderno Dugnano, Italy facility, an API development facility in Uppsala, Sweden, and a beta-lactam plant for the lyophilization of bulk APIs in Lainate, Italy. On the drug-product side, it provides development and manufacturing services for solids, semi-solids, liquids, injectables, and ophthalmics.

CordenPharma is a contract provider of both small-molecule APIs and drug products (including solid-dosage products and sterile injectables), and it has made several recent expansions to add to its capabilities on both sides. In November 2017, the company acquired a former Pfizer facility, an API manufacturing facility in Boulder, Colorado. The site specializes in the development, scale-up, optimization, and production of highly potent and cytotoxic/cytostatic APIs from development quantities to commercialization. The acquisition of the Boulder facility is aligned with a broader corporate strategy of offering fully integrated supply (APIs, drug products, packaging, and logistics), including a broad range of expertise in the development and manufacturing of highly potent and oncology products.

Also on the small-molecule API side, in 2017, the company announced an investment of €3.7 million ($4.2 million) in the manufacturing site infrastructure of its CordenPharma Switzerland facility located in Liestal, Switzerland. The investment includes an expansion of the square footage dedicated to small-molecule, peptide, and carbohydrate development services as well as an approximate €2-million ($2.3-million) investment in new automated development and optimization equipment. On the drug-product side, in 2017, the company completed the addition of an early-development suite for highly potent, oral solid dosage products in CordenPharma Plankstadt (Germany). The new facility allows for the production of small batches, from 100 g to approximately 1,000 g.

Another example of an end-to-end provider is **Siegfried**, headquartered in Zofingen, Switzerland, which provides both small-molecule API and drug-product (solid-dosage and sterile manufacturing/aseptic filling) development and manufacturing servi-

ces. On the API side, it has facilities in Switzerland (Zofingen and Evionnaz), Germany (Minden), France (St. Vulbas), the US (Pennsville, New Jersey), and China (Nantong). On the drug-product side, it has sterile manufacturing/aseptic filling at facilities in Germany (Hameln) and the US (Irvine, California), and solid-dosage manufacturing at facilities in Switzerland (Zofingen) and Malta.

Siegfried has further developed and expanded the company's global production network resulting in an integrated supply offering forward and backward integrated service and critical size expansion. The company has built its API and drug-product capabilities organically and through acquisitions. Among recent investments, in 2016, Chinese authorities issued Siegfried a final operating license for large-scale production at its API manufacturing plant in Nantong, China. Also, in 2016, the company's headquarters in Zofingen put into operation a new production building constructed in vertical flow technology in accordance with the latest technology. Siegfried also integrated three manufacturing sites (Evionnaz, Switzerland; Saint-Vulbas, France; and Minden, Germany) for intermediates and APIs that the company acquired from BASF in 2015. The acquisition of the BASF sites followed two earlier acquisitions on the drug-product side: the 2012 acquisition of California-based Alliance Medical Products, which added to the company's sterile-filling capabilities, and the 2014 acquisition of Germany-based Hameln Pharma, a provider of development and production of sterile liquid pharmaceuticals, which strengthened Siegfried's sterile-filling segment. In March 2018, Siegfried added to its drug-product manufacturing network with the acquisition from Arena Pharmaceuticals of a solid-dosage manufacturing facility in Zofingen.

The company says it plans to grow within the value chain of its existing businesses by reaching critical size in the drug-product sector and through backward integration. Siegfried plans to diversify into adjacent new businesses by enhancing its technology base in micronization, lyophilization, spray drying, and by adding additional high-potent manufacturing capabilities.

Piramal Pharma Solutions, the contract manufacturing arm of the Indian pharmaceutical company Piramal, is another example of an end-to-end provider. In 2016, Piramal acquired the Riverview, Michigan-based contract small-molecule manufacturer, Ash Stevens.

Pfizer CentreOne, the contract manufacturing arm of Pfizer, provides custom small-molecule APIs and contract services for sterile injectables and highly potent oral solid dosage forms. Pfizer added to its sterile injectables contract business through its $17-billion acquisition of Hospira in 2015, which added to the company's drug portfolio for sterile injectables and biosimilars but also provided contract sterile manufacturing services.

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From East to West

The Changing API and Early Intermediate Supply Chain Landscape

The topic of supply chain security is not a new one for the pharmaceutical industry, and much of that discussion has been dominated by the cGMP portion of the API supply chain. The discussion regularly addresses reduction of risk, superior quality systems, dependable supply, innovation and competitiveness. These elements are often referred to as the "Value Chain." Recently, however, the conversation has begun to expand beyond the cGMP portion of the supply chain to a wider focus including the early supply chain, specifically for the supply of non-cGMP materials for API production. Due to changes in conditions related to the supply of these materials from typical sources, supply chain experts are now in need and in search of non-cGMP materials that once again secure the supply of their APIs by embracing Value Chain principles — including from suppliers based in the West, a departure from historical trends.

In the late 1990's, global chemical capacity expanded dramatically, causing a substantial excess. The expansion mostly took place in India and China, and the raw materials and non-cGMP intermediate production shifted towards the East as a result, with Western producers largely focusing on downstream cGMP manufacturing.

During this same outsource expansion period, quality systems evolved considerably with more oversight needed for the entire supply chain, not just the regulated components. Supplier audits of quality systems were beginning for the non-cGMP suppliers as well, recognizing quality gaps as an issue. Risk mitigation strategies were widely implemented to reduce supply risk, which often meant companies needed to find a second source of materials supply. However, the dependence on the region, particularly Chinese suppliers, continued.

In the early 2000's chemical capacity in India shifted focus to downstream cGMP manufacturing. This meant that supply chains for non-cGMP materials became even more dependent on suppliers in China. Chinese producers embraced a great deal of chemical technology and were willing to perform difficult to manage chemistries such as nitrations, flourinations, cyanide chemistry, Grignard reagents, and many others that were difficult for Western producers to manage, particularly due to EHS constraints. Therefore the "value" that the downstream manufacturers were receiving was quite good as the supply was mostly dependable, the quality minimally acceptable, and the price very attractive.

Sean Diver, Lonza

Risk-based supply chains continued to evolve through the 2000's into the 2010's and many customers noted that the Chinese chemical industry required an enhanced ap-

The Visp, (Switzerland), complex can manufacture early intermediates for both internal and external cGMP advanced intermediate and API supply.

proach to EHS and quality, and the "value" of the supply chain was weakened as costs rose. Chinese supply of raw materials used in pharmaceutical production, however, had become well established. It has recently been estimated that 80% of active ingredients used in US pharmaceutical consumption come from China and India, with Indian companies also relying heavily on raw materials from China.

Over the last few years, the security of supply of non-cGMP materials to customers has changed. As the Chinese government embraces more stringent EHS requirements, many manufacturing facilities have been closed due to poor environmental conditions, and the government has levied substantial environmental taxes on those who remain. The supply of materials from China has seen substantial price increases at a minimum, and often customers' supply chains have been left with no qualified suppliers of non-cGMP materials. Also, overreliance on a small set of producers can lead to shortages in supply — for example, when a Chinese API manufacturer's facility exploded in October 2016, a global shortage of an antibiotic drug occurred, since that site was the sole source of the drug.

With the "value" of the value chain no longer driven primarily by price differentiation, the supply of non-cGMP materials is once again shifting — this time reducing the strong regional dependence of Asia, and particularly China, and embracing more Western producers so that the risk of the supply is diversified and reduced. While many Western producers reduced or removed older non-cGMP chemical capacity, some have remained engaged in the supply of non-cGMP materials for pharmaceutical supply chains.

Western partners with deep experience in technology, manufacturing and innovation for the pharmaceutical industry can decrease regional dependency for API supply, increase quality systems and provide the manufacturing and delivery service needed for ensuring uninterrupted availability of critical medicines for patients. Companies can benefit from engaging suppliers with assets for cGMP production as well as non-cGMP materials. Lonza is a case in point with over 600 m^3 of chemical capacity at the Visp, Switzerland, complex that operates under a strict ISO quality system. The complex can manufacture early intermediates for both internal and external cGMP advanced intermediate and API supply, in response to changing demand dynamics for non-cGMP services. The right suppliers can also enhance the value chain by engaging the appropriate technologies in the appropriate facilities that drive competitiveness. Value Chain improvements are critical for all pharmaceutical products. The evolving global API production landscape offers new opportunities for companies to partner with suppliers who will add value throughout the API supply chain and reduce overdependence on Chinese raw materials.

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A list of references can be requested from the author.

Thriving Amid Consolidation

How CDMOs Tackle the Current Market Developments

Recently, the pharmaceutical contract development and manufacturing organization (CDMO) industry has been extremely active in M&A, as is the pharma and generics industry itself. The recent acquisitions of Capsugel by Lonza and of Patheon by Thermo Fisher Scientific constitute only the tip of the iceberg of the rising M&A activity in the CDMO industry.

Amid consolidation, the industry thrives.

There continues to be a demand for contractors that offer full-service manufacturing, but industry expectations for such suppliers are evolving. In recent years, many drug companies have tried to reduce the number of suppliers they work with, forming strategic partnerships with contractors that offer a broad range of services. The aim is to speedup time-to-market, increase efficiency, and minimize oversight burden.

While this trend continues, other factors such as the increasing quality expectation from customers and authorities and the demand for traceability have emerged, influencing the range of capabilities that a full-service contractor is expected to provide. Further, pricing pressures (particularly in the generics sector), the advent of new production technologies, and the entrance of new players are changing the market dynamics and put even more pressure on CDMOs, worsening also the overcapacity problem. CHEManager asked executives and thougt leaders in the chemical and pharmaceutical market to share their opinion, experience and advice. We wanted to know:

- What current market developments are most challenging for Pharma CDMOs and how can they tackle them?

Read the insightful answers of the experts here.

CDMOs Need the Ability to React Quickly

Timothy Compton, vice president Sales, Avista Pharma

One of the most challenging areas we face in the pharma CDMO space today is “timing”. Every innovator that approaches a CDMO has a specific timeline to deliver in order to achieve their next milestone and ensure the success of the program or, in some instances, the success of their organization. While it’s not economically practical to have a team of scientists waiting at the bench for programs to arrive, a CDMO needs to be able to react quickly to the innovator’s requests and achieve their timelines. Here at Avista Pharma it’s a delicate balance to maintain enough depth at the bench to deploy resources immediately upon contract execution, while ensuring we don’t have much idle bench and manufacturing suite times. To date, we have scaled our resources (facility, equipment and scientists) to the demand and it’s an area we evaluate weekly.

CDOs and CMOs Demand a Specific Focus and Individualized Support

Andreas Lekebusch, business manager Healthcare, Biesterfeld Spezialchemie

Being a distributor for specialty chemicals across Europe, one of our central business sectors is the sale of raw materials for pharmaceutical production. There, we rise to the challenge of working with contract development organizations and contract manufacturing organizations, which demand a specific focus and individualized support. There are high standards in this sector regarding the selection of raw materials, assistance during development and production, support when facing regulatory and qualification issues as well as the guarantee of a qualified supply chain. Our response to this involves ensuring balance in our portfolio so that we can offer products both for new developments and production as well as for solving formulation problems, where our expert teams can also help through technical support.

In addition to a specialized product portfolio, there is a strong demand in the pharmaceutical industry, in particular for a GDP- and GMP-certified distributor, to ensure the quality and safety of pharmaceutical products. We have made it our strategic undertaking to stay abreast of these requirements. Therefore, during the last year, we established an ongoing qualification process for SAP in order to ensure that our IT processes are in line with the pharmaceutical industry. In addition, we have also been awarded the GDP certification by an independent audit.

Big Pharma Continues to Consolidate Supplier Lists

Simon Edwards, vice president Global Sales & Business Development, Cambrex

There have certainly been years when conditions are better or worse but innovative, flexible, customer focused organizations that operate at the highest quality level in a price competitive market are likely to succeed.

The small molecule CDMO market continues to grow for perhaps the most sustained period since the 1980s and 90s. In such periods it is normal to anticipate the onset of a downturn, however, there is no sign of that, but key factors, such as the number of NCEs approved, related investment in clinical development, and propensity to outsource could change. Competition among CDMOs is always increasing and at Cambrex we believe that we need to maintain a leadership position by ensuring the highest quality, and making a difference with our customer service, innovation and delivery. Our experts really make the difference.

Big Pharma continues to consolidate preferred supplier lists which can mean a CDMO finds itself excluded from a particular customer for years. However, CDMOs are not in a position to be a preferred supplier to more than just a few Big Pharma companies, otherwise the volume can be too high. Also, the supplier lists change. The customers find that there is a technology its suppliers cannot provide or they are operating at full capacity and cannot meet a new deadline, this is when new suppliers shave the opportunity to break in. It is not really any different to winning any new customer. But tenacity and patience are key during the years you are somewhat frozen out.

Increase in Finished Dose Outsourcing

Chris Halling, director Global Communications & Marketing, Catalent

Generally, today's drug development pipeline is more complex, often using molecules with particular delivery challenges. With so many programs driven by small, venture-capital backed companies without the resources of large pharma, finished dose outsourcing will increase. The number of new drugs approved per billion US dollars spent is falling, mainly because of a lack of efficacy, often discovered at phase 2 or later, when significant resource has been invested. The industry needs to work to find programs that offer the best chance of the active reaching, engaging with the target, and eliciting a response, or otherwise killing the program before spending more. It's far too expensive to develop all candidates that show promise, and is why customers often turn to development partners to help get to a "go/no go" decision fast.

But no drug shows efficacy if it stays in its pack! There is increasing recognition that for a patient to comply with their dosing regimen, we need to make drugs in forms that aid compliance to the end of the course of treatment. Whereas it was once enough to be able to treat a condition, it's now increasingly about "How can I live a normal life with my condition?". Many patients endure having to take medicines at whatever prescribed interval, that may be hard to swallow, taste awful, or induce some undesirable side effect, but apply those same conditions to the young, the old, or the already infirm and most would agree we need to find better treatment technologies.

Contractors Need to Proactively Evaluate Process Steps

Ross Burn, CEO, CatSci

API batch failure is a problem that has plagued the pharmaceutical industry for decades, with a historically high rate of manufacturing defects causing significant financial losses and potentially delaying drugs reaching the market. Process optimization, in which the steps in a manufacturing route are refined to improve efficiency and robustness, is a crucial tool in helping to avoid this problem. However, a great challenge faced by contract organizations is ensuring that their customers' assets undergo fit-for-purpose process development at each stage of drug development.

The traditional linear model of drug development, in which a manufacturing route is defined sequentially, with lean investment in the early stages and intensive process optimization at the end stage, is still commonly used in the industry. However, with this model, any process steps that fail upon scale-up will often not be uncovered until late into development. By proactively evaluating process steps early, contractors are able to immediately address any problems and reduce the risk of batch failure occurring further down the pharma pipeline.

A further challenge presented to contract organizations is that customers often resist investment in making process improvements early in drug development. High drug development attrition rates and the continuous need for process development can lead customers to believe that it will not add immediate value to their product, or provide a return on investment. An outsourcing organization must therefore build up strong relationships with all customers, effectively communicating how affordable process development can be incorporated into their programs — thereby reducing the risk of future batch failure in addition to improving efficiency and achieving an acceptable return on investment.

The Flexibility to Adapt to Each Project Dealing with Different Customers

Gabriel Haering, CEO, Cerbios

A simple question but difficult to answer in a simple way. Outsourcing of drug substance and drug product manufacturing is strategic for start-ups and small to medium pharma companies with no in-house manufacturing capabilities. Internal know-how and competences are usually very technical and cGMP manufacturing is not an internal competence usually compensated with consultants.

As CDMO the first challenge is receiving a proper tech package. Expectations are to go directly to the cGMP production based sometimes on medicinal chemistry processes developed at milligram scale.

The second challenge starts from the quotation submission and negotiation. If a familiarization run at R&D to confirm a proper technology transfer is understood, the proposal to work on the development in order to make the process viable at industrial scale is seen as unnecessary.

Start-ups have cash — sometimes limited — and their priority is to spend it in clinical trials not in API development and manufacturing in a proper way.

There is often a lack of understanding of the ROI for investments done in the development and manufacturing at companies with high reputation and excellent track record.

In fact, the CMC part will be carefully reviewed during the due diligence prior to finalize a licensing agreement. A weak CMC part will lower the value of the deal.

Last but not least, an important challenge that CDMOs are facing is the flexibility of their internal portfolio & project management system, leader and teams to adapt to each project dealing with different customers. Having a CDMO leadership or a partner leadership is very different and there are all variables in between the two opposites.

CDMOs Need a Broad Toolkit and Depth of Expertise

Lee Newton, vice president & business unit head API Development & Manufacturing, Lonza Pharma & Biotech

Outsourcing and partnering are growing — and changing — across the pharmaceutical industry.
We see more outsourcing as part of the business models of smaller biopharma companies that 1) hold most of the early-stage pipeline and 2) typically need both development and manufacturing partnerships. Accessing end-to-end solutions, at phase- and product-appropriate scale, can be especially attractive for smaller companies and can help reduce complexity, timelines and risk for their drug programs.
Pipeline challenges are also driving increased outsourcing across biopharma. The majority of small molecules face bioavailability challenges requiring enabling technologies (or combinations of technologies) to meet target product profiles. An increasing number of molecules are highly potent and require specialized handling. Additionally, the ability to meet accelerated development timelines — from fast track / breakthrough designations, orphan drugs, 505(b)2 requirements — has become increasingly critical. To meet these challenges, a range of specialized technologies, processing and infrastructure is needed with the phase-appropriate capacity in place to support drug programs from concept to commercialization.
Finally, it is worth citing the role of "flexibility" in meeting the needs of today's biopharma customers. Medicines are increasingly specialized, with patient-centricity trends continuing to drive product development. Customer needs differ from virtual companies to established "big pharma". And the needs of drug programs themselves can differ between programs — from end-to-end solutions or any combination of product requirements from API, particle engineered API, to finished drug products. CDMO business models also have to be flexible and tailored to the customer and program.
To help pharma companies overcome drug development challenges, CDMOs need a broad toolkit and depth of expertise, qualities which we are constantly working to create, refine and grow to help our customers find continued success.

One-Size-Fits-All Does Not Work

Martin Bauer, head of Precious Metal Powder Catalysts, Evonik

Pharma customers are constantly being challenged to improve their processes in terms of cost reduction. For Evonik, as a supplier/developer of catalysts, this means constantly developing tailor-made catalysts for each process.
A "one-size-fits-all" catalyst grade does not work for our customers who expect a catalyst with a high selectivity — meaning less by products — and at the same time a high yield. To achieve this, we need to use all of our experience and tools, including for example high throughput screening, to find the best catalyst in our portfolio or develop a new catalyst which will exceed their expectations.
The cycle times for bringing new synthesis generations to launch are shortening. For us this means developing new catalyst generations faster. We addressed this challenge by operating R&D groups in each region to be in close contact with the customers enabling us to react faster to their changing needs.
In addition, regulatory requirements from government agencies are increasing. For this aspect of the business we need to stay in close contact with our customers and follow their lead, constantly improving our quality systems to match our customers' requirements.
Pharma customers in the Western world are still shifting production to contract manufacturers in e.g. India. We have seen this trend and reacted accordingly. Evonik manufactures catalysts for the pharmaceutical industry in Dombivli, close to Mumbai, where we can offer the whole catalyst cycle: fresh product — refining — precious metal handling.

Competent and Effective Project Management Is Key

Mark Griffiths, group CEO, Dishman Carbogen Amcis

There are many factors, and not only one drives the CDMO industry.
Firstly, our customer base has changed dramatically. A large percentage of our revenue came from big pharma companies; however, it's significantly reduced within Carbogen Amcis as we also now service many small biotech companies.
No longer is our business just about chemistry or biology, whether your customer is large or small there's a need for competent and effective project management to ensure deliverables are met. This is a key element to a CDMOs survival.
Everyone is feeling the pressure from the rising costs and increasingly scarce resources. There needs to be some understanding between clients and suppliers that addressing these issues will take time. This is still a conservative industry in many respects and consequently, we may miss opportunities to move the technology needle further than other industries.
To create strong customer relationships there has to be an agreement which serves both. The practice of deferred payment terms can be a burden for suppliers and can (in the long run) drive up the price of the project for clients. This doesn't benefit both organizations and most importantly doesn't help patients.
The key to establishing great customer relationships is having clear goals, communicated at the start and embedded in the culture of that relationship from all levels of the organization, not just management. We need each other to survive and to create new drugs for patients; this is a serious responsibility and cannot be emphasized enough.

More Flexible and Reconfigurable Solutions

Gerhard Breu, chairman, Optima Pharma

Currently, we see a trend for more biotechnology products and individual therapies for patients. The variety of products increases drastically and many of them are very potent. Therefore, machines have to be highly flexible to process these products, containers and batch sizes. It has to be recognized that the life cycle of products will be much more dynamic and new product varieties and containers have to be filled. This calls for more flexible and reconfigurable solutions that will enable the life cycle management. We will definitely consider this during the conceptual design in order to meet our customer requirements. Two specific examples: the trend towards flexibility is solved with the utilization of robots. We are also developing a process solution for the isolator and freeze-drying field at the Metall+Plastic location in Radolfzell and at Optima Pharma in Mornshausen, that will reduce the current cycle times significantly. Another development that we recognize: we have an increasingly wide range of customers from small start-up companies to manufacturers of biosimilars. Our customers also include those that are highly specialized contract manufacturers up to large pharmaceutical companies.

Global Harmonization not only of Rules but of their Interpretation

Lukas von Hippel, managing director, Pharma Waldhof

Data integrity is for the time being one of the top priorities of the US FDA during audits. And the increasing number of warning letters does indicate that quite some companies struggle to fulfill all documentation for historical data. Such lack of data does not necessary mean a creative approach to data and quality, but may be the result of new interpretation of guidelines.
In times of supply chains going around the globe, the need to have a strict control over all materials entering a manufacturing process becomes more and more time consuming and expensive. Depending on the state a company is located, even the same law may be interpreted differently. In addition, depending on the region, the regulatory status of supply chains can be seen differently as well: some may define a material as being a starting material, in other regions the same material in the same process may be categorized as an advanced intermediate. So, from a company's perspective, the decision not to make a product available to all countries worldwide may be the consequence. Here, one may ask whether it will be best from a patient's perspective not to get access to a drug because the need for documentation differs from region to region.
For years, at Pharma Waldhof we have been investing continuously to keep our knowledge about our supply chains on a high level. However, we do believe that a global harmonization not only of rules but of the relevant interpretation would be helpful.

Expansion of Critical Size

Rudolf Hanko, CEO, Siegfried

In a strongly fragmented and rapidly consolidating CDMO market, which has high demands on quality and technological innovation, one cannot be satisfied with the status quo, but has to continue developing and to actively shape one's business environment. Siegfried's challenge for the future is to reach critical size also in the drug products sector. This will add to our high level of dynamics and continue to raise the company's intrinsic value. The core of our strategy aims to strengthen Siegfried's position as a leading integrated supplier to the pharmaceutical industry. Additionally, we to enter or enhance our exposure to new technologies like micronization and fill/finish of biologics. We plan to reach this level of growth by developing internal structures as well as acquiring strategically suitable companies.

Establishing Sustainability as a Competitive Edge

Christophe Le Ret, global marketing director Precious Metals Chemistry, Umicore

Responding and proactively addressing the ever-changing trends in pharma is perhaps the largest challenge for a CDMO. One of the most impactful developments is the rise in popularity of digital healthcare. It has placed increased pressure on CDMOs to develop and manufacture the high value chemicals required to manufacture digital solutions. This includes synthesizing electronic chemicals or high purity materials for equipment amongst others, demanding innovative chemistries.
But, developing sustainable syntheses are becoming a necessity for the pharma industry. To meet these needs, Umicore's Horizon 2020 strategy aims to establish sustainability as a competitive edge for Umicore and its customers, and position the company as a recognized leader in this space. Umicore has demonstrated its commitment to sustainability in three key areas.
Firstly, it provides access to the vast metathesis technology competence, made possible through the successful acquisition of Materia's catalyst business in January. Secondly, it has established expertise in large scale manufacturing of complex metal containing chemicals and catalysts. It provides our customers with easy access to sustainable technologies, allowing the creation of highly efficient synthetic routes or elegant chemistry powered by renewables. Finally, it's societal alignment to the United Nations Sustainable Development Goals (UNSDGs) has translated into doubling its metal recycling capacity. Umicore can now address the issue of metal scarcity by offering customers increased capacity to recycle waste catalysts. In addition to sustainability advantages, it also translates into our sustainable procurement framework, ensuring our supply chain conforms to the UNSDGs.

Growing Competitive Situation Puts Budgets Under Stress

Tore Bergsteiner, managing director, Main5

The pharmaceutical industry suffers from many unspecified processes and misses the interdisciplinary understanding of interfaces and deliverables to seamless integrate services outsourced to CDMOs into the own value chain. While the CDMO industry historically has been growing decentralized, the IT infrastructure and data flows approach a central business process model for R&D, including the onboarding of all elements in the process chain such as manufacturer and contract partners. Within the implementation of the new clinical trial regulations, quality management needs to be a central digital hub for any process connected with product quality and patients' safety. The growing competitive situation puts budgets under stress and increases the pressure on lean development and organizational structures. Especially those R&D projects with involvement of co-development partners need solutions to embrace the complexity. The CDMO industry is facing major challenges within the next five years – and any solution model needs to consider the R&D business process model, the supporting IT architecture and the human as main elements.

Managing the Cost-Time-Risk Triangle

Nick Shackley, global vice president Innovator Products and Solutions, Johnson Matthey

Focusing on customer needs is the key to a successful contract development and manufacturing organization (CDMO) like Johnson Matthey (JM). In addition to managing client expectations, perhaps the biggest challenges for any project is balancing the parameters that direct successful project completion: development cost, time taken to deliver a solution, and the risk to the customer. This triangle must be optimized for all pharmaceutical development projects.

With any development project, it is essential to minimize the risk, while working within available time and cost limits to maintain the project scope and client expectations. One of the most challenging developments occurs when unforeseen difficulties with synthesis, formulation or development requires a detailed solution. In such cases, it is important for the client to know they can rely on the CDMO to find an appropriate solution.

Experience and on-demand expertise are two critical components that help ensure a CDMO can guarantee a project's success. At JM, we have both, offering customers a broad range of scientific expertise and physical capabilities covering custom pharma solutions, APIs and life cycle management, controlled substances, and catalysis. Our combined offering helps us identify practices that reduce the risk of any project, while also allowing us to explore time-saving opportunities for instance by potentially running processes in parallel. It is our experience in research, development and manufacturing that allows us to design bespoke and pragmatic approaches to customer problems.

Need for Innovative Facility Design Solutions

Steve Attig, senior process engineer, CRB Group

As more and more CDMOs emerge, they begin supporting larger, sometimes global, client bases with the necessity for products that are more targeted, efficacious and cost effective. In recent years, we have noticed that our CDMO clients need to incorporate flexibility into their facilities in order to have a marked competitive advantage. The companies with room to expand and with equipment and facilities that can be adapted for multiple products or changes in process platforms are the most equipped to take on major industry changes. In essence, we need to build the facility to be able to handle a range of platforms, scales, throughputs, containment strategies, etc. such that our CDMO clients can then market their facility based on that bracketed range with a "if you build it, they will come" mentality. It's the complete opposite of traditional facility design because it forces us to "option-eer" and design off assumptions. Over the past few years, the pharmaceutical industry has seen a plethora of new processing technologies, design approaches and construction methodologies that allow for increased flexibility — closed/continuous processing, single-use systems, ballroom manufacturing, modular/"podular" construction and prefabrication — to name a few.

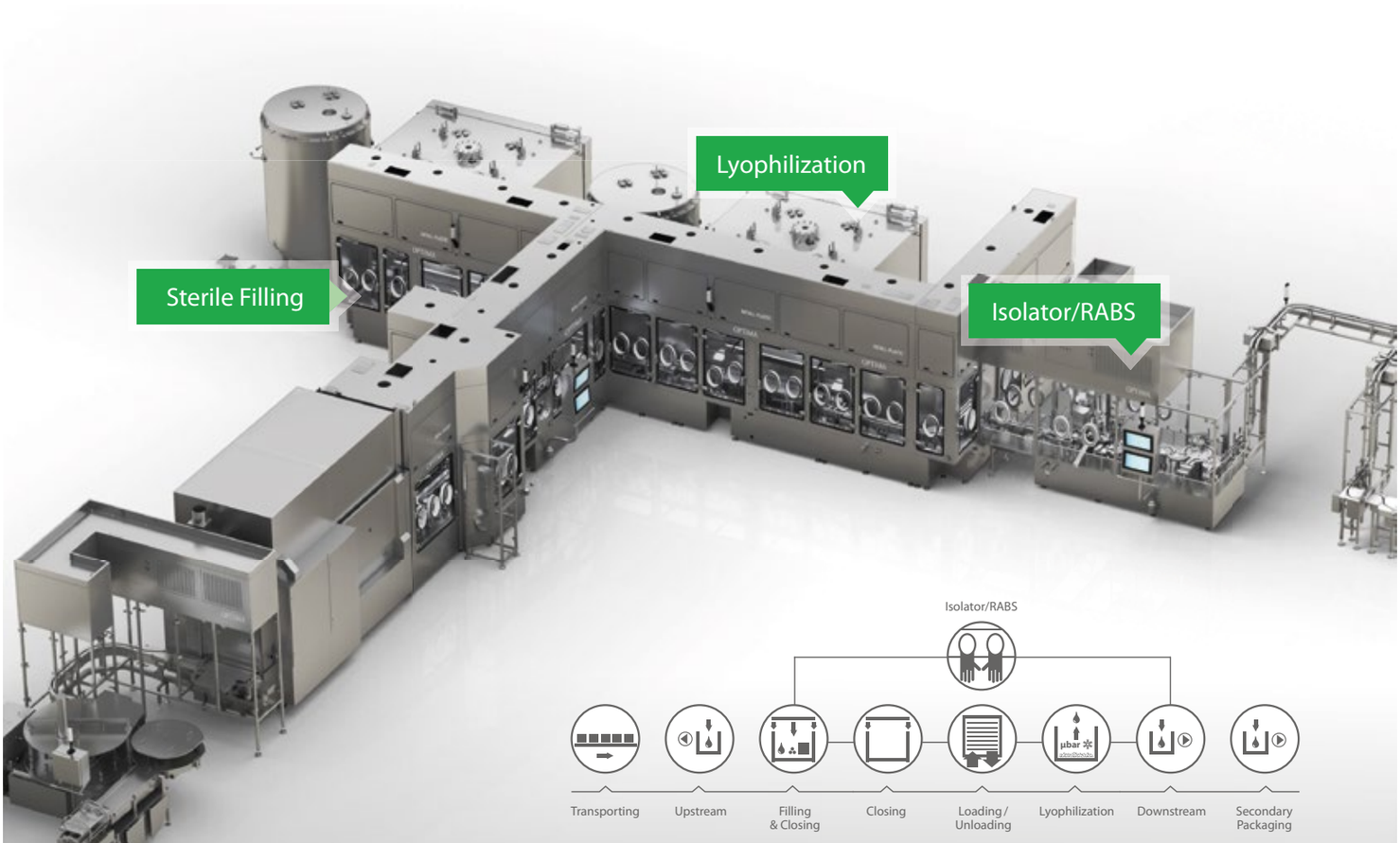
By bringing together the best in current industry thinking and process closure technologies, companies can create innovative facility design solutions that dramatically reduce capital and operating costs while increasing regulatory compliance. These methods significantly reduce facility complexity, initial capital investment, energy consumption, project schedules and cost of goods.

Drug Companies have Increasing Quality Expectations

Stephan Maier, pharmacist and qualified person, CG Chemikalien

We perceive that drug companies reduce the number of their contractors by consolidation. They are looking for full-service providers, have increasing quality expectations and presuppose high flexibility. To ensure a continuous supply and mitigate the impact of any product shortage, most drug companies follow a second source supplier strategy, challenging the planning certainty for the individual contractor. CMOs, on the other hand, are expected to provide sufficient production capacities for long-term projects based on potentially increasing demands. This is hard to fulfil, especially when it comes to expansion of human resources. In a market suffering shortage of skilled labor due to full employment, short-term hiring of qualified personnel is a real challenge.

These challenges are tackled by specializing in high-quality bulk products, e.g. consumables for the expanding biotech industry, by continuous improvement of process know-how, and by increasing the level of automatization. We offer high responsiveness and flexibility combined with attractive logistic solutions. Our company strives for strategic cooperation with drug companies and supports them very early in product and process development. Our goal is to let our capacities grow along with their increasing demand over several years.



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Digital Transformation

Implementing an End-to-End Strategy for the Digitalization of the Pharmaceutical Value Chain

The pharmaceutical industry has gone through two decades of rapid technological innovations. These include combinatorial chemistry, recombinant DNA technology, development of knockout animal models & high throughput screening, and lately the rise of the genome area. But none of these innovations will have come close to what lies ahead with the rise of the digital era.

Philip Boehme, Bayer

Hubert Truebel, Bayer

Ted Castellon, Bayer

Ronenn Roubenoff, Novartis

In contrast to the innovations from the last decade, which mostly only partially affected the value chain, the digital transformation could enable an end-to-end change and potentially apply to the pharmaceutical value chain as a whole. As a result, companies that adapt their product development and market access models more quickly will have the chance to gain a competitive advantage while others failing to adapt will face challenges.

Driving Forces

Several forces can be identified driving this process. The strongest is the rise of value-based medicines, enforced by the pushback from payers regarding mass market and blockbuster drugs. Most healthcare systems with large pharma markets have been trying to cap increasing heath care spending in recent years. At the same time, industry costs for R&D have been increasing with a declining ROI across the industry. One factor is the increasing number of so called late-stage (phase III) failures, where already large investments have been made. This is largely driven by improved Standard-of-Care, harder-to-treat indications that require larger and longer studies, lack of translatability of phase

3D visualization is key to a deeper understanding of binding events between drug molecules and their protein targets.

II endpoints to phase III, and challenges of finding promising new targets.

Additionally, the industry is seeing an increasingly competitive landscape. In many of the large chronic diseases such as cardiovascular disease, inflammatory diseases, and diabetes, the standard of care is already advanced with generic drugs broadly available. Healthcare systems are not willing to pay high prices for only modest benefit. Moreover, new competitors are entering the healthcare market from various ends: e.g. the GAFA economy giants (Google, Amazon, Facebook, Apple) have lately been active along the pharmaceutical value chain.

An agile digital end-to-end strategy for the transformation of the entire value chain will help pharmaceutical companies overcome those challenges. Here we provide some examples, how such a digital strategy can be put in place.

Drug Discovery

It may seem counterintuitive that the breeding ground for pharmaceutical innovation, which is based on cutting-edge science and technology, lags behind the digital curve. But today most pharma companies still focus most of their R&D budget on internal resources. Due to the rise of digital technology and the availability of data this should be refocused to a more open innovation strategy. The coming of age of open biomolecular platforms, including genome and patient data along with the availability of technology to easily perform genome editing, produce antibodies or even CAR-T cells, will lead to a democratization of preclinical research. There is an increasing landscape of academic groups and start-ups that perform research based on these technologies to develop unique insights into the disease biology for either a single disease or disease areas. It is not physically and financially feasible to capture all this knowledge within a single company. Therefore, drug discovery organizations should be partnering in exploring targets coming out of these networks providing technologies such as artificial intelligence for the analysis of data as well as for the design and optimization of new molecular entities.

Bayer's G4Targets and the CoLaborator initiative are examples how such a strategy can be put in place successfully. A core in-house competency should be how to accelerate the asset from concept to candidate. In that spirit, Novartis and GSK, among others, are investing heavily in digitizing their internal data to make it searchable under FAIR (Findable, Accessible, Interoperable, and Reusable) principles. The new candidates should then be tested in disease animal models using digital telemetry systems to mimic human diseases. The data gained across those early experiments should flow into an asset-independent data base to guide and evaluate future experiments and collaborations.

It is important to note, that this strategy should not be limited to molecular candidates. Digital health applications as well as devices should be included and evaluated alongside of these new therapeutic entities. Such an approach has been lauded by the new FDA commissioner Scott Gottlieb but these technologies will help to enhance the efficacy of the drug in a value based healthcare market.

Drug Development/ Translational Medicine

The phase between late pre-clinical development and confirmatory clinical development (phase II+III studies) is commonly called as translati-

Continued Page 30 ▶

Cell line development workstation in the Cell and Protein Sciences unit at the Bayer Pharma Research Center in Wuppertal, Germany.

onal medicine and has a tremendous chance to benefit from a thought-out digital strategy. The main goal of translational medicine is to show in human proof of concept studies the true potential of a new therapeutic and if it translates from bench to bedside. Early prioritization of the evidence valued by the payer is critical. Here, digital biomarkers such as real world walking speed can not only help to reflect patients' needs more accurately than traditional clinical endpoints, they also offer the chance to be used as surrogate markers in trials for diseases with low event rates. Additionally, these markers (including smartphone data) can be later applied in a value-based care setting for reimbursement purposes.

It needs to be demonstrated that these digital biomarkers can be developed and validated in a cross-industrial approach as endpoints for clinical, regulatory, and payer use. A joint strategy with multiple pharma sponsors has several advantages, as biomarker validation is expensive, slow, and requires acceptance from across the clinical spectrum (patients, doctors, pharmaceutical companies, regulators, payers). An excellent example is the IMI initiative Mobilise-D, where Bayer and Novartis among other academic and industrial partners aim to establish real world walking speed as a new endpoint for multiple indications. In general, the selection of these digital markers should be based on, and take advantage of, the growing acceptance of Real World Evidence (RWE) data by health authorities and payers.

Furthermore, in late-stage development data science enabled decision making for clinical trials can help to find the right patient that will benefit from the new drug. RWE could be even used whenever possible to replace randomized clinical trials (RCTs). With a currently widening regulatory window, RWE has been already used to expand the labels of drugs. RCTs, with their costs, complexity, and duration, could then be prioritized for high-payer-value subpopulations. It can be expected that with the ongoing digital transformation of medicine even more data will become available.

Marketing

Our customers' world has changed. Millennial physicians — true digital natives — now are a majority of practicing doctors. Along with their patients, they expect companies to engage with them in a personalized way in our digital world. Pharma marketing is no longer just about pure promotion, but also about personal digital services which engage physicians and patients to help solve problems in the moment and at their fingertips. Every other industry has gone through a digital transformation, including highly regulated industries like financial services. Companies that have successfully navigated this transformation and emerged as the clear leaders have not only transformed their customer engagement, but also their core products, processes and company cultures.

Successfully engaging with customers across channels, especially digital channels, requires building new skills, capabilities and platforms. Over the past 5+ years, pharma marketing has responded to these changing demands by investing in and deploying these capabilities. Given that other industries have already gone through digital transformation, there is much pharma can and should copy from proven best practices, while adapting them to the unique realities of the pharma sector.

At Bayer, we are using these core digital capabilities in a fully integrated way — integrated customer experience, platform and data. Expanding on these foundational capabilities, for example, we use artificial intelligence in Japan to suggest the next personalized action to be taken for an individual customer, regardless if the engagement is to be digital or traditional. We see these current investments as the foundation for future digital innovation

Conclusion

Beside the examples provided above, the most important issue in order to generate a digital end-to-end strategy is to have the right teams in place along the pharmaceutical value chain. Those teams need to have an armamentarium of digital capabilities, such as expertise in data science, data processing and data storage as well as digital marketing and digital health in general. Equally important are team members with deep understanding of the biological and medical issues; otherwise there is a risk that a digital solution will be developed that is precise and efficient, but not useful.

It is important to note that it is not the technology that will enable the successful digital transformation of the value chain — it is the mindset and capabilities of the team. The technology itself will become a commodity sooner or later. Like anyone living through a time of rapid change, it is hard to see where the digital revolution will take us. But it is already clear we will not be working the same way in 10 years as we are today.

Philip Boehme and Hubert Truebel, Research & Development, Pharmaceuticals, Bayer Pharma AG, Wuppertal, Germany
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If You Want to Go Far, Go Together

Navigating Differences in Communication, Culture, Personality, Distance, and Language in Multinational Project Teams

Having successfully executed over 70 integrated programs with customers, Piramal Pharma Solutions has ample experience in managing multinational project teams. This article presents some key takeaways of the learnings that have been identified during the programs.

Piramal Pharma Solutions (PPS) has experienced dramatic growth having served over 500 customers in FY18 and achieved a 7-year revenue CAGR of 16%. We have helped launch 34 new chemical entities (NCE's) for customers to market, and expect to launch another 10 this year, with an additional 110 late-stage programs (phase II/III) in clinical development. This rapid growth, fueled by both NCE launches and the development pipeline, is managed between 11 PPS locations; approximately half of them are located in the East (principally India) and the rest in the West (3 sites in North America, 2 in Europe). One of the fastest growing areas in terms of customer interest is integrated partnerships. These integrated programs typically involve more than a single site, are spread across geographies, and always involve more than one capability (i.e. drug substance/product).

Single Point of Contact

A single point of contact (SPOC) helps provide accountability, which is of vital importance to the customer. A single point of contact for both the customer and vendor also helps minimize confusion and cross talk. This point of contact could be a business development person or a program manager (fig. 1). In multi-national project teams these contacts serve to distribute information within their teams and also collate feedback. For cultural fits and communication within the same time zone, one can consider having the SPOC's for both partners to be located in the same region.

Communication in General

At PPS, we have analyzed programs that have gone very well and ones where we have identified areas for improvement. The common denominator that underlines successful programs is clear verbal and written communication between both parties, and a commitment to make the project successful. When in doubt, we encourage "more" communication between partner and the vendor, especially when dealing with multi-cultural teams. For all programs, we at the minimum, recommend regularly schedule bi weekly calls.

Face-to-Face Meetings

We have a large pharma client based out of Europe who is carrying out multiple integrated development programs from two of our sites in India, and our site in the UK. While a recurring phone call is scheduled to monitor program progress and address challenges, the client also makes quarterly site visits for a face to face interaction with the PPS development teams. These visits have led to a strong relationship between the two teams, seamless communication channels and strong results.

Stuart Needleman, Piramal

Culture

Even if project teams have a SPOC from the same culture/time zone, regular interactions with team members from other cultures and nationalities are a necessity. Some things to consider: importance of hierarchy in Asia, directness in conversations out of West, consensus based decision making vs directed decision making and understanding what is being conveyed as opposed to what is being said, among others. Since this is a topic that requires a write up of its own, we will simply state that, in our experience we have found that partnerships, which recognize these differences and patiently work through them, are the most successful.

Language

Written and verbal communication is key towards progress and execution of any project. Each customer partnership is unique and communication needs should be customized for best results. Nevertheless, it is imperative that good English skills are essential for any western collaboration. We have an internal learning and development program that all customer facing personnel, whose first language is not English, go through. In addition, if we have personnel that have experience with a particular region (say Japan or certain European regions) and know the local language, we make them a central part of customer interactions.

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Travel to Customer Sites

Over the past few years, we have seen customers who we have long-term relationships with invite key Piramal program and project team members to visit their sites. This allows the vendor to meet with all project team members from the customer side. This reciprocal arrangement of the typical face-to-face meeting, where customers visit CMO sites, is a positive trend that leads to stronger connection between the teams

Review of Collaboration

For key strategic partnerships that involve multi-national teams and several disciplines, PPS carries out a minimum of two meetings in a year at a senior management level with the partner. We have found these meetings to be very beneficial, as the intent is to further strengthen the areas that have gone well, while focusing on what needs to be done from a management level to address any challenges. Key decisions on new hires, any changes in project team structure, investment needs on people/capabilities are all identified during these meetings. We then review progress regularly until the next formal get-together.

"Partnerships, which recognize cultural differences and patiently work through them, are the most successful."

While it is important to focus on the details above while managing multinational projects, it is equally important to make this a part of the fabric of the organization. At Piramal, we have a simple and clear mission: to assist our customers and patients by reducing the burden of disease. We are here to make our customers succeed by getting medicines to patients rapidly and cost effectively. We expect to do this by building around the three pillars that form our foundation: customer centricity, quality, and innovation. For ensuring a culture that puts customers first Piramal has a unique organogram. Our organizational structure is not defined by hierarchy or by our management. We have the customer at the center of our internal organogram. All functions work for the customer, report to the customer, and are focused on delivering a differentiated experience to the customer. This philosophy is instilled from the shop floor to the executive suite and has played a key role in our significant growth.

To summarize, managing multinational programs and teams brings some unique challenges. While some of these can be addressed at a macro level, others require customized solutions. For example, biotech and big pharma collaborations are different since biotech companies quite often use consultants, while big pharma has their own teams. A partner who understands the potential issues that may arise, and works collaboratively towards solutions by keeping the customer first, is essential for a successful relationship. Once the issues are worked out, these multinational partnerships make for some of the best success stories: if you want to go fast, go alone…if you want to go far, go together!

Stuart Needleman, chief commercial officer, Piramal Pharma Solutions

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The Definition of Quality

Managing Highly Challenging GMP Processes

The German service provider Pitzek GMP Consulting, based in Neustadt/Weinstraße, has nearly 30 years of consultancy experience in GMP processing for pharmaceutical and life science product. In Germany, a team of almost 30 experts in biochemistry, process engineering, bioprocess engineering, pharmaceutical engineering and biology is active. After continuously expanding its presence in Germany, the company recently opened an office in Singapore. CHEManager asked founder and CEO Thomas Pitzek about the reasons for the expansion into the Asian market and his strategy for the further development of the company.

CHEManager: Mr. Pitzek, which services does Pitzek GMP Consulting offer and in which areas do you focus your activities?

Thomas Pitzek: Pitzek GMP Consulting stands for nearly 30 years of GMP processing for pharmaceutical and life science products, high competence in GMP consulting, qualification/validation, GMP engineering and project management. What makes Pitzek GMP Consulting special — short ways through an actively cooperating management. As a GMP expert, Pitzek GMP Consulting offers the highest quality in compliance issues, from consulting through conception to the implementation of new production lines. Due to decades of experience, we have specialized in isolator technology

In which geographical markets is your company active?

T. Pitzek: Our location on the wine route allows us to operate throughout Germany and beyond. In addition, we are currently developing our subsidiary in Singapore.

What is the typical course of a project that your company is entrusted with?

T. Pitzek: We advise in advance on the alignment, take care of the right machine builder if necessary, take care of customize equipment and document everything strictly according to GMP guidelines, always under the aspect of the highest quality standards and cost-efficient.

What were the reasons for the decision to open a branch office in Singapore?

T. Pitzek: The new subsidiary is located in the heart of downtown Singapore, which is now considered the international hub for the pharmaceutical industry and the medical technology in Southeast Asia (SEA). There are also numerous known pharmaceutical and medical technology businesses as well as customers of the German business established. Now with the established representation in Asia, our consulting firm wants to support its globally operating pharmaceutical customers with even more

Thomas Pitzek,
Pitzek GMP Consulting

targeted consultancy, qualification and validation, as well as engineering and additional GMP consulting.

Do your clients tend to be large companies or are small and medium-sized companies among them?

T. Pitzek: We work with small, medium and large sized companies equally. The company size of the customer doesn´t matter, we always de-

liver the best quality. That is the claim on ourselves.

You recently started a cooperation with GAT — Gesellschaft für Automatisierungstechnik. What are the benefits of this partnership for your customers?

T. Pitzek: In the context of Industry 4.0 and the comprehensive digitization of industrial production, we can better prepare ourselves for the future and handle projects along the entire value chain, including automation technology.

You are also involved in/heading the regional Community of Practice (CoP) Aseptic Processing of the International Society for Pharmaceutical Engineering (ISPE). What are the objectives of this group?

T. Pitzek: The aim of CoP Aseptic Processing is to offer operators, planners, manufacturers and interested parties who are dealing with the technology of aseptic manufacturing in their professional lives a discussion platform for specialist topics and the exchange of experiences. This objective is supported by annual expert discussions on aseptic processing topics. It is a particular aim to include in the expert discussions the dialogue with representatives of the authorities. In addition, an exchange with the CoPs of other affiliates takes place regularly.

> *"In the context of Industry 4.0, we can better prepare ourselves for the future."*

pitzek-consulting.de

News

Shire Sells Oncology Portfolio to Servier

Ahead of its acquisition by Japan's Takeda Pharmaceutical, Ireland-domiciled, London-listed and US-focused Shire has completed the sale of its oncology portfolio with $262 million in annual sales to French drugmaker Servier for $2.4 billion.

The deal, announced in April during Takeda's grab for Shire, will allow privately held Servier to establish a direct commercial presence in the US while boosting its presence in the cancer segment in countries where it is already present.

After Takeda made five bids for Shire, starting in late March of this year, the £46 billion transaction due to complete shortly was approved by both companies' boards in May and given unconditional clearance by the US Food and Drug Administration (FDA) in July. (dw, rk)

EU Clears Merck's Consumer Health Sale to P&G

The European Commission has approved the sale by Merck KGaA of its global consumer health business to Procter & Gamble (P&G). The regulator said it had no competition concerns, noting that the activities of both companies are generally complementary and give rise to a limited number of horizontal overlaps, with sufficient competition remaining post-merger. In April of this year, the German company signed an agreement to sell the division to the US consumer products giant for around €3.4 billion in cash. The acquisition adds Merck's vitamin and food supplements, such as Seven Seas, to P&G's portfolio that features a range of over-the-counter medicines including Vicks cough and cold products, along with well-known brands such as Pampers diapers and Gillette razors. (eb, rk)

Novo Nordisk Buys Ziylo Spin-out

Danish pharma Novo Nordisk is boosting its efforts to develop the world's first glucose responsive insulin and transform the treatment of diabetes following its purchase of Ziylo, a spin-out from the UK's University of Bristol.

Novo Nordisk said that glucose responsive insulin can help eliminate the risk of hypoglycemia, the main risk of insulin therapy, and help people living with diabetes achieve better metabolic control. Ziylo has been developing synthetic glucose binding molecules for therapeutic and diagnostic applications. The molecules are said to display an unprecedented selectivity to glucose in complex environments such as blood.

Novo Nordisk spun out certain of Ziylo's research activities into new company Carbometrics before the acquisition was finalized. (eb, rk)

Affimed and Genentech in Immunotherapy Pact

German biopharma Affimed has agreed a collaboration with Genentech to develop immunotherapies for multiple cancers.

Affimed will apply its proprietary Redirected Optimised Cell Killing (ROCK) platform, which enables the generation of both NK cell and T cell-engaging antibodies, to discover and advance innate immune cell engager-based immunotherapies that are of interest to Genentech. The deal includes candidate products generated from Affimed's ROCK platform and multiple undisclosed solid and hematologic tumor targets.

The partners will cooperate on the discovery, early research and late-stage research phases, while Genentech will be responsible for clinical development and global commercialization. (eb, rk)

Innovative Anti-Infectives

Synthetic Biology for the Production of Complex Peptides

Natural products have been used since thousands of years for the treatment of a wide range of medical conditions in the form of traditional medicines. Today 60% of all new small molecule drugs are still derived from nature, and natural products have been the source or an inspiration for several approved drugs, e.g., for cancer treatment (taxol, epothilon), as immunosuppressant (ciclosporin) or anti-invectives (vancomycin, daptomycin).

Kenan A. J. Bozhüyük, John Innes Centre

Helge B. Bode, Goethe University Frankfurt

Today infectious diseases are still the second major cause of death worldwide with some 700,000 deaths. According to the World Health Organization (WHO), the world is facing a global public-health crisis as there is a growing risk of entering the pre-antibiotic era since more and more infections are caused by multi-drug-resistant bacteria. There are several reasons for the loss of antibiotics' effectivity, both in wealthy nations and in poor. Economic, regulatory and scientific causes are further tightened by the increasing number of multidrug-resistant bacteria due to the misuse of antibiotics in clinics, agriculture, livestock breeding and feed industry. Diseases that were easy to control or had almost been eradicated due to the use of antibiotics have become or are soon becoming a threat again.

One source for new drugs with improved clinical properties, e.g., breaking antimicrobial resistance, is the chemical modification of existing drugs. To date, most clinically used natural product derivatives are created by means of semi-synthesis; a process where the original natural product is chemically modified after its isolation from a biological source. However, due to technical and chemical limitations, such modifications are mainly targeting the molecule's periphery but leaving the backbone structure untouched.

Developing Novel Drugs Using Non-ribosomal Peptide Synthetases

One structurally highly diverse and pharmaceutically relevant class of bioactive drugs are peptide-based natural products. For instance, peptides have been identified with antibiotic, antiviral, anti-cancer, anti-inflammatory, immunosuppressant and surfactant activities. The market for peptide drugs is estimated around 10% of the entire pharmaceutical market and will increase in the future. In order to alter the backbone of these peptides, often bio-synthesized by non-ribosomal peptide synthetases (NRPS), the respective enzymatic machineries must be engineered.

NRPS are very large and complex enzymes with a strict modular architecture. Each module consists of several catalytically active domains and is responsible for the activation, modification and elongation of the growing peptide chain. These non-ribosomal peptides are renowned for exhibiting unique structural elements, like D-amino acids, N-terminal attached fatty acids, N- and C-terminal methylated residues, heterocycles, glycosylated as well as phosphorylated amino acids and to date >450 different amino acids have been identified in these non-ribosomal peptides.

Very early on, the modular composition of NRPS raised expectations and desire for their reprogramming — realized for the first time in 1995 by the group of Mohamed Marahiel. Since then NRPS research dreams of using these enzymes like a molecular toolkit to modify bioactive peptides and create novel non-natural peptides in a tailormade way. During the last 20 years all NRPS core domains were biochemically characterized and crystal structures of domains and even whole modules were solved. Yet, to date most attempts to achieve NRPS re-engineering have yielded biosynthetic machineries that are either greatly impaired in their activity (0.1-0.5% compared to wildtype production titers) or that are completely non-functional.

The same applies even for the currently most successful domain substitution campaign, reported by researchers at Cubist Pharmaceuticals (Lexington, USA), in the daptomycin (Cubicin) producing NRPS of Streptomyces roseosporus. Most of the re-engineered NRPS assembly lines were impaired, resulting in reduced titers of the desired peptides. Moreover, the campaign failed to introduce generally applicable and reproducible guidelines that may be transferred to other systems.

In the 2010s, the fundamental biochemical issues of NRPS were solved and recent advances made in the areas of crystallography and cryo-electron microscopy (cryo-EM) delivered new insights on the dynamics, mechanics and domain-domain interactions of NRPS and other megasynthases like polyketide synthases. In brief, it became clear that NRPS are only functional if, besides preserving the catalytic activity of individual domains, domain-domain interactions are maintained, too.

First structure-based strategies maintaining interfaces of NRPS domains were published by the groups of Piel (2013) and Hilvert (2015). Both groups successfully exchanged the active site forming amino acids of adenylation domains to alter their substrate specificities resulting in the production of new peptide derivatives. Another very recent strategy, published by Meyer, Süssmuth and colleagues (2017), enabled the biosynthesis of enniatin and beauvericin derivatives by combining structurally and biochemically highly related NRPS. The new peptide derivatives showed up to twelve-fold increased activity against Leishmania donovani and Trypanosoma cruzi compared to the reference drugs miltefosine (Miltex) and benznidazole (Rochagan), respectively. Noteworthy, besides the very good bioactivity of the new derivatives, it had been possible for the first time to produce new-to-nature peptides in an industrial relevant scale (1.3 g/L^{-1}).

Generating Novel Non-ribosomal Peptide Synthetases

All strategies introduced so far are based on re-programming certain NRPS to alter single amino acid positions of naturally available peptides to create new derivatives. Moreover, all reported and successfully applied strategies lack transferability and applicability to other systems. Consequently, a reliable, stable, fast and cost-effective technology platform enabling the de novo design of any desired peptide from scratch has been lacking completely up to now.

In 2012, a research project funded by the Federal Ministry of Education and Research (BMBF) in Germany dedicated to close the lack of knowledge, has started to develop new and reproducible strategies for both reprogramming naturally available NRPS templates and designing novel "synthetic" NRPS machineries. To face the complex task, a structure-based and mechanistic in silico approach was chosen; all publicly available NRPS crystal structures were analyzed bioinformatically to identify feasible recombination rules. After a five-year research phase, a first technology platform enabling the biotechnological production of tailormade new-to-nature peptides was established that is backed-up by several patents. The eXchange Unit (XU) technology provides, for the first time, both reproducible and explicit guidelines for the design, cloning and biosynthetic production of non-ribosomal peptides of desired length, composition, modification and configuration. While considering the identified guidelines as well as applying non-natural domains for termination and regeneration naturally available peptides, peptide derivatives, and new-to-nature linear-, cyclic-, and lipo-peptides were produced by recombining up to five XUs from four different organisms with good yield.

Outlook

Due to the very urgent need to develop new innovative anti-infectives and general efforts to reduce the use of petrochemical precursors, reagents, and solvents, synthetic biology as well as the biotechnological production of peptides is highly attractive. Recent advances in the field of combinatorial biology will attract and inspire other scientists to develop solutions that extend the boundaries of what is currently possible. In the near future, progress made in the areas of crystallography, electron-microscopy, genome mining, editing, and gene synthesis, machine learning as well as 3D printing will enable the in silico calculation of novel biosynthetic gene clusters. These will then be synthesized (or even 3D printed) and finally heterologously expressed in an industrial super host to produce the desired tailormade drug.

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Evolution of Technology

Customized Solutions for Large Scale Production of Monoclonal Antibodies

In terms of development of high-value pharmaceuticals pharma industry is pressed for time: there is a huge demand for new reliable and innovative solutions to guarantee maximum yield in shortest time. On the way to production at industrial scale, numerous planning steps are essential, by requiring deep process understanding and experience. Apart from that, the implementation from basic engineering to commissioning at the customer's site is going to be executed either at green field or by exact fitting into existing facilities.

Daniel Maier,
Zeta Biopharma

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Fermentation plant for monoclonal antibodies (mAB)

Competent plant engineering has to include the development of new technologies, intelligent parallelization of process units, hub optimizing and last but not least a high level of flexibility thus allowing realization of projects in short time. Therefore, pharma industry needs a partner providing the best strategy for the customer by comprehensive engineering and services.

The development of pharmaceutical products and the optimal production processes are challenging the pharma industry. Projects need to be realized in shortest time. Despite of time pressure it has to be considered that occurring mistakes at an early stage may have a high impact later on. This causes significant extra costs and the up-scaling from lab to pilot scale turns out to be problematic as well. Plant engineers often face a dilemma in being requested to accept operational guarantees while not having the possibility to influence the planning process. This is why they are interested in contributing their expert knowledge as early as possible, in order to identify problems in a timely manner and to make processes more efficient. Because of that, Zeta decided to assign the individual elements of the range of services to the different development stages of a medicinal product. Concept design, basic and detail engineering are the most important pillars of the company's "solution path" (see graphic).

The earliest point in time where the engineers dock on to the life cycle of a biopharmaceutical agent is when a customer has mastered its production process at lab scale (pre-clinical phase). Even at this early stage it is worth analyzing processes with a view to industrial-scale production and develop a concept for a pilot plant. Afterwards, all services along the "solution path" aim for support through the entire process of clinical studies, the parallel scale-up to industrial scale and the customized plant engineering in order to assist a professional product launch in shortest time.

Production of Monoclonal Antibodies

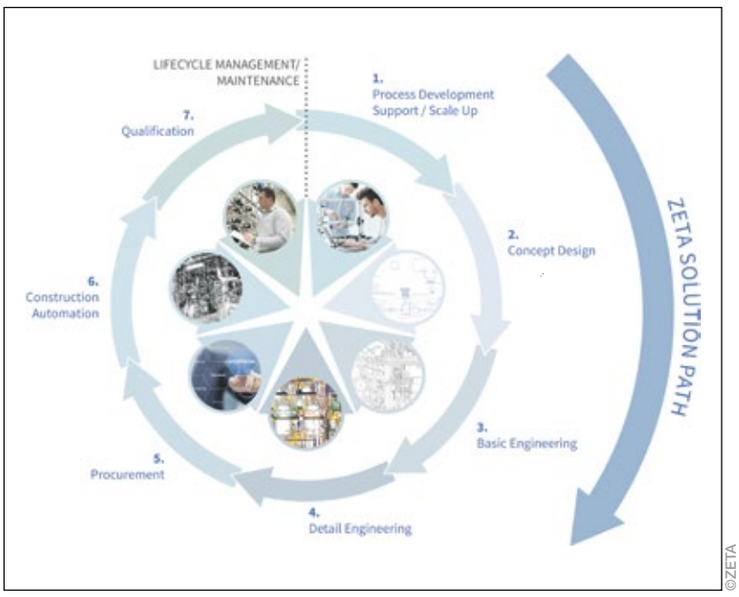
One of the fastest growing sectors in pharmaceutical industry is the production of monoclonal antibodies (mAB). The rapid growth of mAB demand requires efforts to increase production capacities as well as product titers. The production processes run in multiple stages — from low-volume seed cultures via intermediate cultures up to the production cultures in 25 m^3 bioreactors.

The medication for the treatment of paroxysomal nocturnal hemoglubinuria (PNH) is also based on mAB. The drug is one of the most expensive therapies worldwide with annual therapy costs of some €400,000. For the development of an ultra-modern fermentation plant for the production of these mAB the services of the solution path were successfully applied.

The end-to-end management of the entire project — from basic to detail engineering and the handling of production, automation and qualification — resulted in increased efficiency as time-consuming interfaces could be saved. In order to manufacture and simulate the actual plant set-up, Zeta had to initially extend its premises and invested in a new manufacturing complex with 430 m^2 providing all utilities for dynamic testing. The time-line for the project was very tight: 22 months only from basic engineering up to commissioning at the premises of the customer.

Industrial Scale-Up

The scale-up of the fermentation process from 50 L to 32,000 L was realized in close cooperation between the process and automation engineering teams working on the creation of functional specifications. The design complexity of the entire fermentation plant was reduced in detail engineering by development of an innovative



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Scheme of the Solution Path

master-copy concept. The high effort and costs of planning were kept to a minimum by mirroring the various bioreactor units. Due to the innovative concept the project term could be reduced by some 16 weeks.

Technical precision ensured by the modular super skid design simplified mechanical and electrical installation work. Furthermore, the skid design made a thorough functional test of each individual skid as a self-contained unit possible, thus significantly reducing the expenditure for the trip and installation at the customer's site. The entire plant (including wiring and piping) was planned and visualized as a modular system in the 3D model as early as the engineering phase, and interfaces between the individual skids were optimized. Due to confined space conditions at the customer's site the automation specialists had to develop a control cabinet design to guarantee a smooth production process at a narrow space.

In addition, a fully integrated IT environment is important for end-to-end and thus time-saving processing of all process data. Data recording ensures full traceability — from mechanical engineering specification, to supply chain management of order placement in the ERP system, testing and documentation by the executive quality department, and commissioning of the individual components for the production process. In the course of qualification, the executive quality department also provided documentation in compliance with FDA and GMP requirements for the project to the fullest satisfaction of the customer.

Solution Path Benefits in Fast-track Projects

The planning of appropriate engineering steps according to quality by design (QbD) considers critical quality aspects (CQA) from the beginning and aims for increased process safety. In order to meet customer requirements completely, a precise coordination between the customer and all relevant experts is needed, who have to cooperate in a common team beyond the boundaries of the company.

The early initial analysis is particularly interesting for start-up companies that deal with the development of pharmaceutically active biomolecules. In joint workshops critical issues that need to be addressed are identified. This service represents a special value, since the project outcome is hard to predict at this stage.

The benefit of this approach is, that experts from different disciplines are working closely together without any external interface — except the one to the customer. This facilitates the complete engineering and development procedure as well as the realization of industrial production. The one-stop solution enables the pharma industry to meet the tight timeline of scale-up production and to execute projects on a fast-track in 22 months — even if it starts at green field.

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Opposites Attract

Blurring the Lines between Small and Large Molecule Manufacturing

The biopharmaceutical industry has grown impressively in recent years, with its global compound growth rate (CAGR) estimated to reach 8.5% between 2018 – 2023, outstripping traditional new chemical entity sectors. Emerging novel drugs show huge therapeutic potential, such as antibody-drug conjugates (ADCs), checkpoint inhibitors and viral gene therapy. But as the industry grows, it may face potential issues securing an expanded supply chain.

Until recently the bio industry's primary focus was to simply get their products to clinic as quickly as possible, with little incentive to focus on product and supply chain efficiency. However, now that the industry is experiencing greater demand and product volumes are increasing — coupled with generics and healthcare reforms — there is an increased desire to explore how overall cost of production can be lowered. It's a mirror image of the small molecule industries maturation some 10 or 20 years earlier. As a result, innovators and bio-generic companies are exploring not only how to speed products to market, but also, how they might lower costs in the commercial phase.

Large biopharma firms now have a greater number of drugs in the pipeline, and with an increased global prevalence of biosimilars, the supply chain will come under increasing pressure. But the industry is still in its relative infancy, and some of the key factors that may allow companies to meet these demands are not yet fully matured.

Additionally, as biologics developers now are more comfortable using outsourcing providers, there is a gradual shift away from performing all production activities in-house. This is due in part to many contract development and manufacturing organizations (CDMOs) developing and investing in the skills and technologies required to make biologic drugs.

Cell Therapies: A Key Opportunity

Looking ahead, the emerging drug pipeline of advanced and newer drug classes should further fuel outsourcing.

In fact, already, despite the pipeline's infancy, there have been significant moves by several CDMOs to build facilities for the emerging cell and gene therapies. Paragon, Brammer Bio, Fujifilm, Cobra Bio, WuXi Advanced Therapies and Lonza are amongst a host of earlier adopters — the latter in fact opened the world's largest dedicated cell and gene therapy facility in April.

Cell therapies could present a key opportunity for CDMOs because the technologies and methods used to make such products are still developing.

There are clearly parallels with how outsourcing in the small molecule space has contributed to increased manufacturing efficiencies and reducing overall costs. In fact, many solid dose CDMOs now sell their services on enabling technologies for compounds that are difficult to manufacture. Over the next few years there will likely happen a "technological arms race" amongst outsourcing providers to help increase efficiencies, lower costs and decrease clinical timelines in bio.

Rutger Oudejans, UBM

Growing Complexity of Biologics

Another aspect that may increase the amount of work in biologics is the growing complexity of biological products. Biotech firms, especially smaller ones, may have an innovative product or idea, but lack the expertise and technology required to develop or commercialize it.

The product classes themselves are also becoming increasingly intertwined, as many advanced therapies now contain a small molecules payload, such as in ADCs; whilst in stem cell therapies, molecules are sometimes used to trigger a therapeutic response. That is without even considering the fact that small molecules themselves are growing increasingly large, and peptides are now routinely synthesized rather than fermented. Oligonucleotides are in many ways a new class altogether — not fitting into the definitions of small or large molecule.

As a result, the level of limited collaborations across both small and large molecules in recent years increased — most notably in antibody-drug-conjugates. Many in the industry now believe there are transferrable skills and lessons that can be shared between the two, particularly in areas such as staff, processing and scale-up, as well as regulation.

API producers are potentially having the most relevant and transferable skills sets. Their experiences are most similar to what a biopharma company is replicating in everyday use. For example, API synthesis is performed in solution, with materials,

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molecules and reactants emerging over time. Thus, the instruments used for chemical and physical measurements for API production may only need minor alterations to be useful in fermentations. Continuous chromatography, which is beginning to become more common in API work, could also be used in bioprocesses.

Potential of a Cross Industry Collaboration

Beyond APIs there are potential benefits in exploring overall manufacturing methodologies. Whilst large molecule companies have only recently begun to generate their own optimization data, the small molecule industry has been around for 50 years, streamlining its supply chain to establish the best practices. Even if their production modes are distinct, there are certainly experiences of the small molecule industry that could pave the way for biopharma's own supply chain to flourish.

Addressing this issue directly, the 15th Annual Survey on Biopharmaceutical Manufacturing Production and Capacity, conducted by BioPlan Associates, asked 120 industry experts several questions about the potential integration.

The result of the study has shown that the most prominent areas where respondents believe they could learn from small molecule firms were:

- Process control (33%)
- Quality management (30%)
- Training operators and technicians (29%)

These top three areas are not particularly surprising since they address current good manufacturing process (GMP) practices, which are consistent across both the large and small molecule industries.

Other areas of potential crossover identified in the survey include scale-up or process development, clean room operations, regulatory compliance, and automation/process control, where just under a quarter of respondents believed that large molecule manufacturing could benefit from small molecule expertise. This indicates that a collaboration between the two industries could lead to greater production levels, with better quality and at a lower cost.

Large molecule manufacturers could also benefit in the future from the use of continuous bioprocessing. Although continuous methodologies have entered the small molecule space and are currently refined, biologics has not adopted it to the same degree. This may be due to the fact that continuous bioprocessing is more difficult because fermentation processes are one of the key requirements, which are restrictive for time, temperature and other factors. This means the drug formation rate may be limited and not allow for a continuous flow.

Whilst there is a lot that the large molecule industry can learn from its small molecule counterpart, there is still plenty to gain on the small molecule side of a collaboration between the two. As small molecule pharma manufacturers have established their best practices over the past 50 years, the industry tends to be risk averse and does not easily adopt new technologies; even though technologies such as continuous processing could lower costs over time.

Biopharma as an industry has been more adept at adopting new methods — such as single use technologies, which reduce the need for scale up, as well as complicated weighing and dispense steps, and cleaning validation.

If these two industries could learn from one another's strengths they will have the capability to manage and even streamline the complex supply chains and development timelines in order to meet greater demand and reduce the overall costs.

Outlook

Even though this trend is in an early stage, the industry is gradually moving towards a new era where pharmaceutical and biopharmaceutical manufacturing are no longer viewed as distinct entities — with workforces, regulatory pathways and new technologies working more closely together. In particular, the biopharma supply chain is becoming increasingly complicated, and managing these intricacies will be key to maintaining the industry's growth. Biopharma industry experts agree there are clear opportunities to learn from small molecule firms in refining their supply chain as well as finding new staff. However, what is interesting, is that in the small molecules space experts argue they may in fact have even more knowledge to pass on to the counterparts in bio. Finally, with novel processes and methodologies now being tested in bio, the small molecule space should explore how these newer approaches are being introduced into a highly-regulated space.

In terms of contract manufacturing, the fastest growth is now coming from bio CDMOs, with newer companies introducing contract cell and gene therapy services over the next 5-years — thus, supply chain learnings and skills from small molecule experts should be in increasingly high demand. Another approach to differentiate and achieve growth for smaller bio CDMOs is novel technologies that accelerate production and lower costs. Big pharma has already partnered with a number of smaller biotechs for anything from AI technologies to 3D micro-organoid modelling and bio process improvements — the latter is where there will likely be a new "arms race" for the best technologies amongst outsourcing providers. Big pharma will also seek to mirror its approach in the small molecule industry, and mitigate supply chain risk, by seeking to partner with several CDMOs in both development and commercialization of its most profitable new targets.

There are clearly short-term supply chain efficiencies to be learned from the small molecules sector, coupled with PAT and scale-up process improvements from the API space. But the willingness to take a long-term view and incorporate modern technologies — that may come with short term regulatory hurdles — is clearly something that bio is embracing much faster than its older compatriot.

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Index

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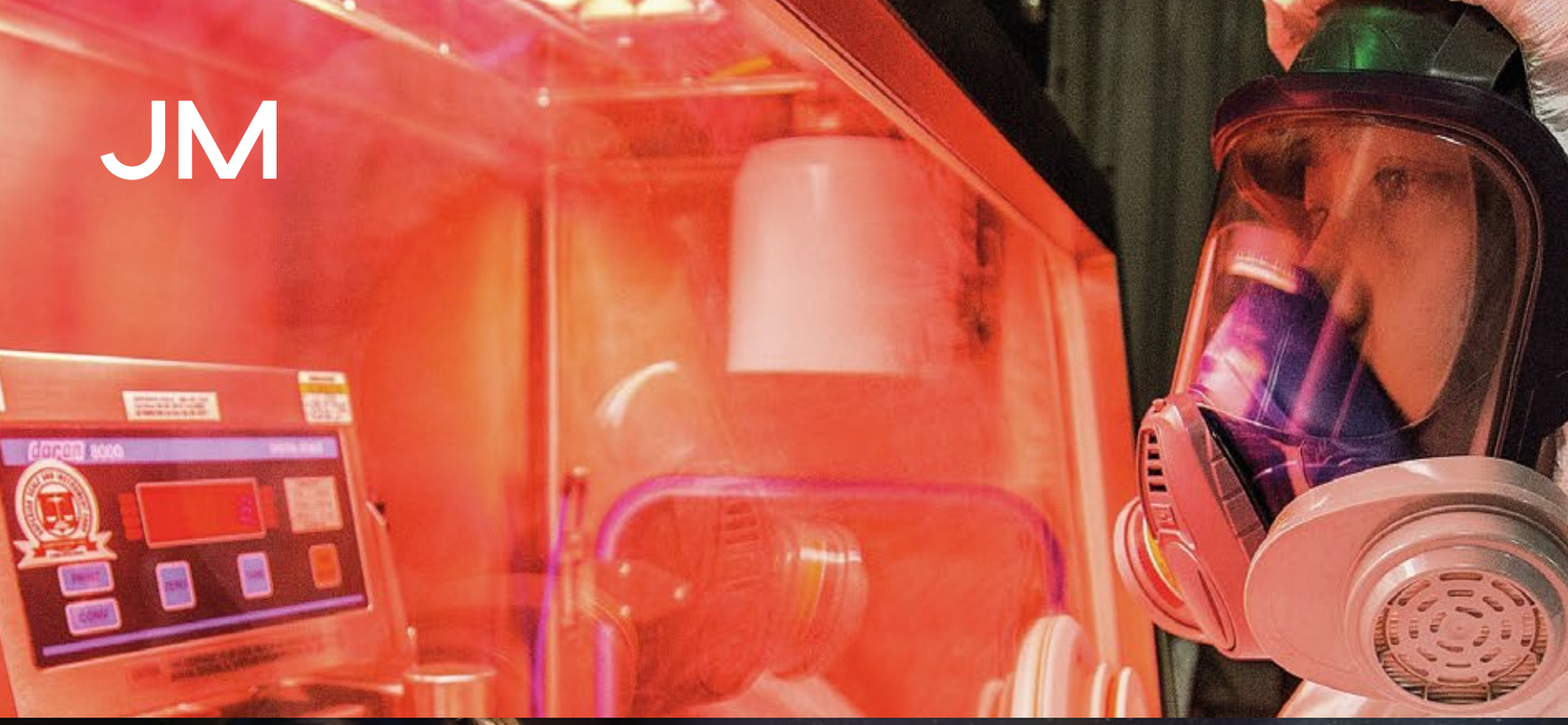

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