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Injecting Growth and Innovation

Pharma Takeover Carousel Turns Hot as Patents Expire and R&D Pipelines Run Dry

Abbvie takes over Allergan, Pfizer merges its generics business with Mylan, Takeda integrates Shire — the pharmaceutical industry is making a name for itself in 2019 with several billion-dollar acquisitions. This is an attempt to find new active ingredients, but also to develop a remedy against rising costs and increasing price pressure.

In the pharmaceutical and biotech industry, takeovers are part of the business model. If a company's own research and development (R&D) department does not produce enough new promising drugs, it may be possible to succeed with the products of a competitor. Conversations and negotiations about cooperations, mergers, and acquisitions therefore constantly take place everywhere in the pharmaceutical and biotech industries. However, such processes become more pronounced on a regular basis when the need for new input raises. In such times, transactions are driven to record values. And 2019 could be another year like this.

In January 2019, industry giant Bristol-Myers Squibb (BMS) announced its intention to acquire the cancer specialist Celgene for $74 billion. If the deal is concluded, it would be one of the largest takeovers in the pharmaceutical industry. BMS CEO Giovanni Caforio is flirting with the deal in order to strengthen his company's position in the lucrative cancer immunotherapy business. With an estimated sales volume of €20 billion, the US player would thus be ranked number two in the oncology sector behind Swiss market leader Roche.

"The era of billion-dollar blockbusters is coming to an end."

However, BMS is currently battling for antitrust approval of the deal. To get the green light, BMS intends to sell Celgene's psoriasis drug Otezla. After it was previously planned that the acquisition could be completed in the third quarter of 2019, the BMS management now expects the acquisition to be finished at the end of 2019 or beginning of 2020 due to the antitrust delays.

Also at the beginning of the year, Japanese pharmaceutical group Takeda signed a deal to acquire Irish competitor Shire for $62 billion. Shire is the largest foreign acquisition to date by a Japanese company. Takeda is particularly attracted by Shire´s cancer products. The Irish also have medicines for the gastrointestinal tract and the nervous system in their portfolio.

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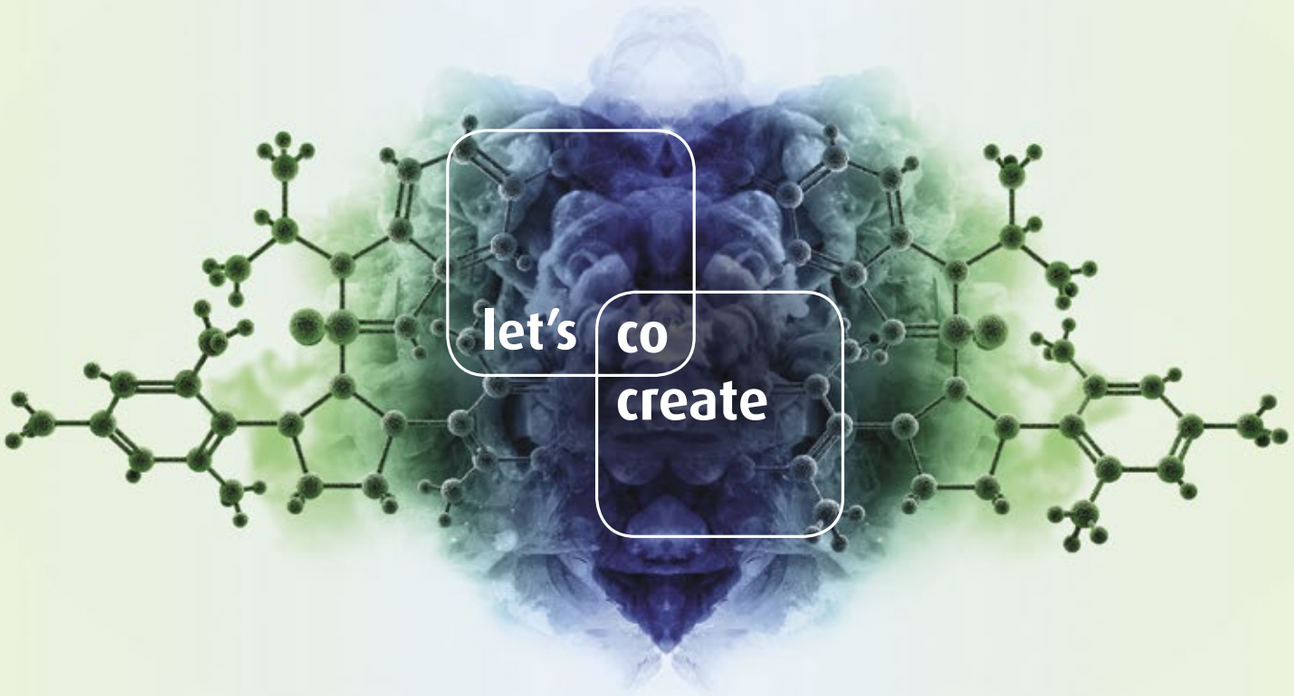

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Abbvie Has an Eye on Allergan

Finally so far, in June, US pharmaceutical group Abbvie announced its plan to acquire competitor Allergan for around $63 billion. In doing so, Abbvie, headquartered in North Chicago, Illinois, aims to reduce its dependence on the blockbuster drug Humira. The drug, which had its origins in the Ludwigshafen laboratories of the former BASF subsidiary Knoll, has in recent years been the world's largest sales driver in the pharmaceuticals business: In 2018 the product reached sales of about $20 billion. This means that the company achieved 60% of its total revenues of almost $33 billion with the rheumatism drug alone.

But the days of the almost inexhaustible cash flow for Abbvie are probably over for now. Last fall, patent protection for Humira expired in Europe, and since then several biosimilars were launched on the market. In order to compensate for the associated decline in sales, Abbvie urgently needs new promising active ingredients. The management hopes to find them in Allergan's product portfolio and pipeline.

"In the pharmaceutical and biotech industry, takeovers are part of the business model."

Allergan is best known for Botox. The anti-wrinkle product is used in cosmetic surgery as well as in neuromedicine. Even though the patent protection for Botox has long since expired, Allergan still generates $2.4 billion per year. Since this product is also coming under increasing competitive pressure, Allergan has been working on the development of new drugs in recent years, and Abbvie is now targeting them.

If it succeeds in overcoming the antitrust hurdles, the takeover will create a new industry giant with a total turnover of $49 billion, which is placed in the view of industry leader Pfizer ($53.6 billion).

Reorganization of the Generics Market

Weights are also being rebalanced on the global generics market. At the end of July, the world's largest pharmaceutical group Pfizer and its Dutch competitor Mylan agreed to establish a joint group for patent-free drugs. While Pfizer plans to divest its generics business with brands such as Lipitor, Celebrex, and Viagra under the umbrella of Upjohn and take over the majority of the new company, Mylan is to be fully integrated into the new company. This will create a new industry leader with an annual turnover of about $20 billion and a profit before taxes and depreciation of about $8 billion.

© Abbvie Inc.

Abbvie has an eye on Allergan, and Botox, a product of Allergan, could belong to the North Chicago, Illinois-based competitor in the near future.

Last but not least, the industry is making a name for itself in the current year through "smaller" consolidations and acquisitions. Pfizer has announced its intention to acquire Array Biopharma for $11 billion. Pfizer's ambitions may have been driven by good results Array has announced for combined therapy in patients with metastatic colorectal cancer. At an industry meeting at the beginning of June, the company also convinced with new data from a combination against a special advanced form of breast cancer.

Eli Lilly also took money into its hands. For $8 billion, the Indianapolis-based company bought its cancer research partner Loxo Oncology — an indication that the precision oncology research field is in great demand.

Just the Beginning

"This is just the beginning of a series of mergers to come," said Sarat Sethi of investment house Douglas C. Lane on CNBC television. That's 47% above the $170.2 billion combined value of the top 10 M&A deals during the first six months of 2018, highlighted in a "Top 10 M&A deals" of Genetic Engineering & Biotechnology News, a specialized information source for the industry. With further deals in the second half of the year, 2019 could close with record volumes after two years of weaker M&A activity.

Patents, Cost Pressure, Competition

The reasons for the intensive efforts of large pharmaceutical companies this year can be found in the pipelines and balance sheets of the corporations. Patents are expiring, cost pressure is increasing, the era of billion-dollar blockbusters is coming to an end and is being replaced by highly specialized products developed for smaller patient groups. In addition, there is competition from chemical and biological imitation products and the efforts of politicians and health insurance companies to keep prices under control. During the past 1.5 years, for example, the US government took various measures to lower drug prices and limit co-payments by patients. In addition, the financial return on R&D activities at biopharmaceutical companies is declining. This means that per each euro or dollar spent, companies often generate less turnover or profit than before. All in all, these developments are reflected in stagnating or declining sales. On the other hand, as the pharmaceutical companies grow in size by acquisitions, they can achieve efficiency gains, for example in research and development, but also in administration and sales.

"This is just the beginning of a series of mergers to come."

Sarat Sethi, Douglas C. Lane

In addition, US pharmaceutical companies in particular often have plenty of cash at their disposal, due among other things to the reduction in corporate taxes in 2017.

Weak Takeover Activity in 2018

In contrast to the good M&A year 2019 to date, pharmaceutical companies have lagged significantly behind their opportunities on the transaction market in the past year: Although the acquisition volume increased by 11% to $198 billion compared to 2017, however, the sum was around $90 billion less than the average amount invested between 2014 and 2016.

This is the conclusion of the auditing and consulting firm EY (Ernst & Young), that conducted and published a study on the financial data of the largest pharmaceutical, biotech, and specialty pharmaceutical companies earlier this year. EY's "Firepower Index" measures the purchasing power of biotech and pharmaceutical companies in M&A transactions on the basis of their market capitalization, cash, and debt capacity.

Companies would certainly be able to do more: the firepower — the funds that companies can mobilize for acquisitions — amounted to more than $1.2 trillion. However, only 16% of this was used in 2018. In 2014, companies still invested 27% of the funds available for mergers and acquisitions. The most common reasons for this reluctance were primarily the high prices that were called for takeover candidates and the global geopolitical and trade uncertainties.

German Companies not in First Place

By the way, German pharmaceutical companies only play a minor role in the takeover concert of the big players. In terms of sales, they also lag behind the global industry leaders, partly because lucrative oncological drugs often come from the USA or Switzerland. While the global market leaders from the USA and Switzerland increased their sales considerably last year, the local representatives dropped back. In 2018, the 22 companies surveyed by EY increased their pharmaceutical sales by 0.9% to €460.8 billion. However, German pharmaceutical companies can still boast one plus for themselves: they invest a lot of money on research. Merck and Boehringer Ingelheim, for example, spend more than the global average.

Thorsten Schueller, CHEManager

CDMO Market Forces Re-shape of M&A Activity

Deal-making in the Contract Development and Manufacturing Industry

Mergers and acquisitions (M&A) have played a pivotal role in the evolution of the contract development and manufacturing (CDMO) industry. However, after an especially active year in 2017 when 12 strategically and financially significant acquisitions were completed, the number of deals has dropped off sharply, with just five in 2018 and only two as of mid-June 2019.

The decline in significant deals reflects a variety of factors, including a shrinking pool of attractive acquisition candidates and the high multiples demanded by sellers. These factors could limit M&A activity in the near future, but other factors are emerging that will shape acquisition activity as well. These include the emergence of "mega-CDMOs," lack of capacity, and uncertainty in the macro environment.

Emergence of Mega-CDMOs

While the CDMO industry remains fragmented, we have seen the emergence of "mega-CDMOs," contract service providers generating $3 billion to $5 billion in revenues with the manufacturing scale, capabilities, and expertise to match all but the very largest biopharma companies. There are now at least four such companies, each offering a broad array of manufacturing and development capabilities and scale on the level of a $20-billion biopharma company: Catalent, Lonza, Thermo Fisher Scientific/Patheon, and Wuxi AppTec.

For these broad-based mega-CDMOs, the significance and drivers of M&A activity have changed. Most have achieved their positions through very expensive transformational acquisitions, but now that they have attained revenues of $3 billion to $5 billion, the typical acquisition target available in the CDMO industry hardly "moves the needle" in terms of the acquiring company's revenue or profitability. Consider the recent very expensive acquisitions of CDMOs providing cell and gene therapy development and manufacturing services: Thermo Fisher's $1.7-billion acquisition of Brammar Bio and Catalent's $1.2-billion acquisition of Paragon Bioservices, two deals completed in May of this year. Despite the large valuations of those deals, they only added about 5% to the acquiring company's revenues, but the strategic significance of participating in the fast-growing cell and gene therapy space made it imperative that Thermo Fisher and Catalent pay up to enter that market.

Jim Miller, DCAT

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The high-priced acquisitions of CDMOs providing cell and gene therapy development and manufacturing services spotlight a major consequence of the emergence of mega-CDMOs: an outbreak of intense rivalry among the market leaders. Such rivalries are common in industries and market segments where a few companies dominate, and they develop because the competitors have developed similar value propositions, e.g., Airbus versus Boeing.

Executives of industry leaders often perceive a need to match their rivals' capability-for-capability. In part that reflects the need to combat Wall Street perceptions that they might be falling behind competitors when they don't match their strategic moves. In the CDMO business, the stakes for matching capabilities are especially high and real because a given capability is often the entry point to a broad relationship encompassing the full palette of the CDMOs offerings: clinical supplies services can lead to a commercial manufacturing contract and an active pharmaceutical ingredient (API) manufacturing client can be convinced to have the drug product manufactured by the same supplier. A CDMO that lacks a critical piece can lose out on the whole supply chain. A perpetual game of leapfrog and catch-up will get played out in this environment.

One can see how rivalry may well have been a factor in the Thermo Fisher–Brammar and Catalent–Paragon deals. Not only do the two companies compete fiercely with each other, but the other two mega-CDMOs, Lonza and Wuxi AppTec, already have well-established presences in the cell and gene therapy market. Cell and gene therapy has emerged as a rapidly growing market segment that has captured the attention of investors, biopharma companies, and Wall Street analysts, and without their respective acquisitions, Thermo Fisher/Patheon and Catalent may have had to stand by while other rivals had the field to themselves. While Thermo Fisher and Catalent had legitimate strategic growth reasons to do those deals, the need to catch up to major rivals may have played a part in their decisions.

Intense competition among rivals can drive up multiples for strategic acquisitions as they outbid each other for prized targets, e.g., an API or drug product manufacturer with substantial revenues and a pristine reputation. There are few such targets left, so if one comes to market, the bidding is likely to be intense.

Need for Capacity

CDMOs continue to benefit from an extremely strong market environment. Emerging biopharma companies raised record levels of funds in 2017 and 2018 and are endowed with ample cash to fund their pipelines. According to the Biotechnology Innovation Organization (BIO), emerging biopharma companies in the US raised $12.3 billion of venture capital in 2018, double what they raised in 2016, and raised $5.2 billion in initial public offerings (IPOs), nearly five times what was raised in 2016. Furthermore, the financial markets' love affair with biopharma has continued into 2019, with 22 companies raising $2 billion through the end of May.

Most of the development spending by emerging biopharma companies is funneled through CDMOs. While financial reporting from CDMOs is limited, results of their clini-

Continued Page 10 ▶

cal and preclinical contract services cousins indicate that the market is quite robust, with first-quarter revenue growth rates typically in the high single digits (7–10%) or even double-digits (up to 25%).

To respond to these robust growth opportunities, CDMOs need capacity, and M&A has traditionally been a favored avenue for getting it. Buying companies rather than building capacity has multiple advantages, including immediate market entry or incremental capacity, an established book of business and customer base, and an established work force. There is an expectation that revenue can be built quickly via the acquirer's sales force, and that some cost savings can be realized through integration of overhead operations.

However, capacity-driven acquisitions of CDMOs are almost unheard of these days because with demand so robust, most CDMOs have little spare capacity available. CDMOs seeking capacity must look to facilities being shed by biopharma companies that no longer need the in-house capacity. The most significant of these deals announced as of mid-June 2019 have been Thermo Fisher's/Patheon's €90-million ($100.6-million) acquisition of a GlaxoSmithKline small-molecule API facility in Ireland and Biogen's sale of its large-molecule facility in Denmark to Fujifilm Diosynth Biotechnologies for $890 million.

While manufacturing facility acquisitions add needed production capacity, that opportunity generally isn't available for development capacity. Biopharma companies generally aren't selling entire development facilities and development capacity is constrained more by the availability of skilled and experienced professionals than it is by equipment. Even large CDMOs are willing to consider very small acquisitions out of desperation to gain needed development capacity.

Macroeconomic Uncertainty

The broader economic environment in which the biopharma industry operates is becoming very uncertain. Anti-trade sentiments and policies are dangerous for an industry whose supply chains are very global. The threat does not come just from tariffs, but regulatory policies that encourage local production and use non-tariff barriers, such as product marketing authorizations and regulatory compliance inspections.

A big concern comes from the fact that the United States is the largest biopharma market and is instigating many of these anti-trade measures. China, Mexico, India and the European Union have all been in the US crosshairs of late. All are important links in the biopharma supply chain because of their low local production costs or favorable tax policies.

Pharmaceuticals get favorable status in many current free trade agreements, but if anti-trade policies are targeted at biopharma companies, they may be forced to redesign supply chains built in a free-trade environment and reconsider where their products are made. Rather than building global centers of excellence or large-scale facilities meant to supply global markets, companies may be forced to re-localize manufacturing operations.

The rejiggering of supply chains could cut both ways for CDMOs. The re-localization of manufacturing could benefit CDMOs, whose multi-product facilities would offer biopharma companies an alternative to building networks of sub-scale captive facilities. On the other hand, CDMO businesses built on leveraging the cost advantages of offshore operations could find themselves disadvantaged by the offshore networks.

This uncertain environment raises important questions that complicate decisions regarding what assets should be bought and where they are located. What are the risks of acquiring a facility in Europe or India or China if the facility is meant to serve more than just local markets? Will the financial return of an acquisition change significantly if the terms of trade are altered? Questions such as these could impact the M&A deal flow going forward.

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Amgen Makes $13 billion Grab for Otezla

Contrary to recent speculation that Amgen was preparing to buy Alexion, the California-based US biotech has announced that it instead will acquire Celgene's Otezla, the only oral, non-biologic treatment for psoriasis and psoriatic arthritis, along with certain related assets and liabilities.

The deal is worth $13.4 billion in cash or around $11.2 billion net of the present value of $2.2 billion in anticipated future cash tax benefits, Amgen said. The transaction's going ahead is crucial for the acquisition of Celgene by BristolMyers Squibb. Sales of Otezla, driven by strong volume growth, totaled $1.6 billion in in 2018.

Commenting on the purchase, US pharma journal Fierce Pharma said the price "easily dwarfs some recent biopharma deals for entire companies and is significantly above the price tag analysts have previously estimated for Otezla, which suggests an intense bidding process."

Robert A. Bradway, chairman and CEO of Amgen, said Otezla "fits squarely" with Amgen's portfolio and is complementary to its existing inflammation franchise of innovative biologics and biosimilar products. He said the company will take advantage of its 20 years of experience in inflammatory disease to realize the franchise's full global potential as an affordable option for patients with these serious, chronic inflammatory conditions.

The drug already approved in 54 markets outside the US, including the EU and Japan, is claimed to be the leading treatment in the post-topical, pre-biologic segment in its three US indications. It is recommended for patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy, as well as in adult patients with active psoriatic arthritis and adult patients with oral ulcers associated with Behçet's Disease. Otezla has patent exclusivity through at least 2028.

Amgen said the transaction should contribute to its near- and long-term revenue growth rate and will be immediately accretive from close to non-GAAP earnings per share growth, with acceleration thereafter.

The company expects "at least low double-digit sales growth" for Otezla over the next five years. (dw, rk)

Bayer to Sell Animal Health to Elanco

Bayer has definitively agreed to sell its animal health business to Eli Lilly spinoff Elanco Animal Health. The $7.6 billion deal will create the market's second largest player, with a share of 13%, behind Zoetis and ahead of unlisted Boehringer Ingelheim.

The acquisition price is in the range mooted earlier and consists of $5.3 billion in cash, subject to adjustments, and $2.3 billion in Elanco shares based on the unaffected 30-day volume weighted average price as of Aug. 6, 2019.

Elanco said the shares transferred to Bayer would be equivalent to around 18.2% of the new animal health player but the number could rise or fall by as much as 7.5%, depending on the closing date price.

The German group said the transaction value represents an implied multiple of 18.8x based on the animal health business's 12-months EBITDA before special items as of Jun. 30, 2019.

The divestment should be concluded by mid-2020, subject to antitrust clearance and other customary closing conditions, it said.

As predicted by analysts, due to Elanco's large debt burden following its separation from Lilly, Bayer will be obliged to retain its equity stake in the divested business for an undetermined time.

Elanco plans to fund the cash payment with a combination of new debt and equity and that the size of the proposed equity increase will depend on future market developments. Bayer itself is carrying a debt load of around €35.7 billion ($39.6 billion), inflated by its $63 billion acquisition of Monsanto.

The deal is the biggest in a series of portfolio measures Bayer initiated in November 2018 to help fund its acquisition of Monsanto. It has already announced to shed its consumer health brands Coppertone and Dr. Scholl's.

Germany's Beiersdorf is picking up the sun care product for $550 million, and US private equity group Yellow Wood will take the foot care portfolio for $585 million.

Bayer will also sell its 60% in site services provider Currenta to Macquarie Infrastructure and Real Assets (MIRA) for €1.7 billion ($1.9 billion). (dw, rk)

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Innovative Pricing for Sustainable Growth

Why CDMOs Should Consider Value-based Pricing

Outsourcing product development and manufacturing has become for many pharmaceutical and biotech companies a strategic activity and an integral part of their business model. In order to capitalize on this trend, contract development and manufacturing organizations (CDMOs) need to continuously optimize their commercial strategy by establishing and enforcing a value-based pricing concept.

Omar Ahmad, Simon-Kucher & Partners

Kaan-Fabian Kekec, Simon-Kucher & Partners

The pharmaceutical industry continues to grow and is estimated to be worth $1.5 trillion by 2021. One important element of this development: the accelerating trend towards outsourcing product development and manufacturing to CDMOs. What sounds like good news for CDMOs also holds its own challenges — many CDMOs are operating in a highly fragmented market that is currently undergoing a significant consolidation. At the same time, many of them are not fully prepared to exploit the maximum potential and willingness-to-pay in project pricing. This calls for new and innovative monetization strategies, with the right approach to project pricing as a vital element. Price is the single most powerful lever to increase a company's profits. However, right now, far too many companies are still clinging to traditional cost-plus pricing logics that usually lack consistency, transparency and control and in most cases are set based on a pre-determined self-fulling margin target. This approach needs to be replaced by harmonized costing methodologies, value-based pricing metrics, and systematic usage of internal project price benchmarks. These three areas will enable CDMOs to develop a value-based price model that fully exploits price potential and monetizes willingness-to-pay.

Pricing-Related Commercial Challenges of CDMOs

Based on our project experience, we observe a number of typical pricing issues at CDMOs:

- **Non-transparent costing:** For CDMOs, every project is different, and costs depend on countless variables. Consequently, determining the full costing is essential to make sure that companies operate profitably. However, in many cases managing directors of individual sites manage their own profit and loss statements and often exert their will for project scoping and costing. In this context, the way costs are calculated and reported can differ based won site-specific preferences and legacy. This leads to costing of projects often becoming a black box to central commercial CDMO functions as sites use different cost calculation methodologies and level of granularity.
- **No value-based pricing:** Pricing is short-term, cost-plus and silo focused; CDMOs do not systematically exploit differentiated margins based on client value or strategic service elements. What we see is that CDMOs often apply a standard site-specific mark-up on their costing without considering the value of individual services and as such simply apply a one-size fits all approach. Some services might be standard, others unique and should ideally call for a higher or differentiated mark-up.
- **Insufficient pricing benchmarks and intelligence:** The limited availability of historic project bench-

marks and post-deal profitability analysis prevents clever and consistent pricing decisions. Since project specificities and prices are not documented systematically, business development managers often don't have full visibility on past projects and their pricing for recurring clients. This gets even more challenging if a CDMO has a global footprint and customers have several touchpoints within the company. The full value of a client is not understood and the CDMO's negotiating position is considerably weakened.

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Solution outlook: A price model concept combining both value-based mark-ups and client specific fine-tuning tools.

In an increasingly segmented market where CDMOs acquire more and more sites to widen their geographical footprint as well as extend their technical offerings, solving these problems can be tough but not impossible. Based on our project experience, we were able to extract some best practice approaches.

Costing: Use Local Cost Levels Following a Globally Aligned Consistent Logic

No two projects are alike, so costs as well as client needs differ greatly. To standardize project costing, companies have to develop guidelines, tools, and processes on top or replacing site policies. This enables site managers to make their own decisions, but within a certain framework, following a company-wide costing logic and granularity. The first fundamental step is to enable every site to assess costs realistically based on a consistent guiding principle. Striking a common balance on the level of cost granularity applied enables different sites to calculate costs coherently on a per service element.

Value-based Pricing: Capture Project-specific Value Drivers to Extract Willingness to Pay

CDMOs then have to identify all relevant value and price drivers as well as their magnitude to apply to the cost base per service element. The problem: They often lack reliable data input. Market research data is not available since projects are unique and the pharma industry is considerably small. Testing CDMOs' customers' value perception and willingness to pay in the same way other industries are able to do so is not easy. Consequently, companies need to work with experts and proxies to determine clients' perception of value. After determining these value and price drivers (e.g. type of drug potential, client time pressure, reliability risk, commercial price potential of drug, site capacity), they are subsequently translated into quantifiable margin mark-ups or -downs. Best-in-class CDMOs even categorize their services according to the level of differentiation vs. competition and apply differentiated value mark-ups instead of always applying the same one across the board. Combined with price benchmarks, CDMOs can now move away from gut feelings and ensure that price variations between similar contracts and customers are narrow.

Benchmarking: Providing Historical Transparency for Pricing Managers

Right now, most CDMOs don't have any system at all that documents project pricing. The result: inconsistent pricing for similar services. This backfires if it happens with the same customer leading to unnecessary irritation and frustration. A database containing historical project information for both won and lost deals provides an antidote and serves as valuable pricing decision support information. In here, every project is registered and sorted based on predefined criteria so that the information can be easily pulled for future pricing decisions. This is especially vital since CDMO projects vary widely which requires that useful benchmarks contain a high level of "definition" granularity. A central system which collects, documents as well as incorporates and institutionalizes price benchmarks will provide pricing mangers the overview to make optimal pricing decisions.

Implementation through Clever Pricing Tools

To ensure CDMOs use a consistent pricing approach, they not only have to develop the value-based pricing metric but also define the processes to use it. A simple solution is to develop an easy-to-use pricing tool that harmonizes costing methodologies and uses value-based pricing methods as well as newly defined benchmarks to support quotes. Such a customized pricing tool allows projects to be configured and priced in a structured way. Along with a systematic project pricing logic — based on value-based mark-ups/downs — this significantly increases the chances for CDMOs to best exploit customer willingness to pay and negotiate optimal prices. In doing so the reward can be significant and from our experience: CDMOs are usually able to improve their margin and profitability by three to six percent return on sales.

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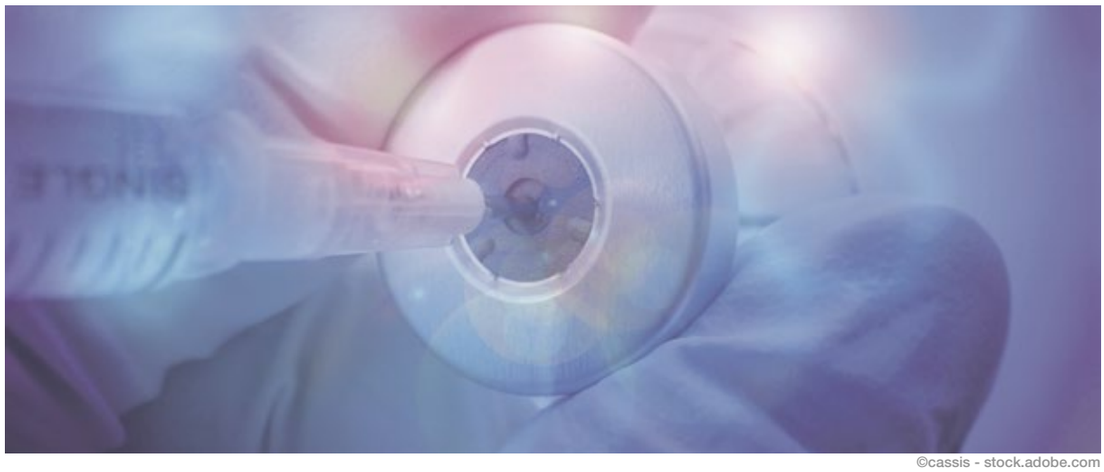
The Pharma CDMO Challenge

Outsourcing Adds Value and Reduces Risk in Development Projects, but Partners Need to Set up Fair Prizing Models

The pharmaceutical industry continues to grow and is estimated to be worth $1.5 trillion by 2021. One important driver is the trend towards outsourcing of development and manufacturing to contract development and manufacturing organizations (CDMOs). What sounds like good news for CDMOs also holds its own challenges — many of these companies are operating in a highly fragmented market that is currently undergoing a significant consolidation. At the same time, many of them are not fully prepared to exploit the maximum potential and willingness-to-pay in project pricing, which calls for new and innovative monetization strategies.



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Since price is the single most powerful lever to increase a company's profits, it is high time for CDMOs to reconsider their project pricing approach. Instead of clinging to traditional cost-plus pricing logic that usually lack consistency, transparency and control, experts propose measures such as harmonizing costing methodologies, incorporating value-based pricing metrics, and systematically using internal project price benchmarks for developing a value-based price model. CHEManager International asked executives and opinion leaders operating in this market to share their experience and advice. We asked the experts to discuss the following questions:

1. How would you describe the current market situation for pharma CDMOs and which trends affecting your project pipeline do you see?
2. Which role can CDMOs play in helping pharma companies to manage development, production and supply chain cost?
3. How do you rate the potential of value-based pricing models as a contracting strategy and how do your customers respond to that?

Read their insightful answers here.

Value Pricing Makes Sense

Harry Christiaens, CEO, Ardena

1 The outsourcing market fundamentals are highly favorable and are likely to remain so. There is still a strong funding environment. Increasingly, innovation shifts from traditional pharma to small venture capital-funded players who are outsourcing many of their R&D activities. There has been a significant expansion in the number of biotech companies that are focused on a business model of developing a molecule through to the proof-of-concept stage, and then selling or licensing the molecule to a pharma partner.

The development of precision drugs with higher efficacy and lower toxicity is an emerging market. We observe an increasing demand for the development and manufacturing of nanomedicines, enabling target delivery of APIs.

2 We strongly believe that a multidisciplinary approach can accelerate the drug development and approval process. At Ardena, we have integrated chemical and pharmaceutical development services on one platform. This provides customer convenience: clients do not have to deal with multiple vendors. We coordinate development programs, streamline communication and reduce any contracting burden. Moreover, by integrating our services, we are able to better mitigate development risks and ultimately reduce time-to-clinic. A siloed, serial and fragmented approach to drug development may lead to poor and delayed distribution of information, causing duplicate work and even rework, particularly in early-phase development where study design is subject to continuous change.

3 Value pricing makes sense, but it needs a deep understanding of what is actually valued by a customer. Is it time, service level, flexibility, etc.? Values are likely to be customer dependent or even project dependent. Moreover, values will need to be defined unambiguously so value capture can be measured objectively upon service execution. Today we offer our R&D-services on a cost plus or FTE basis. Customers that want to secure capacity or prefer all-time flexibility are more in favor of FTE contracts.

A Shift to Smaller Pharma Companies

Matthew Moorcroft, vice president Global Marketing & Intelligence, Cambrex

1 Until very recently, the majority of small molecules in the clinical pipeline were being developed by the larger, top 30 pharmaceutical companies. Today, however, data shows that this trend is strikingly different with approximately 65% of the current pipeline being developed by small and virtual pharma companies, many of which do not yet have revenue from commercial products and are backed by venture capital or private equity funding.

Instead of the traditional model where smaller, less capital intensive, companies would have typically looked to out-license their candidates halfway through the clinical trial process (usually stopping soon after phase II), the recent rise of drugs being tested in smaller patient cohorts, such as oncology or orphan diseases, has allowed the development of these molecules to stay at the original innovator. This shift to smaller companies can bring additional changes or demands on the supplier base and the preference for working with CDMOs with end-to-end or integrated capabilities. Typically, these companies have limited resources in corporate functions such as procurement and supply chain management, and these roles are typically filled with people with other responsibilities. The benefits of using CDMOs that can manage more of the supply chain (drug substance, drug product, clinical and commercial supply) means a reduced set of CDMO partners to manage, fewer supplier agreements to negotiate, fewer people involved in decision making, and can avoid multiple points of contact for each project.

Cambrex made two recent acquisitions — Halo Pharma in 2018 and Avista Pharma Solutions in 2019 — adding drug product manufacturing and analytical services to the company's expertise in drug substance, and broadening its capabilities to support small molecule drug developers looking for an integrated service provider. As well as new services, it allowed Cambrex to broaden the customer base and potential complementary customer service offerings.

SMEs Need an Experienced Outsourcing Partner

Jessica Cao, vice president, Marketing & Strategy, Rx Oral Dose, Catalent

❶ Around 75% of the current development pipeline comes from small and mid-sized companies, contributing to an increase in outsourcing from smaller companies that do not have the resources of large pharma. They need an experienced outsourcing partner such as Catalent to assist in every aspect of development, from drug candidate selection, formulation, clinical supplies, to commercial manufacturing. CDMOs can help solve challenges and de-risk projects, leading to time and cost savings. Drug design targets can be set, focusing on the key goal, to deliver the best possible treatments effectively, safely and conveniently to patients. CDMOs must adapt to a range of customer needs, by offering access to proven technologies, or by improving R&D effectiveness through candidate selection or developing drug delivery systems which improve patients' experience. Catalent's $27 million investment will commercialize Zydis Ultra technology, a next-generation oral disintegrating tablet (ODT) at its Swindon, UK facility. This enables an increased drug load and taste masking to be incorporated into the conventional Zydis ODT, a unique freeze-dried tablet that disperses almost instantly in the mouth without water. This advancement will further improve patient compliance, leading to better outcomes.

The project pipeline is changing as novel technologies such as biopharma therapeutics and cell and gene therapies mature in their development. CDMOs have begun to invest in these technologies, broadening their offerings to meet the demands of the industry's evolving research directions.

Another example is bioavailability enhancing technologies such as spray drying. Poorly soluble compounds continue to dominate the pipeline. An increased demand for commercial-scale spray drying has created a significant capacity challenge, with customers waiting an average of 15 months to access commercial spray drying, delaying new treatments. Catalent structured a creative deal with Sanofi, providing the industry with access to Sanofi's state-of-the art commercial spray drying facility in Haverhill, UK.

Flexible Solutions for Gene and Gene-modified Cell Therapies

Kai Pohlmeyer, managing director, Richter-Helm BioLogics

❶ We have seen the biologics market growing steadily over the last years. This growth goes hand in hand with a noticeable shift from big blockbuster products to niche drugs for the treatment of rare diseases. As a complement to monoclonal antibodies, recombinant proteins and vaccines, gene and gene-modified cell therapies which have been firstly approved in 2017 will bring even more variety into the biologics market in the next years.

❷ Starting from research and development over the different clinical phases up to market supply, CDMOs flexibly offer services and manufacturing capabilities covering the whole value chain of biopharmaceutical production by a one stop shop approach. Collaborations with CDMOs can significantly reduce total development risks and cost as well as time to market. Flexibility means availability of capabilities at different scales and qualities to supply customer's needs during development of a product and its whole lifecycle.

A good example is manufacture of plasmid DNA which is used as a critical starting material for virus-based gene and cell-therapeutic approaches, mRNA manufacture or as drug substance itself. For the different applications Richter-Helm offers capabilities under R&D conditions and GMP manufacture at different scales ranging — from gram-scale to the 100-gram-scale — providing plasmid DNA for development of a product up to market supply.

Closing Gaps

Lukas von Hippel, managing director, Pharma Waldhof

❷ No company in the world will be able to have all technologies and relevant production assets in own hands. This may lead to several strategic options.
Option 1: Companies may develop only products that fit their actual permissions, and, if needed, invest in fitting equipment. Such approach does mean the company is limited in potential developments since no company in the world can combine all technologies and does have all relevant talent and techniques on hand in-house. Even there are more and more companies trying to broaden their technological foundation, limitations will apply.
Option 2: Companies may look for partners which are able to close gaps. Such gaps may be driven by technologies, skills, size of equipment, just to name a few aspects for outsourcing. In our current world, equipment is no longer a factor. The worldwide capacity is more than enough to oversupply the world's demand. What limits success are other aspects: A sound understanding of quality, a proven ability to deliver, and skilled people who understand their customers' requirements. It may be an active part of risk management to work with those organizations that have the assets and technological skills.
We can spend our money only once, following option 1 or 2. Most opt for option 2 since it does offer more flexibility and opens access to talent and technologies. This is why more and more companies are reaching out to us asking for development of certain products that use our skills which not too many other companies have: Bridging chemistry and biotechnology, we are the logical hub to discuss possibilities to develop certain products. The more and better chemistry and biochemistry develops, the more our products, our technologies and our skills are getting recognized.

Providing Expertise

Michael Quirmbach, CEO & president, CordenPharma

❶ As the pharmaceutical industry is evolving towards targeted drug delivery platforms with a much stronger strategic focus on niche indications, the molecules which are being developed as a consequence tend to be more complex — e.g. gene cell therapy, biologics, ADC's, oligonucleotides, and peptides — just to name a few hot areas. This trend requires a very different range of development and manufacturing capabilities to ensure these new drugs will be cost-effective and efficiently produced. This is where CDMOs today play a major role — by providing expertise not available in-house at biotech / pharma companies. Furthermore, the increasing complexity and necessity to both reduce time-to-market and development costs make it nearly mandatory to rely on outside expertise and collaboration with strong, well-run CDMOs. Both large & small pharma companies are therefore evaluating strategic, integrated partners who can seamlessly deliver on multiple projects, thereby reducing the complexity of their supplier network. Currently, the pharma CDMO industry benefits from continued demand in many areas such as injectables (combination products), high-potency, and oncology and biologics.
❷ CDMOs support pharmaceutical companies by either providing a single development or manufacturing service (API or drug product) in their area of expertise, which the pharma company lacks, or by becoming a strategic partner on multiple projects with broader product offerings, including the ultimate end-to-end service model. In particular, the latter has gained increasing interest due to the number of high-profile acquisitions within the CDMO industry. This growing demand for enhanced capabilities, greater capacity and oftentimes global reach will continue heading towards the full-service supply chain model for CDMOs, making them a recognized and respected strategic partner to their pharma customers. This is a great opportunity for the pharma companies to potentially simplify their manufacturing and distribution network, reduce their resources, and ultimately accelerate development and manufacturing within transparent cost control parameters.
❸ In the past we saw value-based pricing principles less utilized in the CDMO industry. However moving forward, I expect that will change as the normal evolution of our industry reflects CDMOs moving away from simply being transactional low-value service (one-time) providers to delivering more sophisticated, value-added strategic services & technologies. This also means the compensation model requires adjustment and flexibility on both sides — allowing the CDMO to continue investment in know-how and infrastructure, while also capturing a fair share of the value added as part of their enhanced contribution, collaboration and support.

An Exciting Time for CDMOs

Ravi Venkataramanan, global head Custom Pharma Services, Dr. Reddy's Laboratories

❶ Insights from our on-field business development team, back-end digital marketing team and customer interfacing departments are immensely helpful. While we meet present needs of our customers, it is imperative to continuously develop new skills in future technologies, and in the process of doing so we come across various data points that indicate current market and future trends. It is an exciting time for CDMOs because their contribution to providing affordable, accessible and innovative medicines is well recognized by the pharma industry. There are CDMOs that are independent businesses, there are few which are from innovator companies and few that are part of generic companies. With this mix of experiences, a CDMO's customer base also varies. A virtual biotech might look for a one-stop-shop, while a small biotech seeks strong regulatory experience, medium size customers look for partnerships for new markets etc. CDMOs are consolidating to offer end-to-end services and investing in R&D to enable new technologies like oligonucleotide chemistry or complex formulations chip-in-tablet. Pipelines are constituted by new drugs, re-purposed drugs and combination products. In terms of chemistries, peptides, oligonucleotides, conjugated products like PEG-lipid-carbohydrate etc. are increasing. The demand for high potent drugs continuous to increase and so are the number of poorly water-soluble drugs that require solubility and bioavailability enhancement technologies.
❸ CDMOs do their pricing in different ways. From what we see, the typical "cost-plus" model continues to be the standard for most companies. And this is more because of the industry's (both CDMOs and customers) familiarity with the concept and its implementation than its absolute benefits. A value-based pricing model is often seen as opportunistic and comparatively exaggerated. But if we look at it across industries, this bias might not be factual. In fact, in the last decade of our work with global customers we see this changing. It is important for the sponsor to have full transparency and to understand the value created by the CDMO as a differentiated product, intellectual property, access to additional markets, ease of regulatory review or as simple as assurance of product supply or service. A CDMO with well identified capabilities and tangible advantages over its peers can provide good reasons for a value-based pricing. Today we see around 8-12% of our customers opting for this model as they have started seeing that it is a "value optimized" pricing that benefits both, CDMOs as well as customers. A holistic assessment of the pricing proposition is of course key. Every request for proposal (RFP) is an opportunity to create value for customers and if the key question as to "what is that value" could be answered then it has the potential to be converted to a value-based pricing model.

Price is the Key Factor

Gabriel Haering, CEO, Cerbios Pharma

❷ A simple question with a complex answer! The approach is very different depending on company size and outsourcing needs. Let us see pharma companies in three segments and approaches.
Big pharma and large biotech (with internal production)Outsourcing can be described as more tactical than strategic. Usually they have established a number of preferred suppliers they know and trust from previous experiences. Entering as new CDMO is quite difficult unless you have unique features and specialties they do not have in house or other CDMOs have.
Medium to large biotech (with no production)For them CDMOs are strategic. Expectations are for long-term partnerships supported by very close communication at all levels, from R&D team to quality team through a very strong project management system. Expectations are not only the deliverables (on time, in full), but also bringing continuous innovation and ideas for process and cost improvements. Value is very important for them.
Small virtual pharma companiesCDMOs are definitely strategic for them. However, they have limited resources (people and money) and often no experience at all. They rely completely on the CDMO know-how and expertise. As CDMO patience is needed. The project depends on financing rounds and the project can move from full speed (need the product yesterday) to a sudden halt. The CDMO needs to act as consultant suggesting what activities need to be done at what stage in order to keep the regulatory needs in line with the budget available. They look for innovative financing models since price is the key factor.
In conclusion. A project price (cost) derived from a request for proposal is different for every CDMO. What the contract giver has to consider and evaluate is the value behind it. A reliable supplier that will maintain the timelines promised that will not delay the clinical trial and potential launch date of the new drug brings value. I already said it in the past: "Price is what you pay. Value is what you get!" And our slogan describes it perfectly: Fostering Value through Innovation.

Accelerating Timelines

Christian Dowdeswell, vice president, business unit head, Dosage Form and Delivery Systems, Lonza

We believe CDMOs have a key role to play in helping customers rapidly design, develop and scale-up innovative medicines and bring them to patients around the world. One of our priorities at Lonza is ensuring that our technologies and capabilities are aligned with the pipeline and approval trends for new medicines. To provide the partnership that our customers value, we also focus on employing phase-appropriate formulation approaches that can both accelerate timelines to clinical studies and be readily scaled.

We continue to align with several key trends that have resulted in more complex drug molecules and requirements for innovative delivery mechanisms. First, there are more highly potent compounds in the pipeline, driven by oncology research, as treatments become more effectively facilitated by improved targeting of disease states. Second, the continued prevalence of molecules with bioavailability challenges, i.e. Biopharmaceutical Classification System (BCS) II/IV classes, with an estimated 90% of the preclinical compounds now estimated to have low solubility.

At the same time, in developed markets we are seeing a continued rise in specialty drug products in the pipeline, as well as orphan, fast-track and 505(b)(2) designations. Specialty drugs accounted for 39% of global sales in 2018 and are expected to be more than 50% of the US market by 2023. Meanwhile, orphan drug products exceeded 50% of new compounds approved by both the FDA and the EMA in 2018 and projected to account for approximately two thirds of the FDA's forecasted approvals through 2023. The impact that CDMOs must consider is the resultant shift towards higher-value drugs that have lower production volume requirements of both API and finished drug product.

Additionally, the majority of today's specialty drug pipeline is held by small biopharma companies and these companies are increasingly commercializing their compounds. Nearly 60% of 2018 FDA filings were from small companies, almost twice as many as in 2011, when only 31% of filings were from the small company category. Establishing market position can be especially critical for small biopharma players, which may have only one or a few compounds, meaning speed to market of their products — often orphan or 505(b)2 applications — is paramount.

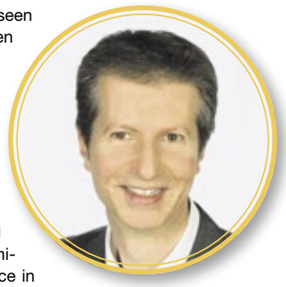
Looking ahead, we see a net shift in our customer mix towards smaller biopharma companies — sometimes even virtual — that have very limited in-house capabilities. These organizations typically need specialized drug delivery technologies and expertise, as well as development and manufacturing infrastructure, often under containment, to progress their compounds. Phase-appropriate and specific drug-appropriate infrastructure is also increasingly required for specialty medicines.

These trends indicate that biopharma companies have an amplified need for fit-for-purpose solutions — bioavailability enhancement and drug delivery technologies, services, infrastructure and commercial arrangements. Flexibility is critical as are partners that can and are willing to tailor their development and commercial approaches to fit the individual customer and drug program requirements. Integrated approaches for API and drug product development can be of huge value and must be available for customers with accelerated timeline requirements.

Biopharmaceutical companies can benefit from working with CDMO partners that have already adapted to the aforementioned trends to help bring innovative drug products to patients.

Introducing Cost Efficiencies

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



❶ The global pharmaceutical CDMO market has seen continuous growth over the past few years, driven by pharma companies striving to lower costs and gain access to innovative technologies. Within the market, oncology continues to grow at an accelerated pace. As a result, we have seen significant growth in highly potent active pharmaceutical ingredients (hAPIs) being developed for use in cancer therapies.
However, there are health risks associated with the manufacture of hAPIs that must be addressed to ensure both patient and operator safety. At Umicore, we have extensive expertise and experience in handling these highly toxic and pyrophoric materials. This demonstrates to our customers that we are the ideal partner for safe and efficient manufacturing of the next generation of hAPIs.
❷ As the regulatory environment continues to move with constantly evolving customer demands, it is important that CDMOs remain dynamic in their business approach. Ideally, CDMOs should be proactive and propose their new technologies to pharmaceutical customers. They should focus on how these new solutions can help to manage development, accelerate production and lower supply chain costs. To achieve this, it is important that CDMOs invest heavily in their specialist field of technology. At Umicore, we understand that technology is at the core of our success, and as such, we endeavor to meet the needs of a rapidly changing industry.
❸ Within the industry, many are seeking new ways to introduce cost efficiencies into all aspects of drug development. As such, value-based pricing models are often viewed as a solution to create a more effective pricing method. The requirements for establishing value-based pricing models can be complex, although this can be made simpler if both the supplier and the CDMO define the important project criteria. If it is agreed that product quality is the key goal of outsourcing, then delivery time can be adjusted to ensure a high-quality product. At Umicore, we leverage our decades of experience in collaborating to provide our customers with innovative solutions and technologies.

Evolving Pressures

Garrett Dilley, global commercial senior director Innovator Pharma, Johnson Matthey

❶ The CMDO market is greatly affected by the evolving pressures on pharmaceutical companies. One result of these pressures is an increase in the development of treatments for rare or orphan diseases with smaller patient populations. The average drug launch is now worth approximately $250 million in annual sales (DCAT presentation, Graham Lewis, IQVIA, March 2019). This provides a construct where most potential launches deliver less than the net present value that large pharma companies typically require in their models.
There has been a shift since 2011, when small and mid-sized companies were driving a lot of the discovery stage but partnering with larger companies for commercialization. Data from 2018 shows that now small and mid-sized companies have been increasingly progressing therapeutics through to commercialization. We have seen a corresponding increase in the number of APIs and intermediates in our pipeline alongside an increase in the number of small and mid-sized company sponsors.
Small and mid-sized drug companies pride themselves on being fast and nimble. They focus their capital on moving therapies through the clinic quickly and less on building end-to-end in-house development and commercial manufacturing operations. So, they benefit from the advantages a strong CDMO like JM can provide in that regard; excellent development capabilities, broad technology offerings, years of experience across numerous development programs and launches, and a global footprint of well-established FDA inspected facilities.
At the same time an industry shift towards increasingly large and complex molecules has also created new pressures for drug developers, especially in regard to bioavailability. Recent research estimates that as many as 60% of new molecules in clinical development demonstrate poor bioavailability. To address this need JM continues to invest in its particle technologies, building on its long-standing experience in solid form sciences.
We offer a suite of techniques for identifying and characterizing salt forms, polymorphs, and co-crystals, as well as crystallization development. These techniques, along with our capabilities in milling, micronization, and spray drying, help our customers to arrive on the ideal physical form of their API.

Many Positive Impulses for the CDMO Market

Marianne Späne, head of Business Development, Marketing & Sales, Siegfried

❶ The pharmaceutical industry is undergoing change. Shifting customer needs and fundamental developments in the industry will provide additional positive impulses to the CDMO market in the coming years. Therapies and drugs are becoming increasingly complex. In this situation, pharmaceutical companies increasingly focus on research and marketing. Their own production activity is losing significance, especially from a strategic point of view. That is where CDMOs come into play.
Besides strategic outsourcing, innovative drug substances and drug products represent a significant driver of above-average growth in the CDMO sector affecting our project pipeline significantly. As a result, the CDMO industry will have to expand its technological basis in order to fulfil the increasing requirements related to development, production and process quality.
❷ It is extremely important that our customers obtain their product on time and in the desired quality. That, however, is only a part of the strategic cooperation. We lower complexity for our customers because they can leave all aspects concerning production to us, namely procurement, development, synthesis/formulation, compliance and logistics. We help them avoid costly investments and lower their financial exposure and risk. This awareness is catching on increasingly. Today, outsourcing is no longer an option in the event of an emergency, but a generally accepted and recognized business model.
❸ For certain products or services, it may make sense to charge a higher amount relative to your costs. You can do this if your product is unique, if you are positioning your product as a high-status item or if it will save your customers money. In the branded pharma industry, they may price their products high and justify this by pointing out their drug can save the patient an even more expensive medical procedure. In the CDMO world, a service industry it is more difficult to apply the value-based price model especially in the manufacturing. Nevertheless, we discuss to implement models where you can measure the service provided with agreed KPI's and quantify the value either as a lumpsum or with a direct impact on product pricing. This thinking is not standard, but we need to work on it as the service level CDMOs gets higher and needs to be evaluated.

Challenging Old Paradigms

João Maderia, business development manager, CatSci

❶ The pharma industry has undergone significant changes in the last decade. A growing and aging population has increased demand, translating to increased R&D efforts. However, the rise in R&D spending has not been accompanied by a proportional increase in numbers of new chemical entities (NCEs). Consequently, we have seen an increase in partnering and the co-development of assets as cost- and risk-management measures.
Additionally, we have witnessed an increase in M&A deals. Although it is expected these factors will affect the resources dedicated to NCEs, the landscape of internal asset prioritization and pipeline attrition continues to evolve and will impact the work outsourced to service providers.
❷ CROs/CMOs provide on-demand capacity in a dynamic environment. This requires agility and flexibility from service providers in order to actively adjust and handle a portfolio of projects. Well-managed collaborations enable highly efficient external research, development and manufacturing as innovator pharma companies seek to manage budgets and internal capacity.
Innovators are challenging old paradigms and increasingly expect more from their CROs — establishing long-term partnerships to share the drug development burden. This aims to create value through a stronger relationship with a deeper understanding of each other's business needs. These partnerships are highly valuable for both parties as they allow for continuity in the communication flow, optimize working interactions, reduce IP scattering and improve project outcomes.
❸ Innovator companies want CROs who are fully aligned with technical project demands and broader commercial objectives. This focused expertise mitigates commercial and technical risk, as clients can make informed decisions on a proposed course of action and ultimately achieve higher ROI on their project spend. The demand for independent CROs to provide R&D expertise de-coupled from material supply is increasing. Customers require excellence across every facet of research, development and manufacturing, which is creating demand for new value-based pricing models.

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Sustainable Chemical Supply Chains

The Together for Sustainability Initiative is Expanding its Global Footprint

The Together for Sustainability (TFS) initiative was launched in 2011 as a joint program of chemical companies for sustainable supply chains. Its goal is to develop and implement a global agenda to evaluate and improve sustainable practices within the supply chains of the chemical industry. Currently, TFS has 23 member companies worldwide and intends to further grow globally. Michael Reubold asked the new president of TFS, Bertrand Conquéret, chief procurement officer (CPO) at Henkel, to explain TFS's strategy and focus to lead and shape the industry initiative in the next two years.

©TFS

CHEManager: Mr. Conquéret, after having successfully gone through its initiation and expansion phase in the early years after its launch TFS has entered its growth phase in 2015. How far have you come in making TFS an industry standard?

Bertrand Conquéret: TFS has indeed reached a certain maturity level since its inception in 2011. The achievements include more than 12,000 supplier evaluations in the form of audits and assessments. The number of members increased from the initial 6 to 23 chemical companies, we have active working groups with more than 50 employees of all 23 member companies worldwide, who are collaborating in global and regional teams. Our joint CPO initiative has been working very hard to make TFS grow into an industry standard and we are well on our way to succeeding in this mission.

In terms of growth, what is next on your agenda?

B. Conquéret: From the beginning, TFS set up regional structures by establishing partnerships with regional organizations and putting regional teams in place. These regional actors from all company members and strategic partners will drive the TFS global agenda while at the same time integrate local needs and requirements.

It is TFS's firm ambition to intensify its global expansion, whether it will be in Asia or in North or South America. In this context, 2018 has been a good year for us, since two new member companies, UPM from Finland and ICL from Israel joined the network. TFS is also very proud to welcome its first Chinese company with Wanhua Chemical Group. By extending its geographic and strategic reach, TFS will not only deliver even more of knowledge and insights into sustainability practices and processes of its extensive pool of suppliers but be able to further improve the sustainability performance of its suppliers as well as the maturity of our member companies' responsible sourcing programs.

TFS currently counts 23 members, all well-known companies, without a doubt, but considering the entire chemical industry the sole number represents only a drop in the bucket. Considering the size of those member companies, however, their combined purchasing power must be significant.

B. Conquéret: Yes! Based on the 2018 financial reports, the TFS members generated an aggregate of €325 billion turnover and represent an estimated spend of €235 billion. Nonetheless, there is certainly room for expansion continuing to grow by inviting chemical companies to come and work with us. On the other hand, we have clear criteria that potential TFS members need to meet, like being a member or public supporter of the UN Global Compact, the commitment of the applicant to the chemical industry's Responsible Care program, or at least a performance close to an EcoVadis gold rank.

TFS has established a standard approach for evaluating and improving the sustainability performance of suppliers within chemical industry supply chains. How does it work?

B. Conquéret: The TFS approach consists of two core elements: TFS assessments, which are based on an expert analysis of a company's corporate social responsibility (CSR) standards, and TFS audits, which are multiple-day evaluations conducted at a supplier facility. Both are carried out by independent, strategic partners who are market leaders in their respective fields.

Each member company can choose to apply either one or both tools to evaluate suppliers' sustainability progress, based on the member's own analyses and supplier selection criteria. The suppliers' sustainability performance is verified against pre-defined criteria that are tailored to the requirements of the chemical industry.

With the consent of the suppliers, the results of TFS audits and assessments are shared among all members. Hence the TFS principle proves true: "an audit/assessment for one is an audit/assessment for all".

> *„Chemical companies need to take responsibility for their suppliers' environmental, social and ethical business practices."*
>
> Bertrand Conquéret, president, Together for Sustainability (TFS)

How does this process improve sustainability?

B. Conquéret: In 2018, approximately 1,500 new supplier assessments were initiated by TFS members via EcoVadis and nearly 360 TFS audits were conducted through the TFS audit program, all results shared with the whole TFS group. Also, within the year 2018, over 2,000 suppliers, who had previously conducted a TFS assessment through EcoVadis, or a TFS audit, documented their progress on improvements.

This program resulted in a pool of supplier audit reports and scorecards and provides member companies with a wealth of sustainability data. TFS members can access insights that cover a significant portion of their procurement base, due to our sharing principle.

The transparency created by the TFS program is a starting point for a constructive dialogue between the supplier and the TFS member company and forms the basis to engage and work with suppliers on implementing tangible, measurable improvements in sustainability as well as shifting their own sustainability performance to the next level.

The aim of TFS is to harmonize requirements and to manage complexity and risk in global value chains. What does TFS mean by 'sustainable sourcing'?

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B. Conquéret: While traditional procurement decisions mainly rely on product quality, on-time delivery and price, TFS adds the sustainability component to chemical supply chains' focus. The TFS concept integrates 5 key focus areas: management, environment, health & safety, labor & human rights, and governance. As such, our approach builds on the established principles of the United Nations Global Compact and the Responsible Care Global Charter.

Growing stakeholder expectations, whether coming from governments, legislation, customers, employees, NGOs, trade associations or others, imply that chemical companies need to take responsibility for their suppliers' environmental, social and ethical business practices. To address potential risks and expectations, "sustainable sourcing" becomes an integral part of the TFS' member companies' procurement and supply chain management processes.

TFS drives and fosters resilience, efficiency and sustainability of global supply chains in the chemical industry. As such, we aim together to build the global industry's standard for sustainable supply chains. It is our deepest belief that sustainable supply chains are built on strong partnerships and commitments of its participants to protect the environment and the safety and health of workers, provide fair working conditions, contribute positively to the livelihoods of workers and communities, and operate in full compliance with applicable laws.

> *"TFS adds the sustainability component to chemical supply chains' focus."*

What kind of feedback have you received from suppliers who participated in the TFS audit program?

B. Conquéret: Suppliers in general are very positive about their participation in the TFS program. Perceived benefits relate to increased transparency and sustainability improvement opportunities, increased efficiency and the opening of business opportunities. Suppliers confirm they receive valuable information about their positioning in all aspects of sustainability. They can identify opportunities for sustainability improvements, showcase the results of their TFS assessments and audits to other customers within and beyond the TFS network, while risks associated with sustainability requirements are minimized. By sharing the results of the TFS assessments and audits, suppliers increase their efficiency and save time and resources by avoiding multiple requests. Participation in the TFS program provides suppliers with increased business opportunities by strengthening long term customer relationships.

In February, Wanhua Chemical joined TFS as the first company headquartered in the Asia Pacific region. Do you have a roadmap or a wish list for membership growth in this region, and in others?

B. Conquéret: TFS is on an expansion course. From the early beginning, TFS under the leadership of my predecessor has put a structure in place that allows to extend its geographical and strategic reach. Through the development of strategic partnerships and the creation of a network of regional teams, our organization is in good shape to grow globally. This will provide our members with deeper insight into the sustainability performance of their suppliers' base, as well as with additional opportunities to adjust the sustainability performance of their own operations.

Since 2015, TFS has initiated and fostered strategic partnerships with a range of organizations such as the European Chemical Industry Council, CEFIC, and the China Petrochemicals and Chemicals Industry Federation (CPCIF) to work jointly on improving sustainability in chemical supply chains. To ensure global reach and the development of specific regional topics, TFS established regional teams in China, North and South America, interlinked with global activities.

Essential to TFS's growth strategy is to attract those members, for whom sustainability in the supply chain is strongly embedded in their strategy. As a member-driven organization, TFS expects its future members to invest time and resources to actively contribute to the TFS activities and shape the future of sustainable global supply chains together. This way, all members as well as suppliers will benefit and sustainability improvements

in the supply chains of the chemical industry will be achieved.

China plays an important role as a sourcing region for Western chemical manufacturers. Which role does China play on the agenda of TFS? In your opinion, how is China embracing the visions of TFS?

B. Conquéret: Given the global nature of chemical supply chains, China, as well as other world regions, plays a crucial role in the TFS organization. The inclusion of Wanhua Chemical Group in early 2019 and their fast onboarding has shown how strong the commitment of Chinese chemical companies can be.

Following a cooperation agreement signed between the CPCIF and TFS back in 2016, both parties continue working jointly to promote and improve sustainability in the chemical industry. Together, they focus on raising awareness and promoting TFS participation to suppliers, organize numerous joint supplier trainings and participate in conferences on behalf of TFS. The TFS China team also took part in conferences to present the TFS membership to potentially interested companies. Efforts continue as TFS is committed to extending its reach in China.

Overall, looking back at our journey since 2011, we are impressed by the commitment, enthusiasm and quality delivered by our member companies, partners and suppliers who have been fully embracing the TFS concept right from the start.

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Currently, TFS has 23 member companies and intends to further grow globally. Essential to TFS's growth strategy is to attract members, for whom sustainability in the supply chain is strongly embedded in their strategy and who are willing to invest time and resources to actively shape the future of sustainable global supply chains together.

www.tfs-initiative.com

Reinforcing the Virtues of the Specialty Chemical Sector

With New Initiatives and Services SOCMA Sets out to Provide Solutions for a Dynamic Specialties Industry

The Society of Chemical Manufacturers & Affiliates, known simply as SOCMA, recently launched a more member-centered brand focused on solutions for the specialty and fine chemicals industry. The US association, formerly known for their annual convention InformexUSA, now intends to solidify its place as the central hub for this sector by offering new services. Michael Reubold spoke with Jennifer Abril, president and CEO of SOCMA, about the latest changes in the chemical industry that — among other reasons — were pivotal for the rebrand.

Jennifer Abril, president and CEO, SOCMA

CHEManager: Ms. Abril, in June SOCMA launched its new brand. Is the rebranding already heralding SOCMA's 100th Anniversary in 2021?

Jennifer Abril: SOCMA's rebrand is indeed reflective of our keen focus on the association's 100th anniversary. It is a culmination of the work and outreach of our volunteer leaders and staff over the last 2.5 years to reinvigorate SOCMA as the hub of the specialty and fine chemical industry.

Our vision is to reflect the uniqueness of this complex and dynamic sector and to celebrate the creativity and innovative nature of our members.

SOCMA's members are international specialty and fine chemical manufacturers. Were they involved in the brand refresh?

J. Abril: Our members are at the very heart of our rebrand, which is also an opportunity to reinforce and promote the virtues of the specialty chemical sector. It is always prudent and responsible to create a baseline for analyzing your organization's relevance and contributions. In this vein, we commissioned two surveys to provide us with objective insights and to validate internal assumptions. Through the two studies we heard that our members want to be known as proactive, innovative leaders who are finding solutions to the complex needs of an ever-evolving value chain. We endeavored to reflect this in both the new logo and tagline. The new tagline — Solutions for Specialties — intends to convey a double meaning. It speaks to what SOCMA strives to be — a solutions provider for the specialty sector, and at the same time reflects that our member companies provide critical solutions for their customers' needs.

What were the two surveys you mentioned about?

J. Abril: In the first survey, we talked to more than 150 industry representatives about current and future industry needs in areas such as operations, regulatory, training, networking, trade association participation, and customer/supplier relations. In the second, we evaluated SOCMA's brand and identified opportunities and gaps for SOCMA programs and services when overlaid on top of those changing industry expectations. The results of these two surveys were crucial in helping us identify major trends and in understanding SOCMA's value to the market.

What were the results of the surveys, what did you identify as biggest challenges for chemical companies now and in the near future?

J. Abril: From the first study, we learned that the industry values a convener to bring companies together with customers and potential business partners in the trade show arena and beyond to promote growth. These companies also desire a trusted source for business resources, industry intelligence and forums to discuss issues influencing growth such as disrupters and trends.

Our second study built upon the first by drilling down to identify expectations and potential gaps. We learned that advocacy continues to be a high priority for specialty and batch manufacturers, and companies continue to look to associations to champion policies that support their ability to grow their businesses and remove regulatory barriers that would impede their ability to compete in a global economy.

We are proud that in the last two years, we have made significant progress in reinforcing our role as a safety net for our members, particularly during challenging times.

What are you offering now to your members that you weren´t before?

J. Abril: We are excited about several new initiatives in the commercial, manufacturing and workforce development arenas that are already receiving positive results.

For our contract and toll manufacturers, SOCMA now serves as a connector for companies looking for business partners with the right materials and the right equipment at the right time. Launched in late 2018, this "Lead Sheet" service improves efficiencies by streamlining the procurement process and identifies manufacturers based on real-time needs. To date, SOCMA has facilitated 22 project requests totaling more than 5 million tons of material, matching an average of three to five companies that have the capabilities and available capacity.

For companies that make proprietary chemicals we launched our ChemSectors program in January 2018. ChemSectors keeps a pulse on what's happening in key downstream markets. Having an additional, trusted source of industry intelligence concerning end-use trends is an asset to any leader making decisions about

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where to invest future resources. To help companies bring new hires up to speed quickly, we will soon launch our revitalized Chemical Operations Training tool. As a new and younger generation of employees comes into the industry, we understand that they learn in different ways, so the new tool includes 3D animation. It is also flexible and adaptable and can be used as a standalone program or as part of an existing training program.

We are also modernizing our ChemStewards program to dovetail with complementary EH&S management programs and to remove barriers for companies to participate. It will be a more robust program with a holistic view of the industry.

Finally, we are excited about two new peer groups formed earlier this year — Emerging Leaders and Women in Specialties. These peer groups connect top industry talent and provide an open channel for dialogue on topics such as professional development and current business challenges.

We are seeing a lot of disruptions in international trade that result in new barriers and tariffs, for example Brexit, the new USMCA or the trade conflict between the US and China. Your members maintain global trade relations. How do you help them to manage these disruptions?

J. Abril: For our US-based members, the specialty and fine chemical industry is facing one of the most disruptive trade climates of our time, the most significant of which is the ongoing trade dispute with China. SOCMA's International Trade Committee and team of staff experts are working closely with member companies to identify hundreds of individual chemical products that are affected and presenting arguments for delisting to the Office of the US Trade Representative.

For example, SOCMA staff recently accompanied a coalition of members in Washington, DC, to ask that Congress support the companies' exclusion request for a chemical input on US List 3, subject to a 25 percent tariff. SOCMA was integral in successfully securing signatures from the US House of Representatives and US Senate on letters of support for the exclusion request and also submitted a letter in support to the US Trade Representative to convey that the industry as a whole backs this exclusion.

Moving beyond the China tariffs, international trade issues such as the United States-Mexico-Canada Agreement — USMCA — and Brexit are also top of mind. Through routine dialogue with our International Trade Committee, SOCMA experts provide the latest recommendations on how to navigate these changing requirements.

How important is it to coordinate SOCMA's efforts with other US-based or international organizations such as ACC or CEFIC/EFCG in Europe?

J. Abril: I believe strongly in building partnerships, both in the US and internationally. Our team is encouraged to look for areas of mutual interest where we can engage with allies to become a stronger voice for the industry. For example, for over 20 years, SOCMA has partnered with the American Chemistry Council on educational programs regarding global chemical regulations. And, through our ChemSectors program, we have strengthened our connection to associations representing end-use markets.

By having a network that is well-informed, we can spot the changing winds and interpret what may be the potential impacts to companies typically situated in the middle of the value chain. The aim is to ensure our members have the intelligence needed to make strategic business decisions.

www.socma.org

Entomoculture: The Future of Food?

Insect Cell Culture and Tissue Engineering for Food Production

Meat produced from cell cultures (i.e., cultured meat) rather than whole animals may be a solution to the problems surrounding our current livestock production system, but it is currently challenging and expensive to produce such food products at large volumes. Insect cells have unique properties that may contribute to relatively more scalable and cost-efficient manufacture of food products. By coupling trends in cultured meat and entomophagy (i.e., entomoculture), the future of food could include steaks composed of caterpillar tissue, rather than cow.

Natalie R. Rubio,
Tufts University

David L. Kaplan,
Tufts University

Driven mutually by population growth and rises in individual economic prosperity, meat consumption is projected to increase by 76% by 2050. Increased public awareness of the public health, environmental impact and animal welfare concerns associated with our current animal agriculture system has generated a demand for more sustainable alternatives to meat and other animal products.

Innovations in meat alternatives include plant-based analogs, edible insects, transgenic animals and meat produced from cell cultures (i.e., cultured meat) rather than whole animals. Each of these options proposes benefits over conventional meat production processes yet also faces challenges with development, scalability and consumer acceptance.

Cultured meat perhaps holds the most promise in terms of reducing impact while retaining most, if not all, of the desired aspects of meat. Although cultured meat has garnered attention from the media and investment communities, it has yet to be commercialized due to technical obstacles of scale and cost-efficiency.

Entomophagy

Entomophagy, the practice of eating edible insects, though not common in Western nations, is routine throughout South America, Africa, Asia and Australia. Insect farming is accessible, affordable and sustainable and many edible species (there are over 2,000) are lauded for their rich nutrient content. The most commonly consumed insects include species of caterpillar, palm weevil and grasshopper. Entomophagy is gradually gaining popularity in America as well, based on the relatively lower environmental impact of raising bugs compared to more traditional livestock.

> *"By using individual cells and tissue engineered cells, culinary horizons begin to broaden."*

Advantages include lower land and water requirements, lower greenhouse gas emissions and higher feed conversion efficiencies. So far, American insect products have largely taken the form of protein bars and baked goods made with cricket flour.

The disadvantage of insect-based products is that they are not often a culinary substitute for meat when it comes to flavor and texture. While insects can provide an alternative for protein and other nutrients, they do not satisfy a meat eater's craving for a juicy steak or burger for the grill, thus cooking, texture and taste remain to be explored in detail.

Cultured Meat

Like edible insects, cultured meat has advantages and disadvantages when compared against conventional meat. Cultured meat could: reduce rates of foodborne illness and antibiotic resistance; require less land, water and generate less greenhouse gas emissions and improve animal welfare by reducing or eliminating the need for livestock in the food chain.

However, to date, no cultured meat products have been commercialized due to obstacles of scale-up and cost reduction. In brief, the process for generating meat from cells involves: isolating skeletal muscle and adipose precursor cells from a donor animal; formulating serum-free media to support cell growth; proliferating cells at high-density in a bioreactor, and coupling cells with a scaffold system for differentiation and tissue maturation.

The majority of the field to this point has largely piggy-backed off advances in the field of tissue engineering for medical applications. However, dissimilar to technologies for implants for clinical utility or as in vitro disease models, tissue engineered food must be incredibly scalable, affordable and free from animal derivatives (for long-term sustainability).

Insect cell culture could provide a preferable platform for large-scale cell culture for food production. Insect muscle and fat cells have previously been cultured and characterized for a number of species. These cells can be

expanded in vitro, differentiated with the help of natural insect hormones and coupled with three-dimensional biomaterials to generate edible and healthful tissues (fig. 1).

Vertebrate vs. Invertebrate Cell Culture

The majority of cultured meat initiatives are focused on cultivating cells from traditional food animals such as cows, pigs, poultry and fish. These cell types have proven challenging to grow at large volumes for minimal cost due to stringent growth conditions, high oxygen demand, and a lack of basic research. Mammalian muscle cells are generally grown as adherent cultures and incubated at 37 °C, with humidity and 5% carbon dioxide to stabilize the pH of sodium bicarbonate-based basal media. Media is supplemented with high concentrations (10-20%) of fetal bovine serum and growth factors, and subculture requires enzymatic dissociation.

While suitable for bench-scale research, these conditions create challenges when considering large-scale cell production; serum and growth factors are expensive and varies by batch, high incubation temperatures result in increased energy requirements and adherent culture requires complex bioreactor design for high-density culture. In contrast, insect cells are more robust, adaptable and tolerant of fluctuations in growth conditions. Many insect cells can grow in adherent or suspension conditions; at ambient temperatures; without humidity or carbon dioxide exchange; without the need for serum or complex growth factors, and in the presence of higher concentrations of toxic byproducts (e.g., ammonia, lactate).

Insect Tissue Engineering

Beyond advantageous growth properties, insect cells are a useful cell culture platform due to the amount of scientific literature available. Insect cells have long been studied in regard to developmental biology and recombinant protein production which can inform culture methods, media formulation and scale-up processes. However, insect-specific knowledge is lacking when it comes to generating organized tissues from harvested cells. While tissue engineering is less of a focus for processed meat products (e.g., burgers, nuggets, sausages), it is important for creating structured meat products (e.g., steaks, chicken breast, pork chops). This process involves inducing muscle and fat cells to differentiate into mature tissues with the help of three-dimensional materials (i.e., scaffolds) to guide morphology and influence mechanics.

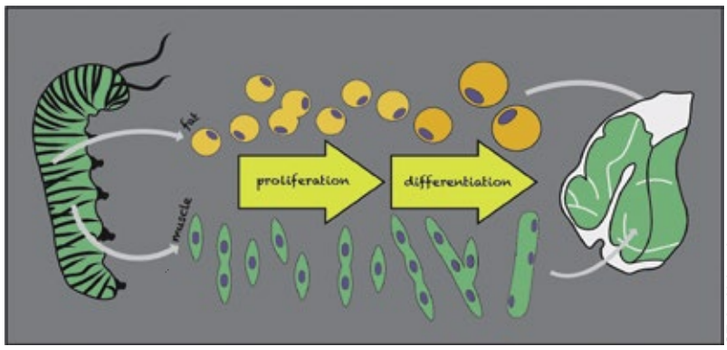

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Fig. 1: Insect muscle and fat cells can be expanded in vitro, differentiated with the help of natural insect hormones and coupled with three-dimensional biomaterials to generate edible and healthful tissues.

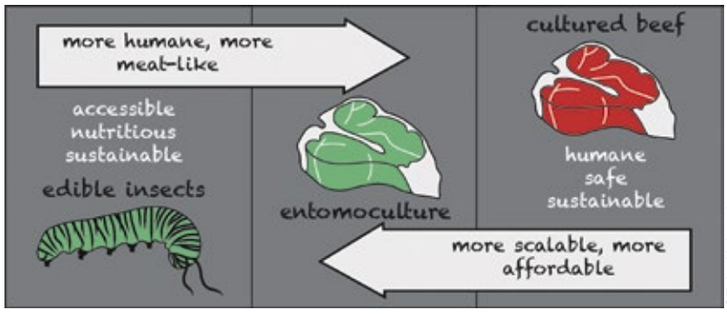

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Fig. 2: By coupling entomoculture with cultured foods, disadvantages associated with the individual methods can be alleviated.

Tissue engineering for mammalian muscle and fat is well-reported and can inform strategies for invertebrate constructs. There is a limited amount of research on generating insect muscle in vitro for bioactuators — e.g., biological robots powered by muscles as opposed to traditional electrical actuators. This has primarily involved culturing insect muscle cells in silicone molds to create bundles of contractile muscle. Mushroom chitosan has also been explored as an edible scaffold to support three-dimensional insect cell growth, inspired by the in vivo presence of chitin within insect exoskeletons.

Texture, Flavor and Nutrition

Due to the innate properties as highlighted earlier of insect cells, entomoculture could provide a compelling opportunity for cultured foods. Through this coupled approach, disadvantages associated with the individual methods can be alleviated; cultured insect tissue can generate more consumer acceptable products than edible insects and insect cells can be easier to culture than mammalian cells (fig. 2).

However, cultured insect meat will undoubtedly be challenging to market to consumers. Rather than creating an entirely new type of food, one approach could be to emulate products that are already on the market. Invertebrate muscle is similar to mammalian skeletal muscle and insects have organs called fat bodies that store lipids, analogous to mammalian adipose tissue. By selectively growing insect muscle and fat tissue and leaving out the eyes, legs and wings, products would embody the appearance and texture of familiar meat products rather than of whole edible insects.

"Insect cells present an important opportunity for novel and sustainable foods."

A second important factor is flavor. The flavor of insects is largely dependent on species, location and age; and they tend to soak up flavors of their own food and ambient environment. Insects are often described as tasting like seafood. For entomoculture, both flavor and nutrition can be regulated via media composition or genetic engineering. Insect muscle cells can be more dense in protein and minerals than mammalian muscle cells and intracellular iron content can be increased by media supplementation.

Future Directions

With appropriate product development and consumer marketing, insect cells present an important opportunity for novel and sustainable foods. However, there are technical milestones to overcome before this concept can be feasible.

First, scale-up processes that have been achieved with insect cells for recombinant protein production must be applied to and optimized for insect muscle and fat specific cells. Second, tissue engineering principles traditionally applied to mammalian cell types should be adjusted to support the three-dimensional culture of invertebrate tissues. Once these milestones have been achieved, prototypes can be further refined to mimic the desired taste, texture and nutrient properties of meat.

Even if entomoculture never catches on in the marketplace, there are still persuasive reasons to pursue this brand of research. For instance, cultured insect protein might prove to be a good additive for pet food or aquaculture feed. Insects are also evolutionarily close to crustaceans and advances in insect cell culture could be translated to generate cell and tissue cultured lobster, crab and shrimp. Furthermore, if the advantages associated with insect cell culture can be correlated with specific cellular mechanisms, these findings may inform the modification of mammalian cell culture systems to improve economics related to cultured meat production.

By using individual cells and tissue engineered cells, instead of whole animals, culinary horizons begin to broaden. As cultured meat becomes closer to reality, researchers and innovators should work on the outskirts of traditional constraints of the food industry to bring new and improved technology to our plates.

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Literature references can be requested from the authors.

Innovation in Pharma Manufacturing

2019 ISPE Facility of the Year Award Winners Demonstrate Excellence in Facility Design, Construction and Operations

Established in 2004 by the International Society for Pharmaceutical Engineering (ISPE), the Facility of the Year Awards (FOYA) recognize innovation and creativity in manufacturing facilities serving the regulated healthcare industry. The award-winning projects selected by the FOYA program set the standard for pharmaceutical facilities of the future by demonstrating excellence in facility design, construction, and operations.

The FOYA program each year recognizes state-of-the-art projects utilizing new, innovative technologies to improve the quality of products, reduce the cost of producing high-quality medicines, and demonstrate advances in project delivery. This year, the category winners were announced at the ISPE Europe Annual Conference in Dublin, Ireland, in April. The overall winner will be revealed at the ISPE Annual Meeting to be held in Las Vegas in October.

"The 2019 Facility of the Year Awards category winners are at the forefront of not only setting the standard for pharmaceutical facilities of the future, but also creating new opportunities to enhance patient health and safety worldwide." said John Bournas, ISPE CEO and president.

© Kantonsapotheke Zürich

Vial-filling robot in sterile production area at the new compounding pharmacy of Kantonsapotheke Zürich, winner of the 2019 FOYA Operational Excellence Award Category.

John Bournas

Tony Crincoli

"We are pleased to spotlight the dedication of these companies who epitomize the future of global innovation and facility design." Antonio "Tony" Crincoli, chair of the FOYA judging committee and senior director, Upjohn Global Engineering, Pfizer, adds: The FOYA program represents the best of the best — what we call benchmarking. All companies want to know what is happening on the forefront of technology, innovation, and equipment. ISPE's FOYA program lets the industry know what is happening all in one place, what is truly exceptional."

According to Crincoli, who feels privileged to work in an industry that improves the lives of patients, it is a myth to dispel, that only large complex projects win these awards. Most are actually smaller projects that improve quality and efficiency, reduce cost, improve transfer of new products, or implement new information technology solutions.

2019 FOYA Category Award Winners

Celgene is the winner of the Sustainability Category Award for its Green Fairy project (La Fée Verte) for their manufacturing facility in Couvet, Switzerland. One of the main objectives for the new facility was to implement an environmentally responsible and sustainable site in-line with their corporate principles.

Eli Lilly won the Process Innovation Category Award for its IE2 small volume continuous facility in Kinsale, County Cork, Ireland. This innovative facility and the process design concepts incorporated advance the industry in three specific areas; process analytical technologies and advanced automation, development of new con-

tinuous technologies, and significant improvement in process safety and environmental impacts.

The Equipment Innovation Category was awarded to **Janssen Cilag** for their project Dosepak Equipment which entailed the design, installation, and qualification of state-of-art equipment at their manufacturing facility in Latina, Italy. The facility integrated advanced robotics and automation into a standard packaging process steps and enabled lean, flexible, and sustainable manufacturing.

Moderna is the winner of the Facility of the Future Category Award for its New cGMP clinical manufacturing facility in Norwood, Massachusetts USA which was designed to be highly-flexible, adaptable and capable of manufacturing both for clinic and research. The digital production environment was designed to enable high throughput with a robust and diverse set of products.

Kantonsapotheke Zürich won the Operational Excellence Award Category for its new compounding pharmacy for Canton Zürich Hospitals — a leap forward for hospital pharmacy compounding operations. The project (photo) realized jointly with design-build partner Exyte, Stuttgart, Germany, demonstrates a transformational step in hospital compounding operations and establishes a new norm for future facilities in this important step of patient therapy.

The Facility Integration Category was awarded to **Pfizer** for the biotechnology center built in the Hangzhou Economic Development Area (HEDA) in Hangzhou, China. The HEDA site was transformed from a strawberry field in March 2016, to producing mAbs development batches twenty-five months later.

Pfizer was also awarded the Project Execution Category Award for the construction of the Pfizer Biotechnology Center. The $195 million project was the culmination of an unprecedented construction schedule, efficient cost control measures, and an unmatched safety record in China.

Avexis received an Honorable Mention for its manufacturing facility for its next-generation medicine. To manufacture its proprietary investigational gene replacement therapy, Avexis built a 49,000-square-foot state-of-the-art manufacturing facility in suburban Chicago, Illinois.

An Honorable Mention was also given to **Takeda** (formerly Shire) for its new 1.1 million-square-foot Georgia manufacturing facility near Covington, Georgia. Planned within a 160-acre site, this state-of-the-art facility integrates the technical requirements of both upstream and downstream manufacturing, while achieving optimal adjacencies between process areas and creating an environment that positively impacts the wellness of employees.

The 2019 Facility of the Year Awards Category Winners will be formally recognized at the ISPE Facility of the Year Awards Banquet and Dinner on October 26 in Las Vegas, Nevada USA. Held in conjunction with the 2019 ISPE Annual Meeting & Expo, the banquet will feature acceptance speeches from the FOYA recipients and presentations from noted industry leaders. The 2019 Facility of the Year Awards overall winner will be announced at the conference during the Membership and Awards Breakfast. (mr)

https://ispe.org

Biomolecules Go Bio

New Platform Technology Revolutionizes Biosynthesis of Peptides

Peptides make up around 8% of all active pharmaceutical ingredients (APIs). Those molecules are short polymers formed from the linking of ≤100 amino acids. They comprise some of the most basic, yet key components of biological processes. Several peptides are significant commercial or pharmaceutical products, ranging from the sugar substitute aspartame to clinically relevant hormones, such as oxytocin and insulin. Today, the peptide market is valued at around $20 billion annually with a compound annual growth rate (CAGR) of 9.4%. However, the peptide manufacturing industry is in a state of change.

In recent years peptides — as new chemical entities (NCEs) — have raised the interest of the pharma industry due to their unique therapeutic properties: high target affinity, specificity and potency, low toxicity and reduced antigenicity. Thus, the number of peptide-based drugs entering clinical trials is rising each year, leading to an increasing demand of peptides as APIs. However, this growth is hampered by challenges in the available peptide manufacturing processes such as production costs (e.g. inefficient processes and high need for expensive raw materials), scalability issues and sustainability. As a result, there is an unmet need for cost-efficient scalable technologies specifically designed for peptide production.

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Current State of Peptide Manufacturing

With a growing demand, the production of peptides at commercial scale has become a barrier to the industry because limited production capacity exists. Thus, there is a shortage of peptides in the market (as stated by the 2019 Peptide Therapeutics Opportunity Assessment) as a result of the limitations imposed by current peptide production processes, which fall into two types:

One is chemical synthesis, which is responsible for 85% of peptide production. It requires high amounts of expensive and partly toxic raw materials and is rather unaffordable for the production of peptides at large scale, especially for peptides over 30 amino acids in size.

The other are bioprocesses (recombinant production) as alternative methods for peptide production that use genetically modified micro-

Philipp Bürling, Numaferm

organisms. However, they entail three major technological hurdles: peptide degradation by proteases; peptide aggregation; and toxic effects of the peptides on the production host. These factors can result in low production titers as well as lengthy and risky development, making this approach often inefficient and less popular than chemical synthesis.

Bioprocesses are, however, very successfully applied for the production of larger molecules such as proteins. As proteins have a very complex folding pattern, their structure protects them against fast proteolytic degradation.

The major players in the contract manufacturing business of peptides, such as the Sweden-based PolyPeptide group or Bachem from Switzerland, have set their focus on chemical synthesis. The reason for that could be as simple as that truly overcoming named hurdles in recombinant production of peptides remains unsolved. Yet, according to a recent annual report of Bachem, recombinant production is a topic that the company keeps an eye on. For good reason: the industry is certainly facing some changes.

Bioproduction Breakthrough

In 2015, the German Ministry of Economic Affairs and Energy approved a grant called "EXIST Forschungstransfer" to a group of young scientists around Christian Schwarz of the Heinrich-Heine-University in Düsseldorf. The target of the funded project was to further develop a technology that can be regarded as a breakthrough for the bioproduction of peptides.

Schwarz could convince the jury, that the peptide-related technical challenges in production could po-

tentially be solved based on discoveries he made during his doctoral thesis at the Institute of Biochemistry. He found a way to secrete specific molecules efficiently using gram-negative Escherichia coli bacteria. Secretion describes the transport of a molecule from the interior of a cell to its external environment. From there it can be harvested.

While this process is rather easy to achieve with gram-positive bacteria, it is challenging for gram-negative strains due to their complex cell membrane. As this transport is difficult for any molecule, meaning also unwanted impurities or proteases, the surrounding of E. coli is very pure, free of proteases and therefore a "safe harbor" for peptides. What Schwarz did precisely is that he modified a type-1 secretion system of E. coli and added a tag to the peptide, which contains a transport signal. As a result, the tag including the peptide as a cargo is efficiently secreted. The fusion construct is subsequently cleaved, leaving the pure peptide ready for the downstream processing.

Apart from efficiency in regard to production titers, another crucial aspect is reliability of the system, especially when it comes to NCEs. Drug development projects face a tight schedule, moving from the discovery to pre-clinical and then to clinical phases. Even though a bioproduction of the API can have a major positive impact on the commercial stage business case, lengthy development times for setting up the manufacturing have to be avoided by all means. The technology now available has success rates that are comparable or even superior to those of chemical synthesis and development times are reduced from months or even years to weeks.

The university project has been a success and the technology could be scaled up and diversified delivering promising results in regard to a commercial use for peptide production. In 2017, the project spun out of the university, attracted prominent investors such as Evonik Venture Capital and is since then growing its peptide manufacturing business under the firm Numaferm.

Outlook

Apart from the manufacturing of generics or NCEs, there are other hot topics in pharma that further drive the demand for efficient, quick and reliable peptide production. One example are antimicrobial peptides, which play an important role in the development of new antibiotics. Another example can be found in the field of immuno-oncology, where personalized peptide vaccines (PPV) are one major strategy. PPVs are cocktails of peptides that help stimulate the body's immune system to attack tumor cells.

With growing demands and additional technologies emerging — like the recombinant approach of Numaferm, enzymatic ligation of shorter peptide fragments or synthetic biology — the peptide production industry is undergoing a major change. A complete substitution of one technology with the other may not be the case. The real opportunity lies in their combination.

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Achieving the Seemingly Impossible

Biotechnological Production of Rare Functional Sugars on an Industrial Scale

Rare functional sugars provide huge market opportunities. The German company Jennewein Biotechnologie, headquarterd in Rheinbreitbach near Bonn, specializes in in the industrial manufacturing of these products for a wide range of applications, including nutritional, pharmaceutical and cosmetic products and has a strong scientific foundation. As well as developing new and more efficient production processes for scarce functional sugars, Jennewein collaborates with selected partners in the preclinical development of its products, including the investigation of their health-promoting properties. The development of innovative processes for sugar molecules calls for broad expertise in biotechnology, process engineering and carbohydrate chemistry. Ralf Kempf asked Katja Parschat, deputy-head R&D, and Benedikt Engels, head of Production, about current projects and collaborations.

Benedikt Engels,
Jennewein Biotechnologie

Katja Parschat,
Jennewein Biotechnologie

CHEManager: Ms Parschat, Mr Engels, Jennewein Biotechnologie specializes in the production of human milk oligosaccharides (HMOs) on an industrial scale. Why was it so difficult to develop a profitable manufacturing process for these functional sugars? What hurdles had to be overcome?

Katja Parschat: HMOs were known for more than 100 years and for a long time people tried to synthesize them. Chemical and biocatalytic synthesis proved to be uneconomical and also not scalable into volumes relevant for food applications. Fermentative approaches suffered initially from low productivity and no cost efficient and scalable technology existed to purify HMOs from fermentative processes. We at Jennewein have addressed both aspects, the metabolic engineering part, as well as the development of suitable purification processes for HMOs and other oligosaccharides and monosaccharides. In 2005, when the company was founded, no industrial processes existed for defined oligosaccharides using a heterologous host.

After trying to synthesize human milk oligosaccharides by chemical synthesis and biocatalysis, meaning performing chemical reactions with isolated, enriched enzymes, the third and most successful attempt was to use metabolically engineered bacteria as cell factories. However, although harmless bacteria like Escherichia coli do provide some of the enzymes needed to synthesize complex sugar molecules, the genetic pathways involved had to be optimized and expanded by genes from other organisms to finally establish bacterial cells that are able to produce, and — what is most important — to secrete the complex sugars into the fermentation medium. By growing these optimized bacteria in a defined medium, the HMOs can be obtained simply from the culture supernatant. In addition, Jennewein developed a unique process to purify the HMOs from the cell-free fermenter solution and optimized the method for drying the sugar to obtain a product that complies with the high-quality standards for ingredients of infant formulae.

Starting at the lab bench, bacterial strains have been developed and optimized to produce individual human milk oligosaccharides with economic and feasible results, whilst processes for the recovery of the sugars from the fermentation solution were invented and refined.

Benedikt Engels: Developing an efficient process which lacked, for example, any use of organic solvents resulting in a high quality and safe product for use in infant formula was a milestone. All these processes had to be scaled up to an industrial size, to run fermenters in a scale of several hundreds of cubic meters and to handle these volumes in the recovery process. These development steps took about a decade with a substantial financial investment.

In October 2018 Jennewein bought the facilities of the former Artus Mineralquelle in Bad Hönningen to build an integrated production plant for HMOs and other sugars. What is the status of the project?

B. Engels: The purchase of the Artus Mineralquelle was a fantastic opportunity to acquire a suitable industrial estate for building an integrated production plant for HMO production. The facility is close-by and due to own water rights and existing infrastructure, perfectly suited to build large fermentation capacity. Currently we are in the planning and design phase of these production facilities. We hope that we will be able to start construction of the plant at the beginning of next year.

Why is it necessary to expand your production capacity?

B. Engels: After being qualified by several infant formula producers and receiving the approval for 2'-fucosyllactose in multiple countries, demands are increasing. In addition, Jennewein is currently bringing further HMO products like Lacto-N-neotraose on the market, and we are also launching the 5HMO Mix, containing the five most abundant neutral and acidic HMOs. These products will all be used in a higher concentration, thus getting closer to the natural concentration found in human milk. Therefore, we are strongly growing in production capacity to cover the increasing demands of 2'-fucosyllactose and at the same time bringing the next innovation cycle of HMOs to the market.

What are the company's current projects?

K. Parschat: After starting with single HMOs we are now producing different mixtures of HMOs. Using its 5HMO Mix, Jennewein is currently sponsoring a multi-center clinical study to confirm the benefits of using infant formula containing HMOs, in a concentration that is similar to the natural concentration in human milk, compared to infant formula not containing HMOs. The study is being conducted in Germany, Italy and in Spain and comprises of three study arms and the enrollment of over 300 in-

fants. The participating babies are assigned either to one of the double-blinded randomized formula groups, receiving either HMO Mix containing formula or the reference formula, or to the third group representing the gold standard of breast-feeding. Besides the evaluation of growth and behavioral parameters, the development of the gut microbiome of the subjects will be analyzed and by determining the HMO profile of mothers' milk from moms in the breast-feeding group, a correlation of HMOs in breast milk and the resulting gut microbiome in the offspring will be drawn. The clinical study started at the end of 2018 and will be finished in 2020. We have applied to the European commission for the approval of the five HMO Mix as a Novel Food and will shortly apply to the US FDA to obtain the "Generally Regarded as Safe" (GRAS) status to open up the opportunity to commercialize this new product.

In the last two decades science discovered diverse effects of HMOs on the human body and on the interaction between the human being and its microbiome. These effects range from supplying energy to support growth of beneficial gut bacteria to direct interaction of the HMOs with certain human cells on a molecular level and supporting brain development in neonates. Thereby different effects can be assigned to specific HMOs or groups of HMOs, like neutral sugars, HMOs containing fucose residues or acidic HMOs containing a sialic acid moiety. By combining HMOs with different properties, diverse effects can be addressed. Therefore, we stress the development of even more complex HMOs to enlarge the possibilities of combinations and to even offer personalized solutions.

In addition to the products mentioned earlier, we are currently extending our portfolio of monosaccharides. Besides L-Fucose and sialic acid, we are also offering Mannose as a monosaccharide in crystalline form.

You are also doing research on the production of designer organisms using metabolic engineering. What improvements do you expect for your production processes?

K. Parschat: Jennewein has always based its metabolic engineering on genomic integration or genomic modification. When designing organisms from scratch, we use modular systems to easily construct large synthetic parts of a bacterial genome. Having the needs for different metabolic pathways comprising several genes for the synthesis of different HMOs, using exchangeable modules makes the development of new strains faster compared to approaches using single genes for single production strains.

B. Engels: Production strains are highly efficient cell factories, customized not only for production of individual functional carbohydrates. Besides giving the strains the ability to produce HMOs by genetic engineering, we address production efficacy by also adjusting primary metabolism pathways as well as import and export mechanisms for building blocks and individual HMOs.

In June 2018, Jennewein signed a long-term lease for a site in Bonn and announced plans for the construction of a new R&D center. How is the development of this center progressing?

K. Parschat: The development is progressing very well, offices for our IP team and scientific communication team are already fully occupied and the R&D department will most likely move to Bonn, when the labs are fully operational, which we expect to be the case by the end of the year.

What will be the focus of the work in this new research center?

K. Parschat: At the new R&D center in Bonn most of the molecular biology used to design new and to improve bacterial strains for the manufacturing of new products will be established. The R&D department is equipped with high quality analytic devices that are implemented in the support of production strain development, but also in the analyses of metabolites from HMO degrading gut bacteria. Jennewein now also forces, besides the production of rare sugars, the investigation of beneficial effects of these products on the human body, like the prebiotic effect of HMOs on the neonatal and adult gut microbiome and the metabolites produced by these gut bacteria while metabolizing HMOs. These findings will hopefully strengthen the conviction that supplementation of diet, and especially infant formula, with HMOs is preferred over the addition of artificial fibers, when looking deeper into the metabolic outcomes of diverse supplements.

We believe that consumers will become more aware of the physiological effects of a healthy microbiome and that HMOs will definitely play an essential role in maintaining and restoring a healthy microbiome not only in infant nutrition.

Jennewein has been cooperating with the Yili Group, China's leading dairy company, since February of this year. What is this partnership about?

K. Parschat: The cooperation with the Yili Group will merge the expertise of Yili in the Chinese breast milk composition and our expertise in producing HMOs and their application. The aim is to obtain a deeper understanding of HMO related effects on the microbiome of newborns and to develop tailor made infant formula for the Chinese market.

The 2'-fucosyllactose produced by Jennewein is already approved and used as a food additive for baby food in the USA and Europe. Are there other countries where the product is used?

K. Parschat: 2'-Fucosyllactose is already approved in the Philippines, Israel, Canada, Malaysia, Thailand and Singapore. Furthermore, products containing 2'fucosyllactose are available or launched in Russia, Mexico, Hong Kong, Saudi Arabia, Colombia, Ecuador, Chile, Kuwait, Oman, Qatar, Vietnam, Cambodia and Myanmar.

What other products or projects does the company have in its pipeline?

B. Engels: Extending our monosaccharide portfolio, which now comprises of L-fucose, sialic acid and mannose. In addition, we are working on additional HMO blends, for example a mix of four sugars (LNnT, LNT, 3-FL and 2'-FL) for microbiome applications.

www.jennewein-biotech.de

Design of Experiments

How to Bridge Statistics and Chemical Engineering

Competition and increased demand for product innovation are placing unprecedented pressures on chemical manufacturing. As well as a seemingly unquenchable need for new products and product variants, the industry as a whole is also burdened with the high cost of research and development, leading to a near constant search for lean and efficient solutions. Though statistical analysis has not always gone hand-in-hand with chemical development, it can be a vital tool for accelerating the discovery and creation of viable new products, and for engineering the processes through which they can be delivered at scale. This marriage is the way to get things "right first time", reducing development risks and relieving the pressures mentioned above.

Experimentation has always been a key aspect of product development, allowing the kinks in chemical and formulation processes to be ironed out. Although such experimentation is good, it is becoming increasingly apparent that the traditional one-factor-at-a-time approach is partly responsible for inefficient product and process development: As well as consuming a lot of resources, it is likely to miss some of the practically important effects that lead directly to later manufacturing inefficiencies and failed product launches.

Fortunately, we now have the tools to supercharge our approach to experimentation. This approach is well-established in other industries, but so far has not been widely adopted in chemical manufacturing, particularly in the case of specialty chemicals. By deploying this new approach throughout the development phase, it is now possible to design quality into the process for making new products at the outset, rather than suffering the impact of failed product launches, protracted time to market, and low manufacturing yields. Even though many revolutionary products have been, and will continue to be, discovered serendipitously, figuring out how to produce them consistently and with commercially viable yields is a natural problem for statistics to help solve.

Julia O'Neill,
Direxa Consulting

The Need to Innovate

Design of experiments, DOE for short, is a systematic method to determine the relationship between factors affecting a process and the output of that process. In the industrial setting, there are usually many factors that might have an effect, and it is crucial that they be manipulated together, not one at a time. DOE has been used to find cause-and-effect relationships since Ronald Fisher first introduced it in 1935 and has continued to evolve

over more than eighty years. This has led to a series of widely applied design families adapted to meet specific situations and experimental objectives, and more modern approaches mean that you can make a design that fits more or less any situation. Software tools like JMP do all the computing work, and make it relatively easy for chemists, researchers and engineers to easily adopt this new approach to experimentation.

If this adoption becomes widespread, it can cut the time required for research and development, helping R&D to support twice as many products, and bring them to market twice as fast. And because knowledge accumulates, researchers can innovate more predictably over time.

This is no small feat. At the moment, the R&D process in most labs is unpredictable. Missed project milestones and incomplete understanding mean that the processes for producing new products are likely to be transferred into manufacturing with issues still unresolved, and with the expectation that the additional work needed will be done in manufacturing. But, even if it is successful, this strategy is time consuming and adds cost and waste. In the worst case, the product might be returned to R&D. Such rework takes away time that could be used to develop more new products.

In industries like chemical manufacturing that need to innovate to remain competitive, this status quo is costly. The way to break this vicious circle is to build quality into the products in R&D at the earliest possible opportunity using DOE.

Overcoming the Curse of Dimensionality

Effective information gathering is already in place in many R&D labs. However, whenever there is more than one input or factor affecting an outcome, testing one factor at a time is inefficient and risks missing the joint effect of two (or more) factors, which are commonplace. To properly uncover how all the factors affect the response, DOE is required. Because of its versatility and ease of use, chemists can easily leverage the software to reveal and model relationships between many factors, and one or more outputs, or responses. Often the best approach is to change the factors according to a plan that maximizes the chances of being able to determine a robust and cost-effective process that delivers the required product characteristics. Actively manipulating factors in this way is the best way to gain useful, new understanding.

In statistics and machine learning, dimension reduction is the process of reducing the number of variables under consideration by obtaining a set of principal variables that still contain most of the information carried by the originals. While this technique has not traditionally been a part of the product development and testing process, it can be especially useful in conjunction with DOE. For example, in drug development, many of the new products in R&D use starting materials that come from human beings or other animal subjects, and there is often only a short list of qualified donors. Thanks to advances in genomics and the characterization of the microbiome, it is easy to generate a very long list of measured properties of any given sample from each of those subjects. This results in a very large set of measurements on a very small number of subjects. Testing this in the lab can be costly and time-consuming, but by using dimension reduction the analysis process can be streamlined.

"The overall goal is to increase the efficiency and effectiveness of chemical R&D."

Increasing Efficiency and Effectiveness

In a real example, 10 years ago a team manufacturing vaccines was faced with a challenge of evaluating around 1,500 parameters affecting nine key quality attributes, measured on a smaller number of manufactured lots. Their task was to identify what was causing some unanticipated results in manufacturing. The team included a chemometrician, a mathematician, and a number of statisticians who, after several weeks of analysis, solved the problem and were able to recommend the changes needed to safeguard the supply of the vaccine in question. The computational challenges were tackled by a large team of people working tirelessly over several weeks and at great cost: Today, using tools like JMP, the same analysis problem can be solved by a single researcher in 30 minutes.

This is not to say that the work of this team of highly skilled professionals wasn't valuable, but rather that through the use of modern approaches and supporting software, it is now possible to free their time and expertise to work on increasing yield and developing more new products. The overall goal is to increase the efficiency and effectiveness of chemical R&D, bringing more new products to market more quickly, and at lower cost. For this greater goal to be achieved, R&D will have to achieve their desired outcomes with fewer resources and in more sustainable ways. This sustainability and reproducibility is a challenge to the chemistry-using industries, and the widespread and consistent adoption of DOE can be a huge enabler.

Powerful Data Management

DOE also allows chemists to confront issues that have been longstanding, and to finally determine the relationships that will get them closer to understanding the true cause and effect at work. The resulting model is an important tool for consensus building, because what shines through is the result: A ranking of all factors ordered by priority, challenging the preconceptions and biases of all those involved. This method of screening many predictors allows chemists to choose how to move forward in a controlled way, and that's where the real benefit of using such an analysis lies. With the addition of contextual knowledge, such analyses are usually very helpful in re-engineering the process so that it performs better.

By its very nature, chemical R&D produces a lot of data. Yet this often is still recorded on paper, even today. It can be time-consuming to digitize swathes of past records into a data management system, but this investment can be very worthwhile. Statistical analysis software is capable of sorting, cleaning, and organizing this data quickly and efficiently, and preparing it for analysis. This data management can be daunting for the uninitiated, but if the data is collected appropriately and prepared it will save time later down the line. There are also growing regulatory guidelines about appropriate data processing that need to be taken into account.

"The widespread and consistent adoption of DOE can be a huge enabler."

A Question of Mindset

In the USA the Food and Drug Administration, FDA, has produced a number of initiatives that aim to support the modernization of the pharmaceutical and bio-pharmaceutical industry sectors. At the heart of these initiatives is a shift away from a conformance-based approach to quality to one of using process-based understanding to manage risk and deliver better predictability.

Appropriate training and know-how remain a big stumbling block for industry as a whole: Many chemists aren't necessarily equipped to work with statistics, have not been exposed to DOE, and may not have had the opportunity to work with software like JMP that can give them the support they need.

More promisingly, it is not uncommon to hear from scientists who were once reluctant to use DOE but who become firm advocates once they see how they can quickly find solutions for problems they had been working on.

DOE Is Becoming Mainstream

Things are moving in a positive direction. Over the past 20 years, and taking industry as a whole, the use of DOE in product development has moved steadily from the fringes to the mainstream. Today it is evident that many R&D professionals are routinely turning to DOE to help answer their questions. Such is the power of DOE to gain the required process understanding that in regulated industries, the regulators may look more favorably on submissions and assessments that explicitly incorporate DOE.

Given this demonstrable success, the wide adoption of DOE in R&D by the chemical-based industries should be seen as both necessary and strategic. Companies in these sectors should be actively investing in developing their DOE capability, and work towards instituting more comprehensive data collection schemes that allow them to better understand their processes through the whole product lifecycle. It is an effort in terms of training and investment, but it will allow them to survive and prosper.

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Continuous Processing

Is Flow Chemistry the Future of Pharmaceutical Manufacturing?

Is it possible to learn from other industries or are we doomed to repeat the same mistakes in the pharma sector? Not long ago, I came across a Forbes article which described how streaming service provider Netflix proposed a partnership to video company Blockbuster. The new partnership would have required them to change their business model. At that time, such a decision seemed absurd and the offer was completely rejected by Blockbuster's senior management. Nevertheless, almost two decades later, Netflix is the leader in home-media and Blockbuster is history — just because decision makers were not ready to commit to new and disruptive ideas.

Even if some people may say that the comparison is not so trivial due to the differences between the two industries (pharmaceutical vs. service provider), one should not ignore the impact that disruptive models can have on companies. This is particularly evident in the current situation of the pharmaceutical industry, which has been caused, among other things, by the fact that politicians have put increasing pressure on the industry in recent years to reduce its costs as a result of ever stricter regulations. These circumstances have lowered profit margins of many generic pharmaceutical companies and, as a consequence, have caused stock prices of some of the major players to plummet (e.g. Teva); led to some planned mergers and acquisitions to reduce costs, become more competitive and/or increase product portfolio (e.g. Mylan and the generic branch of Pfizer); or prompted companies to focus on generics that are difficult to copy (i.e. Sandoz).

A Technology on the Upswing

In this competitive field, some companies in the pharma sector have realized the benefits of continuous manufacturing and started investing in this "new" technology. For other industries, however, this technology is not new.

Novartis was one of the pioneers of this trend: In 2007 the company started a collaboration with the Massachusetts Institute of Technology (MIT) to evaluate the continuous production of a solid dosage drug starting from the chemical reagents.

Later, most of the news about investments in this technology focused on the big players (including GlaxoSmithKline, DSM, Lonza, Ely Lilly), but over time the interest of CMOs and CDMOs has increased. Contract manufacturers are already receiving requests to perform some of the processes continuously. In some cases, they are not able to offer this technology, which can lead directly to a loss of business opportunities. Some CMOs prevent this situation by building capacity and expanding their knowledge of continuous manufacturing to anticipate future requirements. Capacity and knowledge building are becoming more and more critical in the pharmaceutical industry, where outsourcing and partnerships are increasing over time.

Walter Linhart, Microinnova Engineering

But why is continuous manufacturing on everyone's lips, what does it have to offer the pharmaceutical industry?

Benefits and Opportunities

A complete article could be written about the benefits of continuous manufacturing, such as better heat transfer, mass transfer, yield and other as-

pects. Most of these aspects have been intensively discussed by science and industry. However, when it comes to doing business and making decisions, the most important factor is cost — and that is the main difference between science and industry. In other words, chemical terms need to be translated into economic terms.

Continuous processes can be scaled up faster, as mass and heat transfer can be kept constant at different scales, which directly results in a faster time-to-market and thus higher economic benefits. Higher yields mean that less raw material is needed to achieve the same amount of end product and therefore less waste is produced — which can save a substantial amount of money.

In addition, a plant with a capacity of 10 l/h requires almost the same investment costs as one with 100 l/h. With a larger and more flexible system designed for more than one process (2 to 5 processes with a production in campaigns), business cases quickly become positive, while they would be negative for a small plant system and only one process.

Another important aspect is that continuous processes can be automated, and, in some cases, intermediate and isolation steps can be completely avoided, thus reducing labor and inventory costs.

Obstacles and Misconceptions

Even though the benefits of continuous manufacturing have already been discussed and are also known in the industry, there are still some obstacles and misconceptions which have delayed its implementation.

One of the biggest obstacles is the hesitant attitude of companies due to the potential risks associated with replacing or modifying an already implemented process. These risks relate primarily to regulatory hurdles. However, continuous production is currently being encouraged by regulatory bodies. For instance, the US Food & Drug Administration (FDA) has released draft guidelines regarding the quality of continuous processes, and the International Conference on Harmonization (ICH) supports the introduction of continuous manufacturing processes in the pharmaceutical industry with its new ICH Q13 guideline.

In addition, already installed batch systems and batch processes, which in most cases have already been devaluated, can hinder the introduction of continuous processes. If continuous processes have to be integrated into batch plants, they compete with the economic viability of existing processes and — by direct comparison — may generate a return on investment (ROI) which is too low for management to consider investing in this new technology. In this scenario, it is necessary for both engineers and management to evaluate the processes in order to assess which one would deliver the greatest economic benefits and might well outweigh the cost of change.

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Fig. 1: Continuous cryogenic GMP plant for a liquid solid reaction.

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Fig. 2: Modular continuous crystallization plant for downstream processing.

Flexible and Modular

Last but not least, another misconception regarding continuous manufacturing is the lack of flexibility. In general, it is assumed that continuous production plants cannot be multi-product plants. This lack of flexibility is usually seen as a major investment risk in a rapidly changing market. In the meantime, however, modular systems have been optimized in such a way that they make use of both the advantages of continuous production and the flexibility of batch systems.

Modular plants are characterized by functional units that are interconnected and can be exchanged according to production requirements. These plants also have their own automation system, which makes it possible to make the necessary changes without reprogramming the entire production plant, as in the case of a printer connected to a computer. The combination of a physical module with its own automation results in short changeover times. In other words, these types of plants are a good solution for short product life cycles and highly efficient processes.

Modular continuous production plants can be used in both the fine chemical and pharmaceutical industries. They can work under GMP conditions and in ATEX zones. Modular systems can also be easily scaled up (increasing capacity of the plant) or numbered-up (running processes in parallel). Another advantage of modular plants is the standardization of the modules, which decreases engineering and designing costs. Additionally, modular plants can be set up with a combination of existing designs which lower investment costs as well as delivery times.

Outlook

Modular plants are already a reality, and some were designed and built by Microinnova (see figures for examples). Modular and flexible plants have also been recognized as a manufacturing concept of the future and several projects have been developed such as the F3 Factory and CoPRIDE. Several large fine chemicals and pharmaceuticals companies, like BASF, Bayer and Evonik, have participated in these projects. This clearly demonstrates that the real question is not whether, but when, continuous manufacturing, like any other batch process step, will become a fundamental part of the pharmaceutical industry.

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Live-Broadcasting of Bioprocesses

Real-time Monitoring of Biopharma Production

The quality specifications of biopharmaceuticals are enormous and require a long list of time-consuming analytics. A big disadvantage of these analytics so far was, that their evaluation was possible only retrospectively. The Austrian Centre of Industrial Biotechnology (ACIB) and its partners Boehringer Ingelheim RCV and Novartis Pharma have developed a new process for real-time monitoring now: integrated sensors and mathematical models give valuable information about product quality and quantity within seconds. This novel process prevents industry from product bottlenecks and allows the reduction of costs.

The market share for biotechnologically produced medicals such as vaccines or pharmaceuticals against cancer or diabetes is steadily increasing and has doubled over the last decade. The biotechnological production allows a more flexible and gentle process compared to chemical methods and opens up the synthesis of vaccines or therapeutics of diseases like rheumatoid arthritis, which have not been treatable before. Compared to chemical synthesis of medical active substances, these biotechnological processes in living cells take place in milder conditions, thus being environmentally friendly. But of course, the application of biotechnology brings along some disadvantages as well: The production in biologic systems is a challenge in terms of concomitant impurities of the product. A multilevel purification process as well as deep process understanding are essential "must-haves" for being able to meet the official purity requirements.

How did it work so far? Currently, quality controls are realized by regular sampling and subsequent analyses outside of the process. This comes along with huge time efforts. Apart from that, this kind of control provides information about quality and quantity only many hours after particular process steps, which means that biotechnologists are constantly lagging behind before being able to adjust process parameters for a better output. A prompt reaction is impossible. Although continuous production and quality control in real-time are state-of-the-art in fields such as automotive or nutrition — enhancing product quality and making production more efficient — these strategies found little to less attention in life sciences so far.

Martin Walpot, Austrian Centre of Industrial Biotechnology (ACIB)

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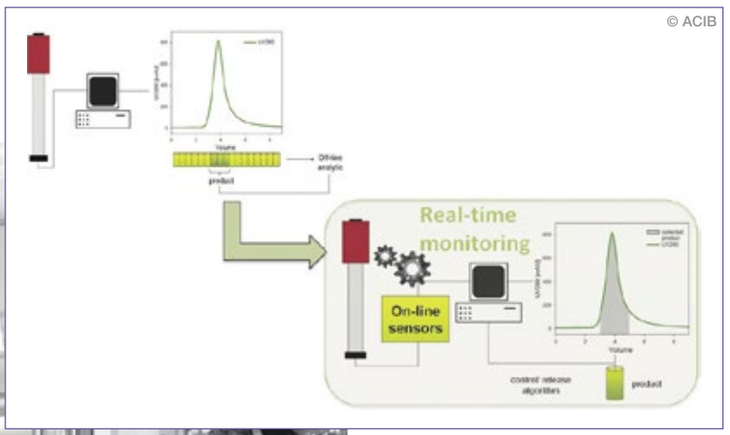

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Knowledge-based process control: The combination of different sensors and mathematical models connect measured signal data with important quality criteria.

Real-time Monitoring through Knowledge-based Process Control

ACIB cooperated with Boehringer Ingelheim RCV and Novartis Pharma for developing a new system that enables for monitoring complex purification of biopharmaceuticals in real-time. "Previous methods gave information only about a single quality parameter in the running system. But what we urgently need, is a monitoring process that gives information about product quality and quantity as well as about impurities within seconds. This is exactly what we achieved with

our new method: We combined different sensors and mathematical models that connect measured signal data with important quality criteria. The keyword is knowledge-based process control", explains Astrid Dürauer, project leader and key researcher at ACIB as well as senior scientist at the University of Natural Resources and Life Sciences (BOKU) in Vienna, Austria.

The research group developed a user interface that integrates the monitoring of the system, the visualization of measured data as well as the transfer of information and direct response of the control unit. Dürauer is more than happy with the new process: "This system significantly reduces the risk of manufacturing errors, the total process duration and the extent for analytics. Industry benefits from a safer, faster and more efficient process." A side effect of increased efficiency is the new availability of production capacities. Manufacturers can produce more different products or more batches of one product. On the long-term, manufacturing costs are reduced, and resources are saved.

Application in an Industrial Environment

ACIB developed the prototype at Boehringer Ingelheim's Vienna site together with both industrial partners and tested it over a period of more than 3 years. Quite recently, the system was successfully put into operation by both company partners and a patent for Europe as well as the USA is in place. For the manufacturers the system means a quantum leap in production, as Christian Eckermann, head of Biopharmacy at Boehringer Ingelheim RCV states: "From a technological point of view the in-process quality control approach in real-time is a mandatory condition for a real-time approval of produced batches, which further guarantees an efficient production of high-quality biopharmaceuticals. The system is an important basis for reduced process duration and offers a significant innovative advantage in terms of process control during the production of biopharmaceuticals!"

This is confirmed also by Michael Kocher, country president of Novartis Austria. In his view, the technology is an important reaction to the governmental demand for process control in the pharmaceutical industry. In other branches such as automotive or food industry continuous production and quality control for real-time production are state of the art and have shown a significant improvement in product quality as well as higher production efficiency. According to relevant authorities it is high time for the implementation of real-time controls also in pharmaceutical industries for drug approvals. However, the biopharma sector was lacking appropriate strategies for successful implementation. Kocher states: "The new system has high potential to herald biotechnological production into a new era!".

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The Importance of On-line Process Control

On-line Sensors Facilitate Production and Help to Ensure Quality by Design

Modern therapies of different diseases very often utilize drugs derived from living cells. However, manufacturing of these biopharmaceutical products is a complex process. One of the biggest challenges in biopharmaceutical production is to ensure reproducibility of the actual product. This challenge is rooted in the heterogeneity of a typical bioprocess. Minimal variations of the process conditions may lead to different yields or quality of a product — and might ultimately jeopardize the effectiveness of the drug.

Therefore, it is crucial to control the production process in the best possible way using quality by design. The Process Analytical Technology (PAT) Initiative, which originates from the 2004 guidance published by the US Food & Drugs Administration (FDA), established a regulatory framework that focuses on enhancing the understanding and control of the manufacturing process.

It is common sense that to properly apply PAT, it is essential to move from the manual sampling and laboratory measurement procedures to automated control. As even minimal variations of process parameters have a major influence on the final product, controlling them on-line (or in-situ) in real-time minimizes the risk of lower yield and purity. Real-time monitoring is possible with sensors that withstand the cleaning-in-place (CIP) and sterilization-in-place (SIP) procedures required to minimize the risk of contamination. In most manufacturing sites, this is already common for the fundamental critical process parameters such as pH, dissolved oxygen (DO) and conductivity.

"In fact, many parameters can be monitored continuously in real-time, but those directly related to cell physiology — one of the key performance indicators — are typically still time-consuming off-line measurements that provide only a reactionary window into the past", says Giovanni Campolongo, market segment manager Upstream at Hamilton Bonaduz.

"Even worse, important process events may be missed if a snapshot of the actual state is only taken sporadically, sometimes only every 24 hours. This significantly reduces the possibility that the cell growth is monitored in a process-safe way compatible with the PAT principles".

For this reason, several efforts have been put forth over the years to find technologies suited for accurate and reproducible real-time measurements. Some efforts for real-time cell density measurement are based on the use of molecular spectroscopy, others on soft sensing techniques (e.g. algorithms based on the evolution of the oxygen uptake rate, OUR, and the carbon evolution rate, CER, both requiring multivariate data analysis, MVDA, to generate application specific calibrations which are labor intensive to maintain).

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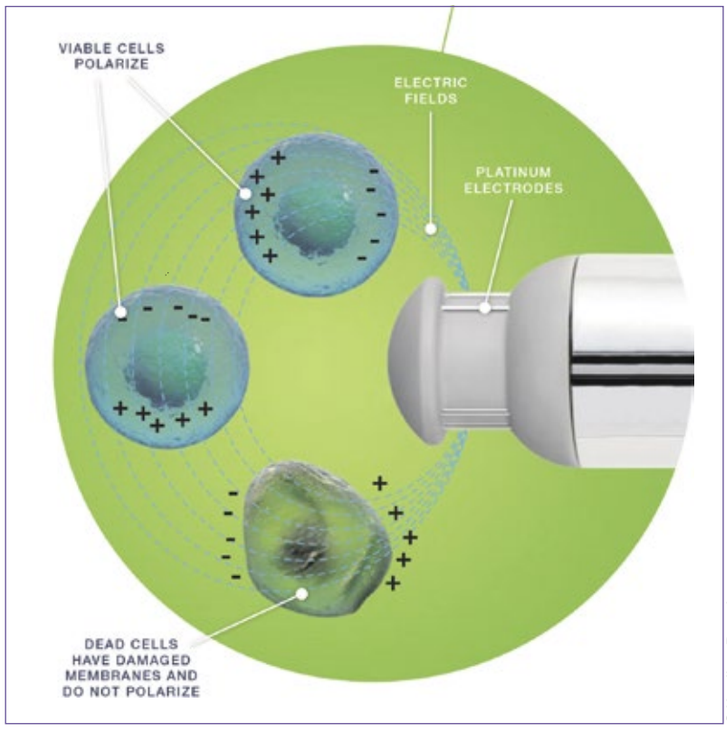
Nowadays, in contrast to these methods, permittivity measurement is the most reliable method of monitoring the viable cell density. The measurement principle is based on capacitance. In an alternating electrical field, viable cells behave like small capacitors. The charge from these small capacitors is measured by the sensor and reported as permittivity (capacitance per area). The measurement is immediately affected by changes in viable cell density and can be used to plan process-specific actions for maximum yield. Permittivity can also be used to detect changes in cell physiology and is the most immediate method for determining the beginning of the cell death phase.

This measurement method is quickly becoming the industry standard because of the robust real-time data. It correlates well to off-line cell counting in the crucial exponential phase without the risk of counting errors.

Hamilton is an established supplier for cell density sensors that use this technology. They measure viable cell density on-line (or in-situ) in real-time, meeting the increasing need for PAT in the biopharmaceutical industry. The measurement is not influenced by changes in the media, microcarriers, dead cells, or debris. "On-line measurement of viable cell density makes it possible to detect process events early and respond in real-time without sampling, which is a huge advantage compared to off-line analytical systems", says Marlene Frank, product manager Cell Density at Hamilton Bonaduz.

Hamilton has recently launched its next-generation viable cell density sensor with an integrated microtransmitter that amplifies the sensor signal for direct connection to the control system. Sensor configuration occurs via USB or wireless Bluetooth. According to Frank, "this sensor simplifies process control and also reduces maintenance efforts to a minimum."

www.hamiltoncompany.com



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The principle of permittivity measurement to monitor the viable cell density.

Pfizer Pumps $500 Million More into Gene Therapy

Pfizer is injecting an additional $500 million into its manufacturing plant in Sanford, NC, simultaneously announcing plans to hire another 300 staff.

The latest investment follows the $100 million it pumped into the project in 2017. Pfizer said the facility will support its continuing investment in gene therapy research and development, similar to its R&D sites at Chapel Hill and Kit Creek, NC.

At Kit Creek, scientists work at a small scale, ranging from 2-liter flasks up to 250 l bioreactors, to develop a process that may eventually be used in larger scale manufacturing. The process is optimized at Chapel Hill, where staff continue to work at a 250 l scale while implementing quality control measures included in GMP standards.

With the investment, the largest player in the US pharma market is widening its berth in the state where it already employs 3,600 people, including 650 at Sanford.

Pfizer said the expanded facility will strengthen both its clinical and commercial scale production capabilities for work on potential genetic cures using custom-made recombinant adeno-associated virus (rAAV vectors). (dw, rk)

Private Equity Takes Major Stake in Aldevron

Private investor EQT VIII Fund has agreed to take a majority stake in Aldevron, a US-based biologics supplier. The transaction is expected to close by the end of 2019, subject to regulatory approvals. The size of the stake and financial terms were not disclosed.

Headquartered in Fargo, North Dakota, Aldevron supplies plasmid DNA for commercial, clinical and research-stage gene therapies as well as proteins, antibodies and mRNA. The company also has operations in Madison, Wisconsin, USA, and Freiburg, Germany. It employs around 400 people worldwide.

Aldevron said EQT's investment will help advance its R&D and innovation efforts in the rapidly growing field of genetic medicine.

Eric Liu, partner at EQT Partners and investment advisor to EQT VIII, added that the private equity group believes Aldevron is "uniquely positioned" as a critical supplier to the gene therapy market.

As part of its support, EQT will provide funds to add production capacity at Aldevron's Fargo campus. Aldevron announced this month that it had broken ground on an expansion of the Fargo site. (eb, rk)

Jazz Pharmaceuticals Buys US Biotech Cavion

Dublin, Ireland-based Jazz Pharmaceuticals has acquired US biotech Cavion for a potential total sum of $312.5 million. The deal, through which Cavion has merged with a Jazz subsidiary, includes an upfront payment of $52.5 million with the potential of additional payments of up to $260 million upon achieving certain milestones.

The Charlottesville, Virginia-based clinical-stage biotech is working on treatments aimed at modulating the T-type calcium channel and restoring the brain's normal rhythms to treat neurological diseases, such as Parkinson's disease tremor, neuropathic pain, epilepsy with absence seizures and essential tremor.

Cavion's lead candidate is a late-stage molecule called CXX-8998, which is being developed to treat patients with essential tremor.

"The acquisition of Cavion demonstrates our commitment to further diversify our pipeline and product portfolio with the addition of CX-8998, which has the potential to provide a meaningful treatment option to patients," said Jazz Pharmaceuticals' executive vice president, R&D, Robert Iannone. (eb, rk)

Mezzan Buys Kuwaiti Pharma Company

Mezzan Holding, one of the Arabian Gulf's largest manufacturers and distributors of food, beverage, FMCG and healthcare products, has bought a 67% stake in Kuwait Saudi Pharmaceutical Industries Company (KSPICO).

The deal bolsters Mezzan's capabilities and offerings in the growing healthcare sector, giving the group majority board seats and effective control of KSPICO, which is Kuwait's sole manufacturer of pharmaceutical products.

The transaction was valued at 21 million Kuwaiti Dinar, or $69 million.

"This acquisition marks a significant addition to Mezzan's core consumer-driven healthcare business and expands its access to local and regional consumer spending," said Mezzan CEO Garrett Walsh.

"In the coming few months, Mezzan will focus its efforts on further growing KSPICO's market share locally and regionally, growing utilization of manufacturing and entering contract manufacturing as well as bringing the Mezzan discipline and balance sheet management into KSPICO to help drive growth and profitability." (eb, rk)

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CIEX 2019 – Chemical Innovation Exchange, 9-10 October, Frankfurt am Main, Germany

The conference is aimed at R&D and innovation experts from the consumer, industrial and specialty chemical sectors. By bringing together all players across the value chain, the event creates a unique platform for participants to learn, exchange ideas, and collaborate. It provides participants with a fresh channel to explore cutting edge innovation in the rapidly evolving chemical industry and connects innovators with investors, potential customers and budget holders.

http://ciex-eu.org

CPhI Worldwide 2019, 5-7 November, Frankfurt am Main, Germany

CPhI Worldwide, to take place October 9–11, 2018, in Madrid, Spain, is the leading networking event and exhibition dedicated to pharmaceutical developments, trends, products and services. Exhibitors include providers of contract research and synthesis services, suppliers of APIs, excipients, ingredients, intermediates and finished dosage forms, as well as producers of pharma manufacturing and packaging equipment.

www.cphi.com

ISPE Europe Pharma 4.0 Conference, 20–21 November 2019, Manchester, United Kingdom

Digitalization of pharma manufacturing can facilitate technological, economical, and logistical advancement. ISPE has created an operating model to anticipate the industry's future by incorporating Pharma 4.0 strategies for business and technology. The conference features business leaders and technical experts that will elaborate on new strategies and best practices for production operations of crucial systems with an information technology point of view.

www.ISPE.org/2019-EU-Pharma-40

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