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CPhI Pharma 2021 Annual Report: Golden Age for Discovery, Technology and Growth

CPhI Annual Survey Findings and Expert Contributions

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Introduction

The fifth CPhI Annual Survey will explore the perspectives of some 370 industry executives from over 35 countries. **Evaluating the likely trends in 2022 and the reputations of all major pharma markets across more than 10 metrics**. The data provides an annual insight into the growth and development of the industry globally.

Contents

Continued overleaf >>

Contents Continued.

Biologics

Nutaceuticals

Regulatory and Excipients

The CPhI Pharma 2021 Pharma Industry Rankings

Overview

The findings from this year's CPhI Pharma Industry Rankings come at a prescient moment, as the pharma industry's ingenuity to produce novel therapies and vaccines has culminated in the world undertaking its largest ever immunisation programme. So, while Covid has sent, and is continuing to send, huge shockwaves through global pharma, it has also shone a light on the industry's best and brightest, and many of these recent achievements owe their expedience to collaboration and partnering. Not least, of course, from the contract manufacturing industry, which has been essential in meeting covid vaccine demand, and the pharmaceutical ingredients industry.

Perhaps, the single biggest perception change between this year and 2020 [when vaccine development was still underway] is that – in addition to vaccine approvals – there is the realisation that immunisation programs and production is likely to continue far longer into the future than expected. In fact, booster shots are already being delivered for waning immunity this year and further vaccines are expected in the years ahead. This means that capacity across the entire pharmaceutical sector will continue to be congested for potentially longer than expected, at a time when demand is extremely high and growing. The implications of this rising demand present many opportunities for the industry, but also many challenges to keep pace with the demand for manufacturing sites, to keep the cost of therapies down and to continue the recent improvements in the speed of innovation.

The key positives from the last year include the remarkable adaptability of private sector companies, increased global collaborations and the ability of governments, academic and industry to align. Alongside this, emphasising the growth potential in the industry, we with have seen a rising number of pre-clinical IPOs[1,2] – with record valuations – and increasing private equity in the contract services industry.

There is the realisation that immunisation programs and production is likely to continue far longer into the future than expected.

However, attention has also been drawn to structural and supply issues in pharma – especially in the United States – that have been bubbling under the surface for some years. For example, how and where drugs are manufactured, and how secure supply chains are in a time of crisis. Consequently, we have seen a wave of protectionist policies from many countries and big pharma is responding with an increased use of diversified geo sourcing strategies – reducing any over reliance on a single region or country for any one item in the supply chain.

Yet, when we look holistically, the overall implication for pharma manufacturing in every region is that globally, we are entering a golden age for the industry – with higher

levels of investment both from traditional and new sources; a larger development pipeline than at any point in history (approaching 17,000 targets in discovery or development[3]); and an increasing demand for drugs and improvements in attrition rates and the cost of development.

These trends have combined with an inflection point for new technologies entering pharma with real-time reporting, AI, automation and continuous manufacturing set to transform manufacturing in the next five years. Meanwhile, biologics and cell and gene manufacturing are potentially entering a hugely profitable period, but one where greater capacity will be needed. And, aside from these pharmaceutical specific issues, the industry must also address its wider role in the world and in delivering sustainability and carbon reduction.

With these macro trends as our backdrop, the fifth **CPhI Annual Survey** will explore the insights of some 370 industry executives from over 35 countries. The rankings evaluate the major pharmaceutical markets across five key indicators – from 'Market Growth Potential' to 'quality of API manufacturing', 'innovation', 'competitiveness', and 'finished product' quality – culminating in overall scores for each country. In addition, the rankings also provide detailed perception scores for the biologics across four categories: 'quality of bioprocessing', 'knowledge of professionals', 'growth' and 'innovation'. In response, to the global challenge of climate change, a new category for 2021 has been added – the Sustainability Index – which will score how far long each country is in terms of achieving optimal sustainability of pharma devices and medicines.

This report is published alongside **CPhI Worldwide 2021**, which will return in-person **9-11th November 2021** at the **Fiera Milano, Milan**. The global pharma exhibition will unite the industry, with six events covering all aspects of the supply chain – from ingredients and finished dosage to machinery, packaging, outsourcing and biopharmaceuticals – and is expected to see over **30,000 attendees and some 1400 exhibitors.**

Pharma market growth potential

Pharma has performed admirably in the last two years when faced with a once in a century pandemic and, a key to this success, has been the ability to innovate at pace. What is encouraging for the industry's growth over the next few years is that this speed of innovation looks potentially set to continue and it is translating into increased investment and more opportunities. Running parallel to this has been a desire to modernise manufacturing and establish extra supply chain contingencies which is helping develop new revenues stream in the majority of major markets.

For the first time in the survey's history, the USA will therefore surpass both India (7.46) and China (7.25)

In fact, according to our industry executives there has been a significant uptick in confidence in 'growth potential' across major pharma economies, with every country seeing an increase in confidence, and overall, the 'growth potential index' has risen by 3%.

Leading the way is the United States (7.47) whose innovative companies – Pfizer & Moderna – have been front and centre in the fight against Covid-19, but many other parts of the pharma industry have had extremely successful year. For the first time in the survey's history, the USA will therefore surpass both India (7.46) and China (7.25) – which have both led the index in the last two years – as the country with the greatest growth potential. Unsurprisingly, the United States also saw the largest year-on-year percentage rise in pharma market growth potential out of all major pharma economies at 10.5%. The results suggest that the country is set to reap the rewards of an expanding R&D pipeline, vaccine contracts and a recent desire to increase support and funding for domestic manufacturing. In addition, the US based contact services companies – and/or those with sites in the country – have also done extremely well out of lucrative covid contracts and reshoring initiatives.

Highlighting the surge in confidence, investment across the United States according to *Statista research* suggests US Pharma companies spent over 20% of their revenues on R&D, with expenditure totalling some $91 billion in 2020.[4] This is expected to further increase over the next 4-5 years given the cost of developing effective Covid-19 vaccines.

In Asia, China's growth potential is now also back close to pre-pandemic levels, with global supply chain diversification no longer hindering its near-term prospects thanks to a burgeoning domestic market. In fact, China may only be at the early stages of its healthcare sector emergence, as the country currently spends just 6% of its GDP on healthcare[5]. In comparison, competitive pharma markets such as the United States, Western Europe and Japan invest 10% to 17% of their GDP into healthcare. The country also has a pharma and biotech centric "Made in China 2025 strategy" launched by President Xi Jinping, which is expected to help the country maintain or better 7.6% growth from 2020.

The United Kingdom (5.77) was another big mover, up by almost 5%, benefiting from strong government incentives, growth in outsourcing and pharma supply chains, as well as R&D tax credits[6].

Assessed this year for the first time was Switzerland, a country renowned for its strength and maturity as a major pharma hub – with biologics innovation, a long heritage in speciality chemicals and strong focus on R&D. In fact, the pharma sector accounts for an enormous 40% of Switzerland's exports, and it is an increasingly popular investment market[7]. For growth Switzerland (5.84) ranked behind Germany (6.13), but ahead of France (5.60) and Italy (5.38). Other new entrants to the growth potential rankings were Singapore (5.31), Saudi Arabia (5.00), the rest of Southeast Asia (5.51) and the rest of Middle East and Africa (5.17).

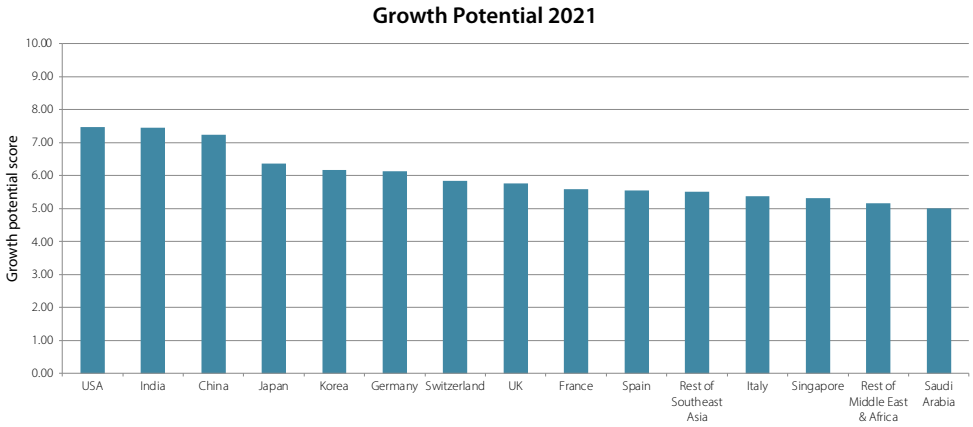


Figure 1: Shows the growth potential of each country's pharma industry (1-10: 1 being the lowest, 10 the highest)

API manufacturing

No surprises were present at the top of the API manufacturing league tables, with Japan (8.01), Germany (7.99) and the United States (7.97) continuing to lead the way as they have done in every year since the inception of the survey. However, newly surveyed Switzerland (7.66) came in ahead of Italy – Europe's largest producer and exporter of APIs – the United Kingdom (7.34) and France (7.01). The other new entrants to the API manufacturing rankings were Singapore (6.39), Saudi Arabia (4.71), the rest of Southeast Asia (4.92) and the rest of Middle East and Africa (4.42).

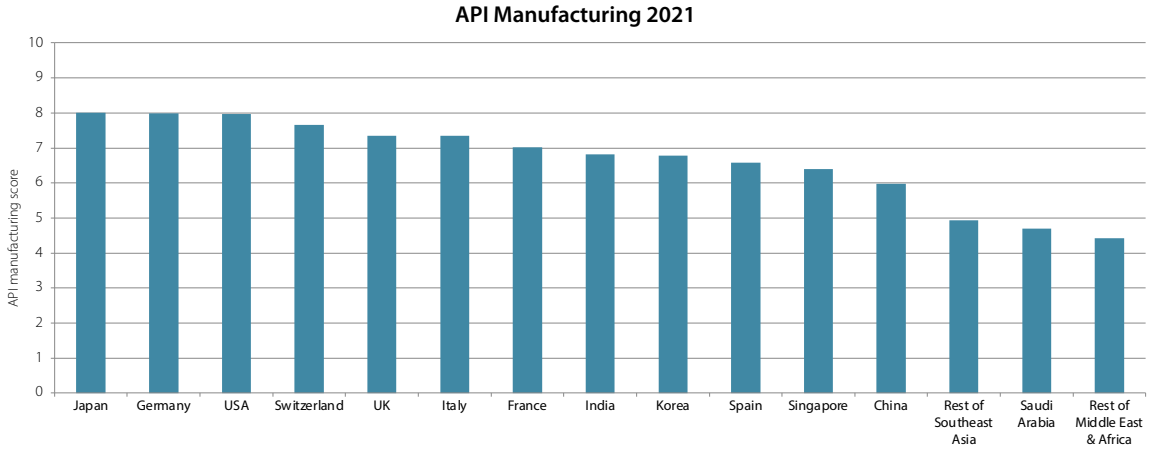
Perception of API manufacturing in major pharma markets is presently at an all-time high, with the overall index (6.66) seeing a dramatic 3.2% rise in comparison to 2020. China (5.99) and India (6.82) are the biggest gainers, seeing 7.4% and 6.8% improvement respectively. India, in particular, is benefiting from a sudden surge in private equity

investment across its API sector with a five-fold increase of inbound capital. To name but a few, recent investments have included acquisitions from The Carlyle Group's of Sequent Scientific Ltd, Advent International's acquisition of RA Chem Pharma Ltd and ZCL Chemicals Ltd, and PAG's acquisition of Anjan Drug Pvt. Ltd[8]. As well CDMOs, like Aragen, who reportedly gained an eight-figure inflow from Goldman Sachs[9].

Historically, India has a duality of approach in regards to API, with a majority of its domestic industry production being exported to overseas nations (particularly those in the West), while its large generics and finished dose sector are paradoxically dependent on API sources from China – importing as much as 70% overall, and in the case of life-saving medicines category, that goes up to some 80+%.[10] However – and only partly in response to pandemic pressures – the Indian Department of Pharmaceuticals, under the Make-in-India initiative, has identified a list of 56 APIs which will now be produced end-to-end in India, with a priority on fermentation products. In the near term, India's Council of Scientific and Industrial Research (CSIR) hopes to have least 10-12 of these 56 APIs in commercial production within the next couple of years. The net result is that India's much famed generics industry may gradually become much more vertically integrated within India. This may not lower costs initially but should increase supply chain security for international buyers.

Another positive for API manufacturing and R&D chemistry services in India is that many global players are looking to rebalance the supply chain, sourcing their needs from a more diverse change of countries – i.e., reducing any sole reliance on China – and this will be a trend we will increasingly see in the next 2-3 years.

Figure 2: shows the quality of pharmaceutical API manufacturing in the major pharmaceutical markets (1-10: 1 being the worst, 10 being the highest)



Solid Dose Innovation

The world's most prominent big pharma economy, the United States (8.01) once again dominates the solid dose innovation space, returning to the head of the table ahead rivals Japan (7.39), and Germany (7.60). The United Kingdom (7.18), France (6.80) and Korea (6.58) all retain their places from 2020 and further consolidated themselves as tier-two nations, while new entrant Switzerland (7.16) immediately joining. However, CPhI Worldwide host country, Italy (6.80), has seen the largest growth of the Western nations at 5.9%.

The emerging markets have seen an uptick in perception, none more so than China (6.22) who saw this year's largest growth up a remarkable 9.5%. The ever-increasing numbers of biotechs in the country, coupled with a rising number of CDMOs and the MAH (Marketing Authorization Holder) programme is driving rapid R&D growth[11].

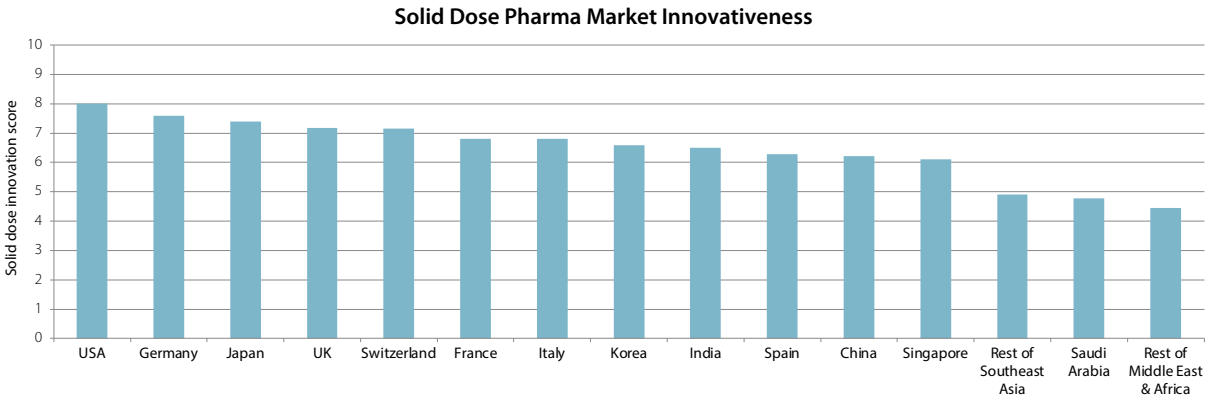


Figure 3: Shows the innovativeness of each market's pharma (solid dose) industry (1-10, 1 being the lowest, 10 the highest)

Competitiveness

The competitiveness category asks respondents to give an overall score for a country. The survey defines 'competitiveness' as a combination of each nation's: tax environment, quality of employees, infrastructure, research potential, labour costs, accessibility and access to funds.

Unsurprisingly, considering the score improvements in other categories, the overall competitiveness of the pharma market continues to rise – with every country showcasing an increase. In fact, the 'competitiveness index', which is a cumulative average score from all countries surveyed, saw a 2.5% increase compared to the previous year.

The United States (7.03) once again ranked first in the competitiveness index – but its increase in score of 3% was nevertheless an impressive return for the market leader – while India (6.72) has notably solidified its position as a globally competitive pharma market. The county once again finished in second position ahead of the likes of Germany (6.54) and Japan (6.30). Driven by strong government initiatives, China's (6.60) latest competitiveness index score improvement (up 6.3%) has elevated them ahead of both Japan and Germany and into third position.

The latter finding will be surprisingly to some and perhaps shows that much of the negative media narrative around China's pharma industry is in contradiction to the reality of growth the market is still undergoing.

In fact, a recent *Chemical and Engineering News* report has suggested that Indian companies – like Syngene, Aragen, Biocon, Jubilant, NJ Bio and Piramal among others – have been big beneficiaries of pharma shifting chemistry and development services to India (from China). Yet conversely, such is the strength of the biggest CROs and CDMOs in China that they have also reported record sales in 2020, suggesting that globally demand for outsourcing is extremely robust[12]. It implies that all markets will continue to see excellent growth potential in the short and medium term.

Among the newly surveyed countries, Switzerland (6.13) leads the way – finishing ahead of Korea (6.01), France (5.79), Italy (5.78) and Spain (5.70) – while Singapore (5.66), 'Rest of Southeast Asia' (5.31), Saudi Arabia (4.89) and 'Rest of Middle East & Africa' (4.86) round up the remaining of the league table.

Quality of Pharmaceutical Finished Product Manufacturing

The overall quality of finished product manufacturing is on the rise globally, per our respondents, with every country reporting an increase. In fact, the previously surveyed countries saw an overall growth in perception of 5% in the 'Finished Product Manufacturing' index. This suggests that the industry believes the push towards QbD, continuous

processing, and other manufacturing process controls and improvements are having an extremely positive effect on the GMP standards of global manufacturing. Global regulators have also been noting this shift in standards and the FDA introduced its Quality Management Maturity (QMM) pilot program[13] within the last year. The aim of which is to 'gain insight from third-party assessments of a manufacturer's quality management system' to inform a future development of an FDA rating system. This system will then enable the FDA to operate 'a more flexible approach' to manufacturers that have shown a mature and robust quality management system.

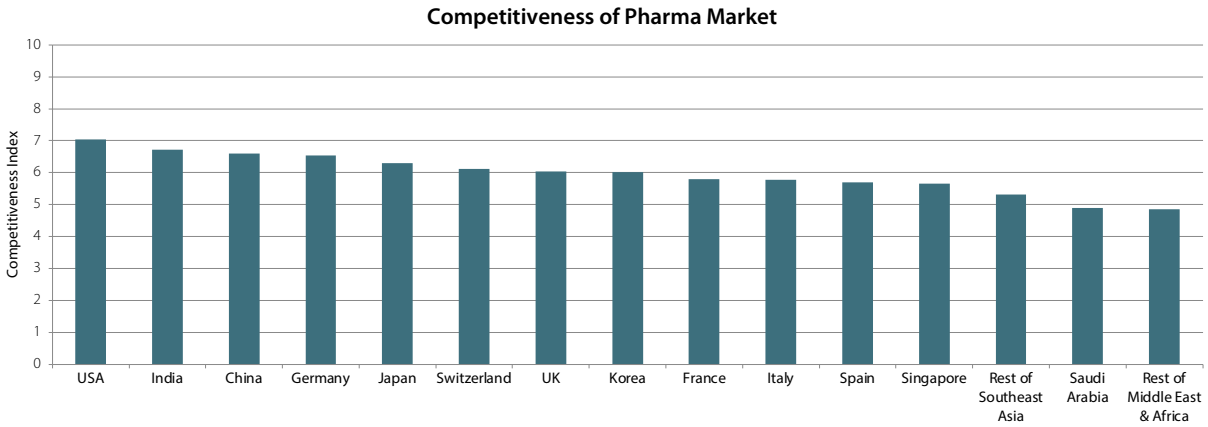


Figure 4: Shows the overall competitiveness of each market as a pharma business destination (1-10: 1 being the lowest, 10 the highest)

Another commonality that has accelerated dramatically in the last year is, of course, the rise in the use and success of digital and real-time monitoring and remote auditing, as well as AI, which is now taking off as a way to further improve manufacturing.

Speaking earlier this year, CPhI expert Bikash Chatterjee, CEO of Pharmatech Associates – a USP company, put these developments into the context of the next five years: *"The biggest prediction I can make in the next five years for the United States is the application of AI. Whether it's on the early precursor chemical synthesis or done in the formulation development processes or in the treatment algorithms that are being used today, it is a huge catalyst to be able to screen and evaluate very, very efficiently. Automation is also taking off quickly and not just in AI-driven drug development. Manufacturing and smart factories are now improving efficiencies and even enabling real-time remote monitoring."*

In terms of national scores, Germany (8.46), Japan (8.28) and the United States (8.43) once again lead the way, with the United Kingdom (8.17) and Switzerland (8.15) narrowing the gap to the top tier. For the second year running, India (6.84) has seen the largest growth in this category (13%), building on from last year's 4% increase. Over the least five years, India has invested heavily in new manufacturing facilities, and is well known to have around 665 approved USFDA manufacturing plants, the highest in the world [outside the USA].[14] Spain, also showed a sizeable increase in score (7.09), seeing a 12% year-on-year growth.

Of the other larger pharma manufacturing economies France (7.72) and Italy (7.67) both reported sizeable increases (5.3% & 8.3% respectively), while Korea remained unchanged, and Singapore (6.88) was surveyed for the first time.

Although starting from a lower base, China (5.63) has also continued to progress with a healthy 5.2% increase in score.

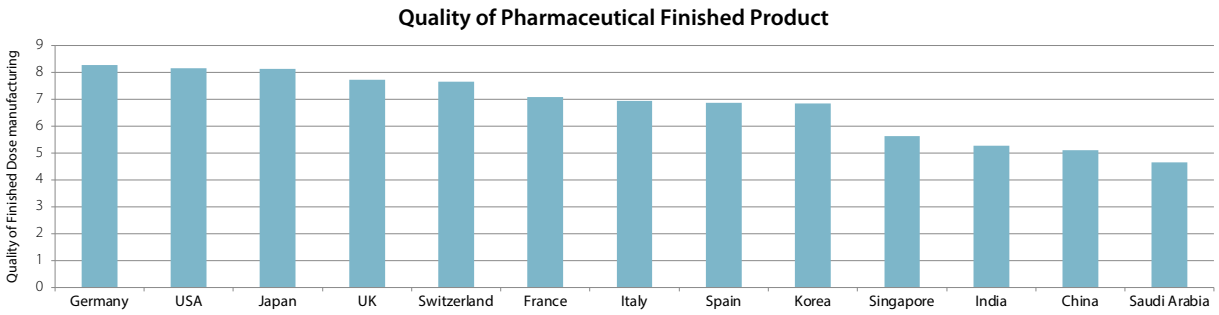


Figure 5: Shows the quality of pharmaceutical finished product manufacturing of each market (1-10: 1 being the lowest, 10 the highest)

Change in Country overall score: the CPhI Pharma Index:

To calculate the **CPhI Pharma Index**, an overall composite score, we compile the findings from each of the **five small molecule categories** with equal weighting given to each. At the very top of the league table there has been no change, with the United States (7.78) once again leading the way after a truly impressive 5% rise in its overall perception. However, Germany (7.35) has displaced Japan (7.27) in second place after a 3.5% year-on-year increase, which was primarily fuelled by significant improvements (4%) across perceptions in API and finished product manufacturing.

In the second tier of the league table, the newly surveyed Switzerland (6.99) has placed in front of the United Kingdom (6.90), becoming Europe's second highest ranked pharma market after Germany. This is despite the United Kingdom's impressive year on year expansion across all categories. Significantly, any worries about the effect of Brexit seem to have eased, with the country reporting a 5% rise in growth potential following on from the 6% increase it saw in 2020. The UK rises mean it has pulled well away of Korea (6.50) and leapfrogged key European markets France (6.59) and Italy (6.59).

CPhI Worldwide host country and Europe's largest producer and exporter of APIs, Italy, has moved up the table for the second year running, drawing level with France, a stark improvement on just three years ago when it placed 10th in the rankings.

In Asia, India (6.87) saw a 5.4% increase in its CPhI Pharma Index fuelled by its storming rise in finished product manufacturing, reaping the rewards from strong government incentives, macro headwinds and extensive investment in new manufacturing sites. In fact, it has been reported that some 15 Private Equity funds have invested in API sites in India during the last few months[15].

After seeing the largest fall in the CPhI Pharma Index last year, China (6.34) has overtaken Spain (6.24) with the largest year-on-year increase of any nation, bouncing up 7.2%. Newly surveyed Singapore (6.07) and the rest of the Southeast Asia region (5.15) along with Saudi Arabia (4.93) and the rest of the Middle East & Africa (4.71) round up the bottom half of the table, although there is an expectation Singapore will climb the rankings in the next few years.

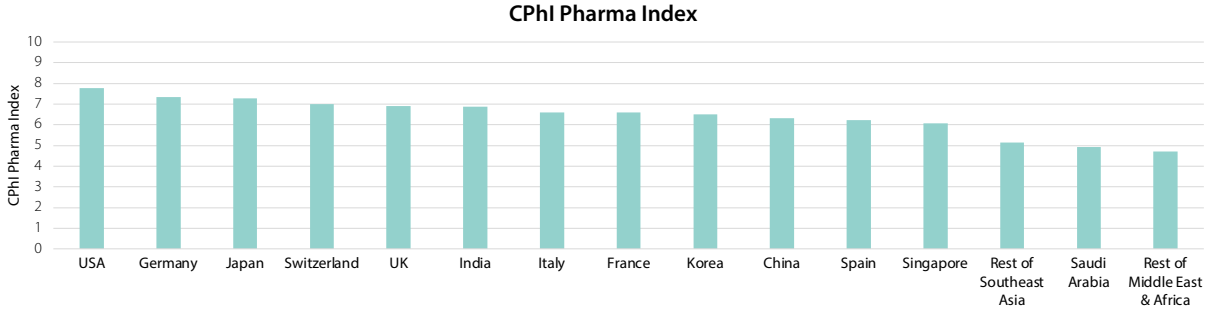


Figure 6: Shows the overall CPhI Index for 2021

The CPhI Pharma Index: what do the collated findings mean for the global industry in 2022?

Following a ground-breaking year where novel therapies and vaccines targeting Covid-19 were approved, the supply chain diversified and become more resilient, and investment from public and private sources increased, the overall industry is in extremely good health. So, when collated across all markets and all primary solid dose categories, the industry's overall increase of **3.54%** is perhaps to be expected. This indicates a significant bounce in confidence in pharma over the course of the last 12 months after the 0.86% decrease of the previous year.

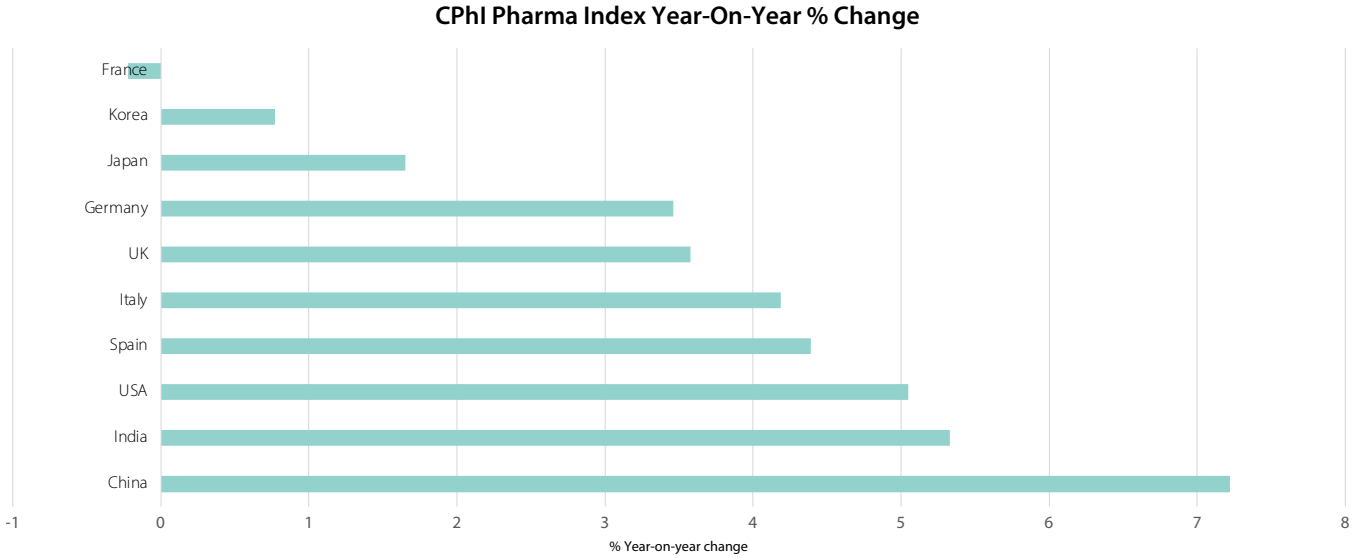


Figure 7: Shows the year-on-year change of the CPhI Index

Cell & Gene Therapy Industry

The global cell and gene therapy manufacturing services market will reach $13.8 billion by 2026, according to new research expanding at a compound annual growth rate (CAGR) of 12.4 percent from its current value of $7.7 billion.[16] As a growing component of the pharma industry, the CPhI Annual Survey has introduced a new metric to explore which countries are perceived to be leading innovation in cell and gene therapies – pharma's advanced therapies that are at the very cutting edge of research.

The United States (8.21) is a long way clear of its next nearest rivals – Germany (7.38) and Japan (7.14) – demonstrating the country is leading the charge on advanced therapies via its hubs in Philadelphia, Boston and California – with 7 approved therapies and more than 40 in late-stage development for launch in the USA over the next few years[17].

The United Kingdom (7.07), which accounts for over 12% of the global gene and cell therapy market, according to the UK Cell and Gene Therapy Catapult[18] follows narrowly behind. In fact, the UK market for cell and gene therapies is expected to soar from £300 million turnover in 2020 to £10 billion in 2035[19]. Switzerland (7.00), renowned for its strong biotech pedigree, follows the UK closely, with France (6.51), Sweden (6.45) and Ireland (6.19) a little further behind.

Rounding up this category is China (6.17) – the country to first approve a gene treatment back in 2003 (Gendicine) – and Singapore (5.84), with the former making significant strides in the cell and gene therapy space, evidenced by China-based Legend Biotech completing its US IPO in early 2020. Per Ernst & Young insights, the Chinese government is making significant efforts to strengthen IP, aligning its strategy to drive national innovation in the cell & gene therapy space.

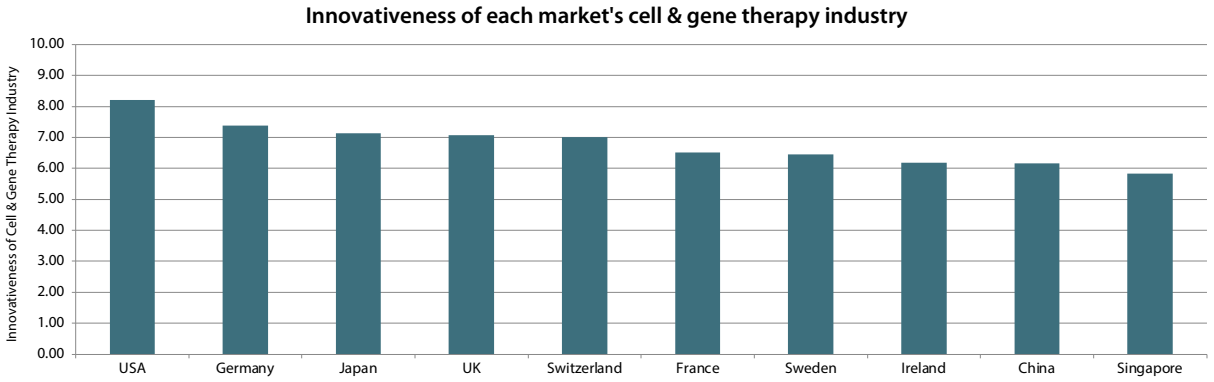


Figure 8: Shows the innovativeness of each market's cell & gene therapy industry (1-10: 1 being the least innovative, 10 being the most innovative)

Quality of Biologics Processing

The United States (8.29) once again leads the way due to its high-level manufacturing facilities and quality of professionals in the country. Newly evaluated Switzerland (7.82) overtook the United Kingdom (7.67) as Europe's second-best ranked market in terms of quality of its biological processing and manufacturing, and in spite of the latter's significant 5% year-on-year upsurge.

The most significant move in the rankings sees Italy (7.17), drawing level with Ireland (7.17) – overtaking Sweden (7.13), Korea (6.79) and Singapore (6.51) – which may reflect the increased number of investments by global CDMOs in the Country. For example, Catalent recently announced its first phase of a planned $100 million expansion program[20] at its facility in Anagni and AGC Biologics announced plans for the expansion of their Cell and Gene Therapy Center of Excellence[21] in Milan. However, China was the recipient of the largest year-on-year growth (11%). China's (6.08) CMO sector and biopharmaceutical industry houses global biologics giant WuXi Biologics, but other companies such as AutekBio, Chime Biologics and MabPlex are also on the rise with an increasing number of CDMOs launching as a result of the MAH programme and a few [like WuXi] targeting sales into Western markets.

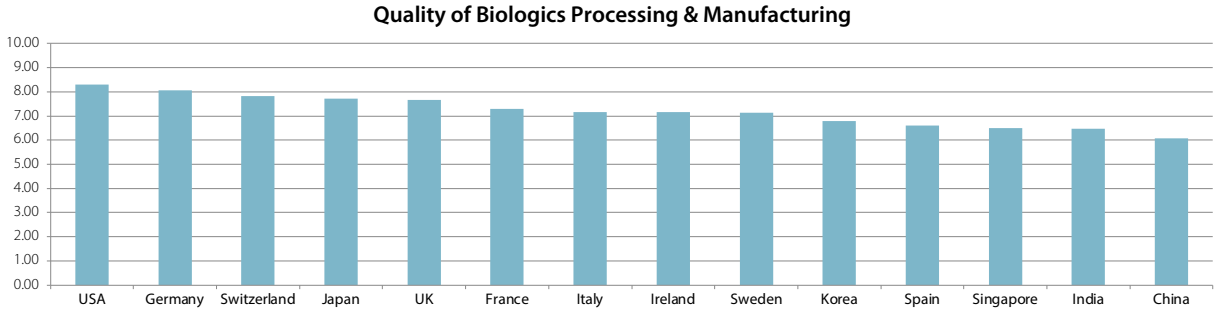


Figure 9: Shows the quality of its biological processing and manufacturing of each market (1-10: 1 being the worst, 10 being the highest)

Growth Potential of Biologics Manufacturing Industry

The U.S. (7.92) is renowned for its role in bio innovation, with strong hubs in Boston, Philadelphia, San Diego, San Francisco, Washington and Texas and is unsurprisingly ranked first again for growth potential in biologics.

Following a 5% decrease in reputation last year, Germany (7.37) has regained its place in the top three with a 5% year-on-year rise. The top 3 was rounded out by Ireland (7.28), who consolidated in third after back-to-back years of positive reputational change.

Switzerland (7.14) and Japan (7.16) followed behind with India (7.09) and Sweden (6.63). India's continued buoyancy will have been helped by the recent change in stance from the (US) FDA on biosimilar versions of biological medicines, which has resulted in an increased number of investments in biosimilar R&D across biotech companies in the country.[22]

However, the most significant mover in the rankings is again the United Kingdom (7.08), which saw an 8.3% rise in their biologics growth potential, perhaps boosted by the success of the Oxford/AstraZeneca Covid-19 vaccines and Innovate UK's continued investment and support for new biological advancements[23].

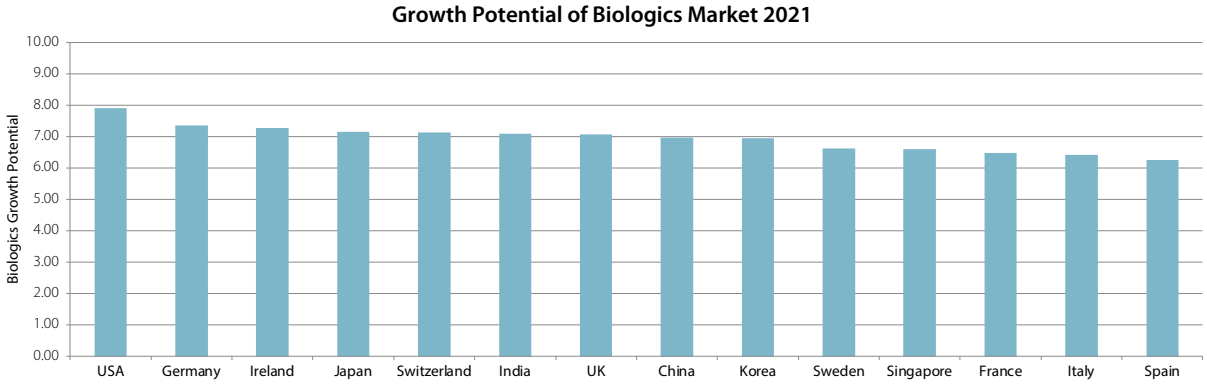


Figure 10: Shows each market's growth potential for biologics manufacturing industry (1-10: 1 being the lowest, 10 being the highest)

Innovativeness of Biologics Industries

This category has historically been dominated by the big three of the United States (8.27), Germany (7.53) and Japan (7.27), but with the introduction Switzerland (8.08) – a world renowned centre of biologics – to this year's survey, Japan has slid out of the top 3. In fact, there is now effectively a top 5 of nations at the head of the table.

Leapfrogging Japan and maintaining their position in the top 4 is the United Kingdom (7.29), which has seen a raft of positive developments in 2021. The country is pushing to be a key centre of global biologics manufacturing innovation – to take just one example, the £5 million investment given by the UK Government to the CPI (Centre for Process Innovation) to develop a 'library of mRNA' vaccines to fight new COVID-19 variants.[24]

Collectively, these findings point to increased profits for manufacturers, high EBITA valuations for sites and continuing issues on access to development partners for biotechs. The implications are explored later in this report in contributions from Dawn Ecker (geo-location of capacity in 2025), Fiona Barry (covid vaccine production), and Vicky Xia (the role of China in bio).

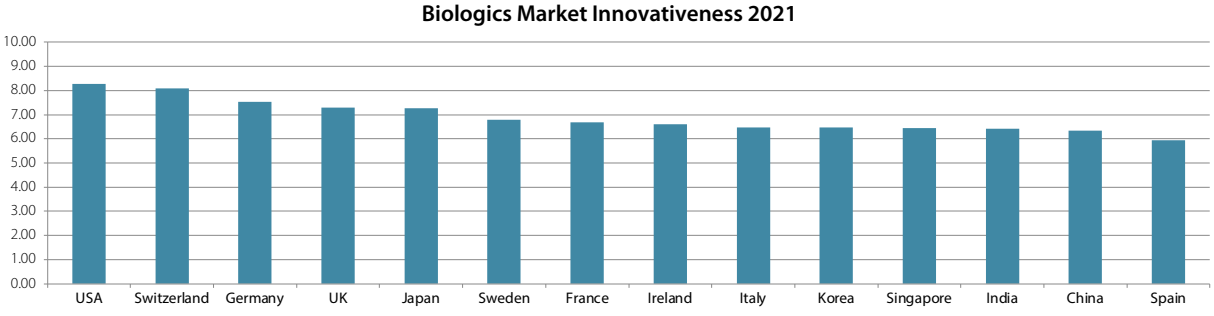


Figure 11: Shows the innovativeness of each market's biologics industry (1-10: 1 being the least innovative, 10 being the most innovative)

Additional Survey Responses

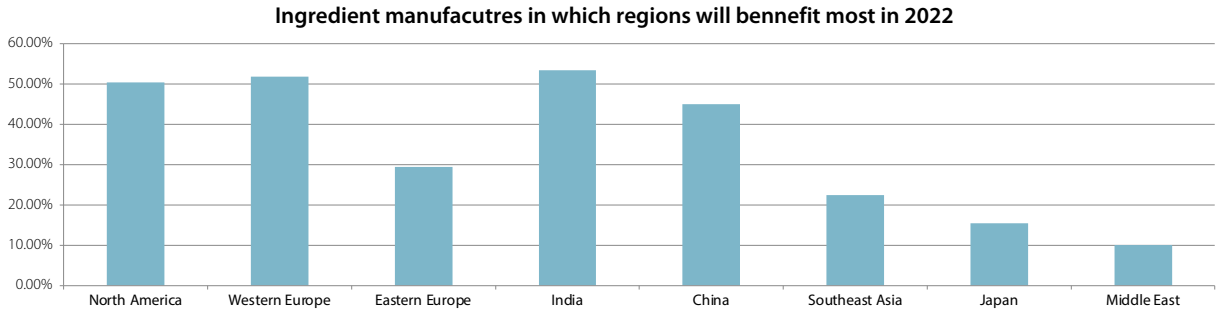


Figure 12: Shows which region(s)' manufacturers will be the biggest beneficiaries of supply chain changes and geo sourcing strategies in 2022 (multiple sections allowed)

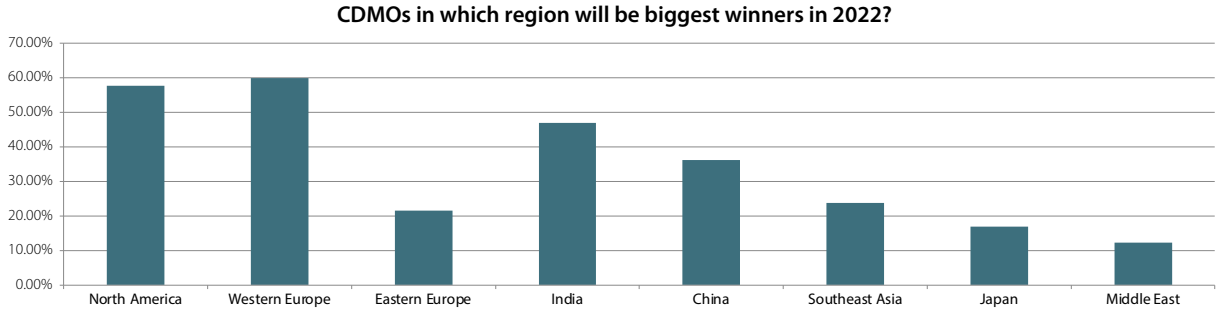


Figure 13: Shows which region(s)' CDMOs will benefit most from supply chain changes and geo sourcing strategies in 2022 (multiple sections allowed)

Commenting on the contract services space looking ahead into 2022, Ramesh Subramanian, Chief Commercial Officer at Aragen: *"The pandemic has ushered a drive for externalization, whether it's research, development, or manufacturing. In terms of the level of activity change, I expect to see customers increasingly looking at externalization, especially since it's their only path towards advancing pre-clinical and clinical assets. In 2022 I expect CDMOs and CROs to continue to invest in new capabilities, acquire new sites, or build new sites, with demand for externalization expected to exceed the current supply. We expect the market for the service sectors in all markets will continue to be extremely robust."*

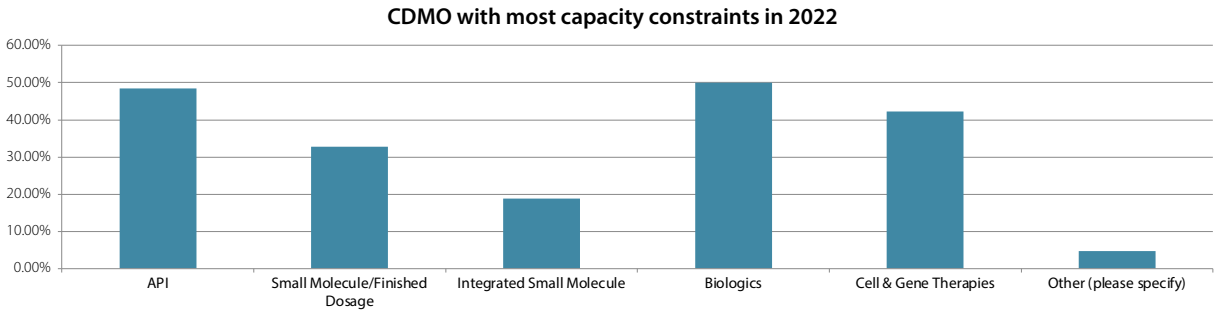


Figure 14: Shows for which type of CDMOs capacity constraints will be most acute in 2022 (multiple sections allowed)

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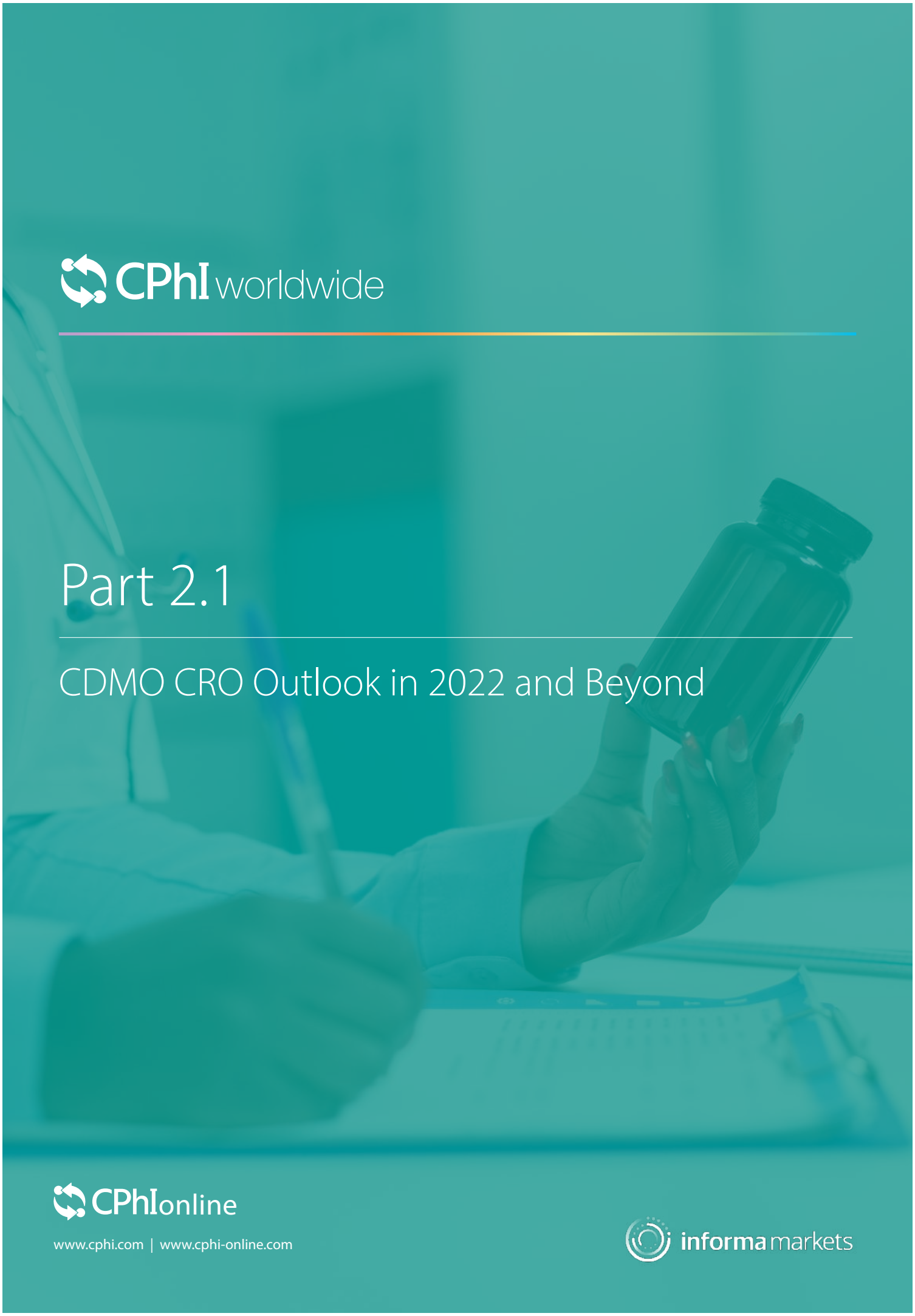
Part 2.1

CDMO CRO Outlook in 2022 and Beyond



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CDMO CRO Outlook in 2022 and Beyond

Why M&A in the pharmaceutical CDMO and CRO sectors is booming and why this will continue

The last five years has seen the pharmaceutical CDMO (contract development and manufacturing organisation) and CRO (contract research organisation) sectors blossom in terms of value, and significance of M&A transactions. The there are many drivers including increased use of pharmaceuticals, retrenching of supply chains to regional and national manufacturing hubs and novel innovative medicines driving strong investor interest in these business sectors.

The CDMO business sector

The CDMO sector benefits from strong growth fundamentals with the increased use of pharmaceuticals, in growing and aging populations.

Covid-19 has been the most significant factor in the life sciences industry in the last 24 months; the industry has been seen as a major source of innovative solutions for this pandemic, quickly developing and deploying several highly effective novel vaccines. This has enhanced the public perception of this industry and particularly the pharmaceutical companies. Investors have followed, and life sciences have attracted investment and are viewed as a safe-haven investment in these challenging times. For example, the Chinese government has very recently led a regulatory assault on internet platforms this year, hitting those in food delivery, ecommerce, fintech, gaming and education. This has tempered investor interest in the Tech sector globally. However, the Chinese Communist Party's desire to advance technologies such as high-end manufacturing has boosted other companies and industries including life sciences, underpinning life sciences as an attractive investment.

Specifically, this has had a profound impact generally on pharmaceutical manufacturing as well as specifically on vaccine manufacturing, both traditional adenoviral vector and validating novel mRNA-based vaccines, the importance of vaccine production and the ability for countries to have the capability to control the manufacturing has driven manufacturing strategies, which has been highlighted by investor interest and executed transactions including M&A.

Strong investor interest in life sciences generally and the pharmaceutical manufacturing industry is reflected in both the number and relative value of recent transactions. In the CDMO sector deal activity in H1 2021 has been incredibly strong. 48 deals were completed in H1 with the expectation that momentum will continue for the

remainder of 2021, compared with an average of c. 50 deals per year for 2017-2020. Q2 2020 saw the lowest level of deal making in the past 5 years with only 5 deals completed. However, deal activity picked up strongly and the year overall was still in line with previous periods thanks to a strong Q1 and Q3. In parallel there has been an increase in valuations from 10x EBITDA 10 years ago, to 12x EBITDA 5 years ago and to around 15.5x EBITDA over the past ~2 years. It is possible with the recent deal making frenzy these values are even greater on current deals.

These numbers do however, hide significant sector and technology differences, valuations tend to be driven by technical differentiation of the company and fundamentals of the underlying market (mainly growth, margin potential & market size):

- Viral vector manufacturing for vaccines and cell & gene therapies (CGT) as well as other CGT manufacturing offerings are currently the most highly valued – we're seeing multiple in the 20-30x EBITDA range;
- Biologics API manufacturing is the next highly valued capability – multiples are in the high teens up to 20x EBITDA;
- Injectables manufacturing is similarly valued in the high teens EBITDA multiples (mid-teens for smaller or less differentiated players). Valuations have been lifted by the exceptional demand for vaccine sterile fill facilities arising from the strong demand for covid-19 vaccines;
- Exposure to the small molecule (medicinal chemistry) market leads to overall lower multiples
- OSD (oral solid dose) and LOC (Liquids, Ointments, Creams) manufacturers tend to currently be valued in the low to mid-teens, depending on scale and differentiation (e.g. HPAPI handling, specialty formulation)
- Small molecule API manufacturers are valued in the same range.

Scale is a major contributor to valuation across the sector due to the scarcity of scale assets. Companies with an EV (Enterprise Value) >$200m command a premium over smaller players. We don't see a significant difference in median valuation between pureplay API vs. drug product CDMOs. There appears to be an investor premium for full-service CDMOs (development services, API and drug product) who on average receive a higher valuation compared with pureplay API or drug product CDMOs.

Deal activity in this sector is strongly driven by private equity. Over 60% of deals in 2020 and 2021YTD have been executed by PE (private equity) or PE-backed companies. The sector is currently highly fragmented with the biggest players only having ~15% of the market, so in addition to the good fundamental business drivers there is the potential opportunity to grow in this sector through consolidation.

The CRO business sector:

The CRO business has flourished over the last 5 years driven by first increased sophistication of the service offering provided by CROs (in the past they would provide basic chemistry and screening services, now more and more they are collaborating and contributing to the IP generated on these drug discovery programs). The leading players such as Evotec, Curia, WuXI AppTec and Charles River Laboratories are companies of scale offering comprehensive research and pre-clinical development services to the pharma (who are increasingly outsourcing more and more of these early-stage R&D activities), biotech, not for profit organisations (e.g. the Gates Foundation) and academic institutions. They are buoyed by the surge in interest in pharmaceutical innovation. Behind these larger CROs are a larger number of smaller but growing companies which PE and investors are taking a strong interest in. Two recent transactions of note are the Symeres acquisition[1] and Sygnature Discovery deal[2], which are both rumoured to value these companies in the high teens/low twenties EBITDA multiples, confirming strong investor interest in this rapidly developing business sector.

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The outlook for the CDMO and CRO business sectors:

For the next couple of years life sciences will retain the "safe haven" endorsement from investors.

Looking further ahead, life sciences is a business sector which we predict will continue to attract strong investor interest and this will drive transactions, both numbers and valuations. Those which are linked to new therapeutics linked to novel technologies.

With respect to the CRO sector we expect to see this grow and consolidate driven both by investment in outsourced pharmaceutical research by large pharma, charities, governmental organisations and biotechs. Over the next five years we anticipate deal frequency and value will remain strong.

For CDMOs this will continue to be a sector of interest for investors keeping transactional activity and valuations high. Within this we expect areas which relate to cell and gene therapies, biologics and high value secondary drug products, such as sterile fill and pharmaceutical device combinations to be of premium interest and valuation. Coupled with the repatriation of manufacturing from Asia to Europe and the US arising from both manufacturing inflation in the Far East and a desire for strategic pharmaceutical products to be manufactured closer to their markets will result in a buoyant CDMO business sector, with good quality assets and people in limited supply.

Additional CPhI Q&A with Kevin Bottomley

Q) *How many CRO/CDMO deal do you anticipate in 2022? (e.g. circa 50 CDMO deals, xx CRO deals).*

"My guess is that the number of deals will return to the annual normal, driven by shortage of suitable acquisition opportunities rather than a shortage of investor interest. But valuations should remain high."

Q) *Any perspective on if we are likely to see any more mega CDMO deals (see thermo fisher), or more in the mid-sized range to acquire scale)?*

"There is lots of desire, they just seem to be very difficult to do, as integration is always a big challenge."

Q) *Are US and European sites drawing in more attention – due to macro/geo trends from Covid?*

"Yes driven by the repatriation of business from Asia to US/ Europe and the increasing nationalisation of supply chains."

Q) *What do you think the exit strategies might be private equity (buy medium sized CDMOs, make acquisitions to become top 10 or 20 and sell after 2-3 years?)*

"This is the universal plan."

Q) *Will we see more mergers/acquisitions of CRO and CDMOs to draw these two sectors closer together – maybe a Cambrex or Lonza with an Evotec or something similar)*

"Evotec is moving into commercial manufacturing (JUST) driven in part by their own pipeline, but these are essentially different businesses and I expect to see them largely remain distinct."

Q) *Do you have perspective on hottest CDMO targets – e.g. is finished dose/cell gene CDMOs in West verses say biologics CDMOs in China etc.*

"Cell and Gene is hottest, followed by biological sites and then sterile fill/finish."

Q) ***With acquisition targets tightening and the best sites seeing high EBITAs will private equity owners look to build facility strategies to meet the rising industry demand?***

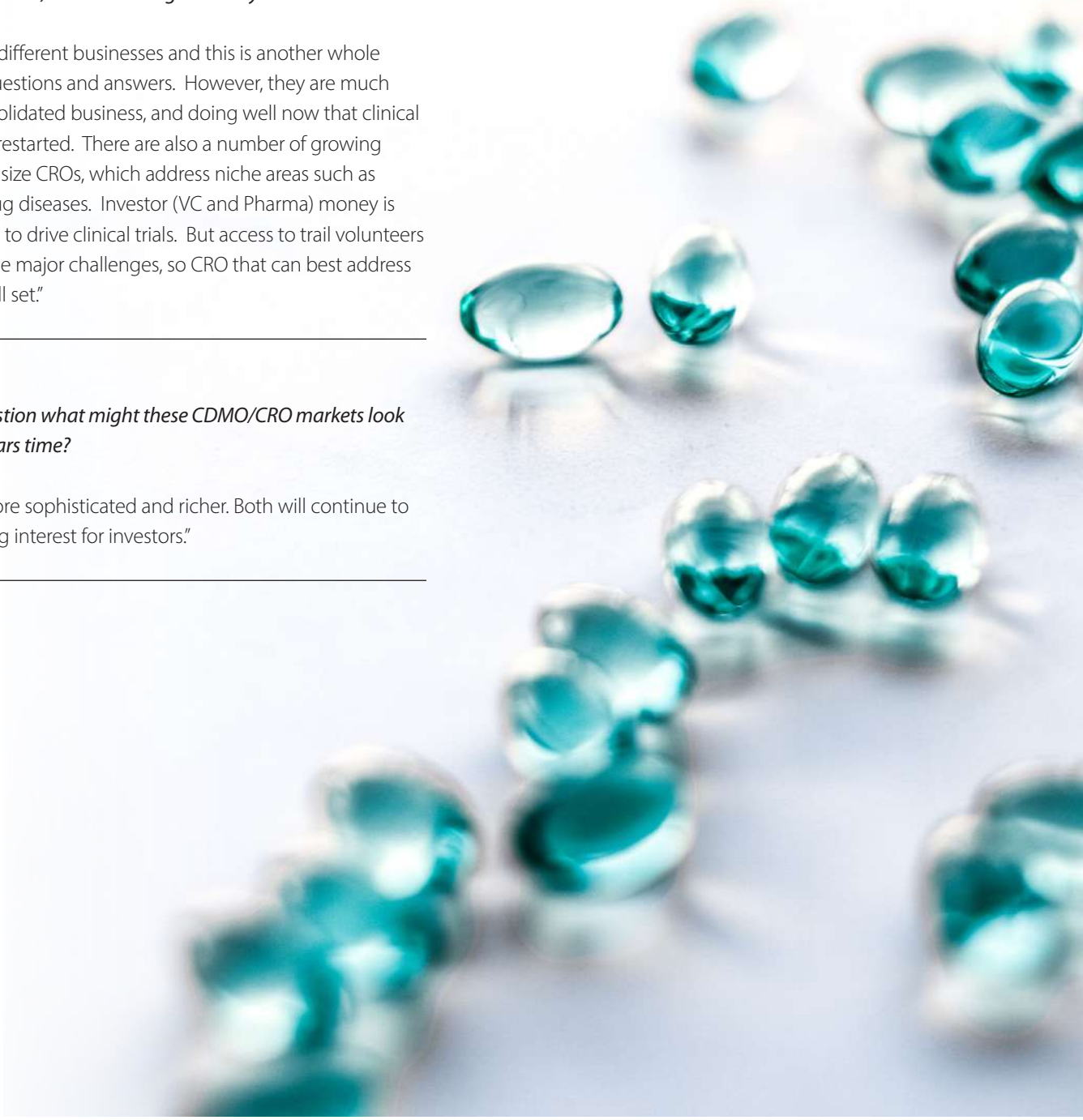
"Yes, you see this currently in the US with both cell and gene therapy and sterile fill."

Q) ***Do you have any perspective on clinical CROs (IQVIA, Emmes, PPD etc) verses the drug discovery CROs listed above?***

"There are different businesses and this is another whole series of questions and answers. However, they are much more consolidated business, and doing well now that clinical trials have restarted. There are also a number of growing small / midsize CROs, which address niche areas such as orphan drug diseases. Investor (VC and Pharma) money is continuing to drive clinical trials. But access to trail volunteers is one of the major challenges, so CRO that can best address this are well set."

Q) ***Big question what might these CDMO/CRO markets look like in 5-years time?***

"Bigger, more sophisticated and richer. Both will continue to be of strong interest for investors."



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Part 2.2

Increasing Private Equity Investment and the Race for Biologics and Specialized Capabilities Drive the CMO Industry's M&A Activity

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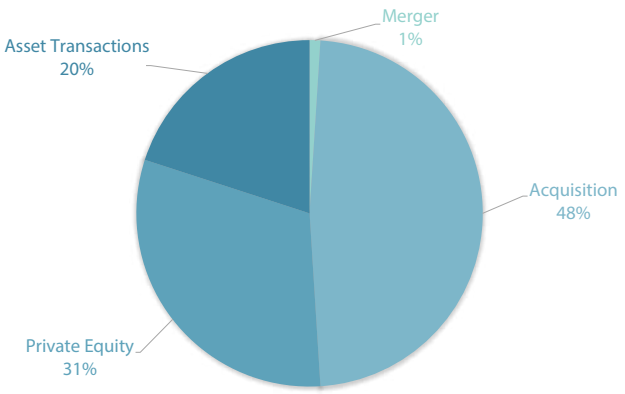
Increasing Private Equity Investment and the Race for Biologics and Specialized Capabilities Drive the CMO Industry's M&A Activity

Private equity (PE) firms have recently shown an increasing appetite for contract manufacturing organizations (CMOs) with rapidly increasing investments in the CMO industry. PE firms now own many of the world's leading CMOs, such as Recipharm, Cambrex Corp, and PCI Pharma Services. Besides the large volume of acquisitions, deal values in recent PE-related deals are remarkably high. In December 2020, EQT IX Fund, through Roar BidCo AB, agreed to acquire Recipharm AB, one of the largest dose CMOs, for approximately $2.1B. Lars Backsell, chairman of the board of Recipharm, and Thomas Eldered, board member and Chief Executive Officer of Recipharm, are shareholders of Recipharm and participated with EQT IX in the offer.

The Tax Cuts and Jobs Act of 2017, which was passed under President Trump, reduced corporate tax rates and increased the spending power of PE companies, leading to rising levels of investment in the CMO industry. According to GlobalData's ***M&A in the Contract Manufacturing Industry: Implications and Outlook – 2021 Edition*** report, the most common type of acquirer was PE firms, which increasingly view the CMO industry as a prudent choice to provide a good return on investment. This group rose to the top among acquirers during 2018–2020, compared to four years earlier when they were in third place. More PE firms were buying than selling, indicating a strong investor appetite. PE firms acquired almost 70 pharmaceutical contract manufacturing companies, and PE-backed CMOs

Figure 1: CMO Merger and Acquisition (M&A) Activity, 2018–2020



Source: GlobalData, Pharma Intelligence Center Deals Database (Accessed April 20, 2021) © GlobalData.

acquired eight companies during 2018–2020. PE firms most commonly bought Active Pharmaceutical Ingredient (API)-Biologic and multi-service offering CMOs. These service types are high value and are most likely to be sold later on for a profit. Supply chain disruption and problems with mass vaccine production mean there are currently significant opportunities for CMOs, and they represent a particularly prudent investment opportunity for PE firms.

Specialist CMOs are experiencing increasing levels of acquisition as time goes on. During 2015–2017, acquired companies with specialized services accounted for 28% of deals. This grew to 33% during 2018–2020. Standard offering acquisitions decreased to 44% from 50% between 2015-2017 and 2018-2020. These trends suggest that CMOs are increasingly targeting companies with sophisticated capabilities to cope with the challenges of manufacturing modern drugs. There is evidence of this continuing into 2021, when Murano Bidco, an affiliate of the PE giant Carlyle Group, acquired Vectura Group in May for $1.4B, followed by Vectura's September purchase by Philip Morris International (PMI) for approximately $1.45B. Vectura develops inhalational products through an integrated inhaled drug delivery platform. Demand for this specialist dosage form, inhaled drugs, may become more of a theme as the COVID-19 pandemic progresses, as many survivors suffer from long-term decreased lung capacity. Philip Morris stated that the deal was motivated by boosting its product pipeline in inhaled treatments, although the acquisition by a tobacco company provoked concerns from healthcare professionals. Vectura's shareholders accepted the 165 pence-per-share offer from PMI, with approximately 75% backing the deal. On September 20th PMI begun the process of delisting Vectura. Following its acquisition by the cigarette maker, Vectura has been barred from pharmaceutical industry conferences. This includes the UK-based Drug Delivery to the Lungs conference which is dedicated to pulmonary and nasal drug delivery, which has terminated Vectura's sponsorship.

FDA approvals requiring special handling have generally increased in recent years. This trend bodes well for CMOs with high containment specialist capabilities, as the regulations for associated facilities can be onerous and out of reach for small and mid-sized companies. As molecules become more complex, future production will require enhanced technologies for the expression, development, and manufacture of these molecules.

High-Demand Biologics

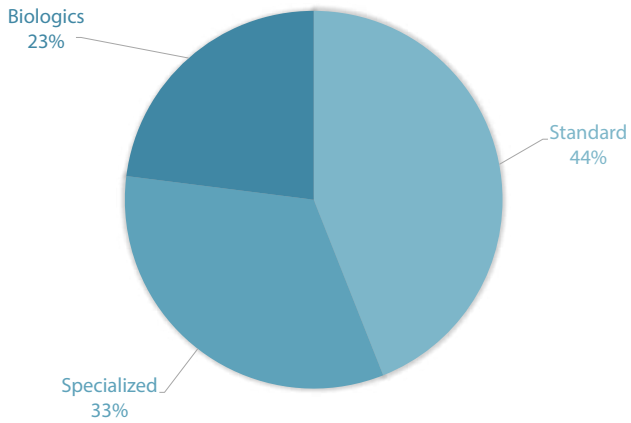
The figure below shows that the largest target group had standard capabilities and lacked specialized, differentiating services, despite being less than half of the targets. The next largest group was specialized targets. Only 23% had capabilities that could be used in API-Biologic (including cell and gene therapies) and dose manufacture. Although most CMOs would benefit from new or addition biologic and specialized capabilities, there is a relatively small number of associated facilities in comparison to those with a standard offering. The cost of acquiring or constructing sites with biologic capabilities is prohibitively expensive. Biologics production and the supply chain are complex and require a wide array of often expensive equipment with a high level of staff expertise. Large-scale biotech manufacturing facilities require $200–500M to build. This is far more than small molecule facilities of similar scale, which often cost $30–100M to construct. This will be financially restrictive for most companies except big pharma. Even after the construction and setup are completed, the running costs of biologic manufacturing facilities will also be far higher, requiring highly skilled staff and expensive materials and equipment while producing a limited yield. Overall, this means that many smaller pharma companies and CMOs will be unable to build or acquire such capabilities, and therefore CMOs with these capabilities can charge a premium to clients.

GlobalData's ***New Drug Approvals and Their Contract Manufacture – 2021 Edition*** report showed that the FDA approved more biologic New Molecular Entities (NMEs)

in 2020 than in any other year in the previous decade. Simultaneously, sponsors increased the outsourcing of these biologics' API manufacturing. However, as pipeline and marketed biologics increase in both complexity and number, most CMOs remain unable to manufacture biologic APIs to meet sponsor companies' needs. Unfortunately for CMOs, larger companies tend to invest in developing their own internal manufacturing capabilities to manufacture drugs rather than outsource production. However, they do frequently dual source to mitigate risk and for other strategic reasons. COVID-19 vaccines and advanced therapy medicinal product (ATMP) manufacturing are heavily outsourced due to scale or technical expertise difficulties. CMOs can benefit from investing in capabilities and expertise (where they have the means to do so) to produce and handle sensitive biologics, as the marketed drugs landscape will become increasingly flooded with these in coming years.

Cell and gene therapy-related acquisitions are currently in high demand and highly valued, with some of the largest CMOs being involved in these acquisitions, such as Catalent acquiring both MaSTherCell and Paragon Bioservices, for $315M and $1.2B, respectively. At the same time, Massachusetts-based Thermo Fisher Scientific Inc, another leading CMO, completed its acquisition of Brammer Bio LLC, a viral vector contract development and manufacturing organization (CDMO), for $1.7B. The contract research organization Charles River Laboratories acquired Cognate BioServices, a cell and gene therapy CDMO, in a high-value deal in March 2021 worth $875M.

Figure 2: Acquisition Targets by Sophistication of Capabilities



Source: GlobalData, Pharma Intelligence Center Deals Database and Contract Service Provider Database (Accessed April 20, 2021) © GlobalData.

Note: Standard service offerings and processing technologies are common to the industry and not differentiated. Specialized service offerings use standard technologies but are applied in more complex products (excluding biologics), such as the manufacture of controlled or highly potent substances. Biologic service offerings and process technologies are not broadly available and are used for biologic drug categories such as monoclonal antibodies, proteins, peptides, gene therapies, or cell therapies.

Future Outlook and Factors at Play

The COVID-19 pandemic has led to investor hesitancy, even when it comes to M&A activity. However, some of the largest CMOs will continue to acquire to enhance their capabilities or scale of production in the future. Even during the height of the COVID-19 pandemic in 2020, large CMOs acquired companies, not only for high-profile capabilities such as gene and cell therapy manufacturing but also for more traditional commercial dose manufacturing services. There is no reason why this M&A activity cannot continue over the next two to three years. COVID-19 vaccine developers signed contract manufacturing agreements at an unprecedented rate during 2020 because many of these sponsors are small companies or non-profit institutions that lack manufacturing capabilities. Even the largest companies require extra capacity to supply billions of doses. Despite many developed markets vaccinating the majority of their populations, vaccine production will still remain in high demand for the foreseeable future.

The US Centers for Disease Control and Prevention (CDC) and FDA have announced a plan to offer the US general public a third shot of either Pfizer/BioNTech's or Moderna's COVID-19 vaccines beginning on September 20, 2021. The FDA and CDC have also said that a second dose of J&J may also need to be administered. The August 18 switch from previous guidance followed a rise in the highly transmissible Delta variant. The US is already administering a third dose to immunocompromised people, and Israel is also rolling out a third dose. Many European countries will offer a third dose to vulnerable groups.

Experts including Andy Slavitt, former senior pandemic advisor to President Biden, have raised the possibility that patients who received the Johnson & Johnson or AstraZeneca recombinant vector vaccines may require an additional messenger ribonucleic acid (mRNA) vaccine shot due to the increasing prevalence of the more contagious Delta coronavirus variant, which studies suggest the Pfizer vaccine offers better protection against.

The global prevalence of COVID-19 is still high. Most countries have not yet vaccinated their populations to an extent that herd immunity is achievable. Several variants have been identified. They developed a short time after the virus was discovered in late 2019, so it is a safe assumption that further variants (and potentially variants of concern) will emerge if case numbers remain high. While Pfizer and BioNTech believe a third dose of their vaccine (identical to the first two shots) would be effective against all currently known variants, including the Delta variant. In the future, if a variant emerges that is not prevented by the vaccine, Pfizer will develop a new version of its vaccine.

These extra doses will bring more highly specialized work, with CMOs making these novel molecules. It will also put pressure on the world's supply chains. Other developments could push volumes even higher, including the fact that companies are currently trialing vaccinations in children and the likelihood that one or more vaccines or therapies currently in clinical development will be approved. If these candidates are found to be safe and efficacious, there will likely be a rapid increase in the number of contract manufacturing agreements.

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Part 2.3

Innovation in Manufacturing Will Fuel the Next Decade of Industry Growth

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Innovation in Manufacturing Will Fuel the Next Decade of Industry Growth

As the world struggles to emerge from the COVID-19 pandemic we have caught a glimpse of what our industry can accomplish when properly motivated. For the last decade we have seen both the pharmaceutical industry and the Food and Drug Administration embrace innovation in nearly every facet of the drug and device development process. We have also seen that the engine driving these innovations is no longer the exclusive domain of large pharma and biotech.

Looking at the more than 3,000[1] drug programs in Phase III clinical programs cited in the congressional budget office report on pharmaceutical research and development, more than 70 percent come from companies with revenues of $500 million dollars or less. Since 2009, more than one third of new drug approvals by the FDA have gone to drug sponsors with revenues less than $100 million dollars[1]. Correspondingly, for the first time in decades, specialty drugs top the ranking based on retail spending whereas classes in which the best-selling drugs are now available in generic form rank lower than they did just ten years ago[1].

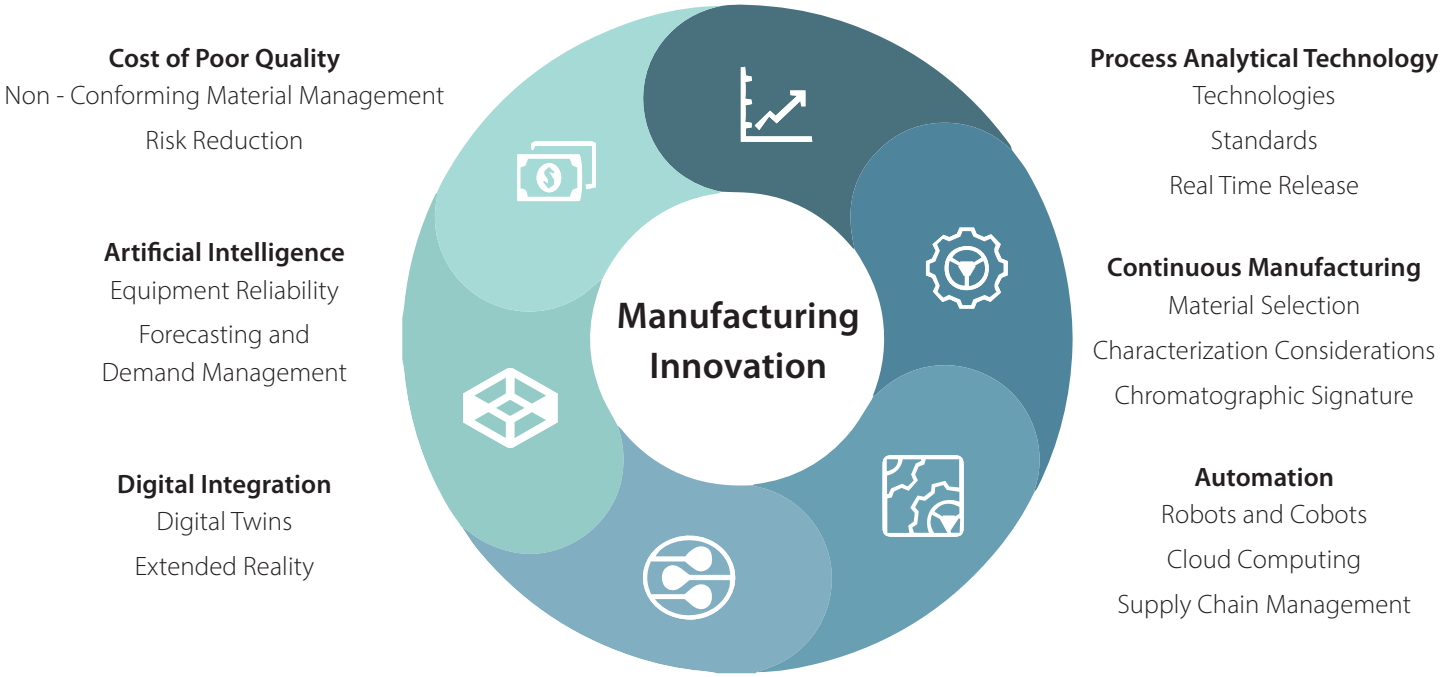
Even if one were to ignore these trends, our industry's ability to innovate, test, scale up, and mass produce highly effective vaccines against the COVID-19 virus illustrates our aptitude to harness latent innovation and execute. Close collaboration and communication between academia, industry, regulators and government policymakers has never been stronger, and will become a foundation for future innovations in our industry for years to come.

Innovation in Manufacturing: Ripple Effect

The innovations we have witnessed in the last decades—particularly for rare diseases—provide hope to millions of people while creating new challenges in the manufacturing and scale-up of cost-effective drug therapies. The FDA expects to approve between 10-20 new Biologics License Applications (BLA) a year for the next four years in the areas of cell and gene therapy alone.[1] But these therapies are costly for manufacturers and patients alike. To realize the long-term sustainability of many new drug modalities and therapies industry must rethink its approach to manufacturing, quality control, and the corresponding path to overall drug quality.

The impact of advanced manufacturing technologies goes beyond the simple implementation of new technology. Broad acceleration in adoption will be achieved, in part, through focused intensive development between academia and industry. We have been slow to adopt paradigm shifting approaches and technologies, because of the industry's aversion to perceived risk, but the pandemic thrust telemedicine and decentralized clinical trial design to the forefront after they had languished for years as an interesting theoretical discussion. Our renewed collective focus on supply chain resiliency, on national preparedness, and the need to drive business performance in a post-pandemic marketplace are catalysts for modernization that will extend throughout manufacturing and the entire value chain, thereby reducing industry risk aversion with a ripple effect upon traditional manufacturing practices. Advanced technologies will affect many future manufacturing operations; some of these key areas are shown below in Figure 1.

Figure 1. Advanced Manufacturing Innovation Areas



Process Analytical Technology (PAT)

Whether a drug sponsor is content to stick with the current hybrid state of batch manufacturing for its drug substance and/or drug product, or is seeking to migrate to a continuous process, the ability to gain rapid insight into the state of the material within each unit operation is central – to having confidence the material manufactured possesses the correct critical quality attributes (CQA) for it to be safe and efficacious. With the FDA's paradigm shifting guidance in 2004[2] encouraging scientific understanding and intelligent application of risk management as the basis for defining drug quality, the ability for drug manufacturers to implement solutions that allow them to see and react to process information in real time has been the goal of the FDA and other regulatory bodies. **Process analytical technology** (PAT) strives to understand processes by monitoring the **critical process parameters** (CPP) that affect a product's CQA. The goal is to monitor and potentially control them—in as close to real time as possible—through either in-line or on-line measurement sensors, thus ensuring the process remains within its process design space.

Process Analytical Chemistry (PAC) Technologies

To fully realize the benefits of a PAT implementation it needs to be combined with process analytical chemistry (PAC) tools to measure the characteristics of the process that have been defined as critical material attributes (CMA, or critical process parameters - CPP). Several PAC technologies have emerged as the most promising and practical for PAT implementation. For active pharmaceutical ingredient (API) manufacturing, Raman spectroscopy has proven to be a very effective optical method to determine molecular structure and chemical composition. Raman spectroscopy as a tool for API analysis has been described for many applications, including polymorph identification, quantitative analysis, in-situ crystallization monitoring, real-time release testing, pharmaceutical unit operations, and process-induced transformations. In addition to identifying isolated polymorphic forms, mixtures of forms can be analyzed and quantified. In-line Raman spectroscopy can control critical process parameters, as it enables real-time process corrections, and ensures consistent production of the correct API form.[3] Near-infrared spectroscopy (NIR) is an efficient surrogate to high-pressure liquid chromatography (HPLC). Another effective measurement technology is energy dispersive x-ray diffraction (EDXRD)—particularly to measure the characteristics of powders—and has shown to have adequate sensitivity and resolution to detect critical material property changes during processing.

Standards

As PAT adoption grows it is likely that the International Council for Harmonisation (ICH) or regulatory compendia will institute practice standards to guide organizations in the qualification of PAT and PAC methods. The application of PAT is completely unique to the material characteristics and specific equipment and sensor technology being applied, and the framework and criteria for qualification should be universal. I would look to compendia organizations such as the United States Pharmacopeia (USP) and the British Pharmacopeia (BP) to lead the way in establishing practice standards that greatly demystify the qualification component of PAT implementations.

The ultimate goal of PAT is to minimize or eliminate the time lost with release testing of intermediate unit operations and the final product. The ability to shrink this time within the overall value stream of the process affects the overall cost of goods, trickling down to inventory carrying costs, plant capacity, and market response capability. One site that implemented a combination of in-line and at-line release was able to reduce its product release cycle time by greater than 80 percent, lessening the normal in-process and release testing cycle time from 30 days to five days[4].

The ultimate goal of PAT is to minimize or eliminate the time lost with release testing of intermediate unit operations and the final product.

One of the greatest impediments to PAT adoption has been the ability to gather, curate and analyze large amounts of data. Today the solutions for handling and analyzing big data are mature. With the right financial motivation, coming from downward pricing pressure, addressing drug shortages or government-sponsored reshoring initiatives, the advantages of targeted PAT implementation should drive much broader implementation in the near future.

Real Time Release (RTR)

The requirements for real time release (RTR) have been defined for most major markets. The European Commission issued Annex 17 Guidance addressing real time release and parametric release. The FDA has addressed this issue in a number of guidances that convey what process controls together with in-line monitoring of the manufacturing process can provide greater assurance of product quality than just a traditional testing of the final materials. As the industry gains comfort and familiarity with PAT, the adoption of an RTR strategy will become more commonplace.

Advanced Manufacturing - Continuous Manufacturing

FDA defines[5] advanced manufacturing as a collective term for new manufacturing approaches and technologies that can improve drug quality, address shortages of medicines, and speed time-to-market. By this rationale, advanced manufacturing is all about innovation and includes integrating novel technological approaches, or using established techniques in a new or innovative way, or applying production methods in a new domain where there are no defined best practices or experience.

At the center of the advanced manufacturing narrative is the potential for the industry to move **from batch to continuous manufacturing**. One might see continuous manufacturing as a way to provide a more consistent and cost-effective process framework for manufacturing small molecule drugs, including both the active pharmaceutical ingredient (API) and the final drug product (DP). Enthusiasm for continuous manufacturing has been rekindled by the government's interest in supply chain resiliency and in reshoring to address the nation's unbalanced dependency on China and India for API and finished DPs for essential medicines.

Batch vs. Continuous

It important to state that step-by-step batch processing to describe traditional small molecule drug product manufacturing is inaccurate description. Most oral solid dose manufacturing processes today utilize a mix of batch, semi-batch, semi-continuous, and continuous unit operations. For example, if you look closely at a traditional oral solid dose process, only the drying and blending steps are truly **batch processes**. Regardless of whether you are doing high-shear or fluid bed granulation you are always adding granulation fluid to the powder, so at best these are **semi-batch processes**. The same goes for coating tablets. In milling and tableting you are continuously processing material as a batch, so these can be considered **semi-continuous processes**. Therefore, a more accurate description of the principles underlying the current state is a hybrid approach.

The International Committee on Harmonization (ICH) accounted for this in the recently published ICH Q13 draft guideline[3] pertaining to **pharmaceutical continuous manufacturing** (PCM) and recognizing that PCM can be applied to some—or all—unit operations in a manufacturing process. PCM modes include both hybrid batch continuous applications of continuous manufacturing to continuous manufacturing across the entire API and drug product manufacturing process.

Most oral solid dose manufacturing processes today utilize a mix of batch, semi-batch, semi-continuous, and continuous unit operations.

Advocates for pharmaceutical continuous manufacturing cite the many potential benefits a continuous manufacturing process brings. These benefits include

lower facility capital costs, smaller process footprint requirements, the ability to more accurately identify and segregate potentially discrepant material, and the ultimate potential benefit of real time release (RTR) that removes or greatly reduces the time required for in-process and release testing of the final API or DP. Critics argue that the return on investment to change over to PCM is poor, given the added complexity of process development, testing capability, regulatory and the recall risk from larger batch sizes.

Material Selection and Characterization Considerations

To grasp the complexity of designing and setting up a continuous process you only have to look to the primary regulatory characteristic that distinguishes a continuous process from a batch process—the residence time distribution (RTD). The RTD characterizes the material as it moves through the process. It is a probability distribution that describes the amount of time a mass or fluid component remains in a process step.

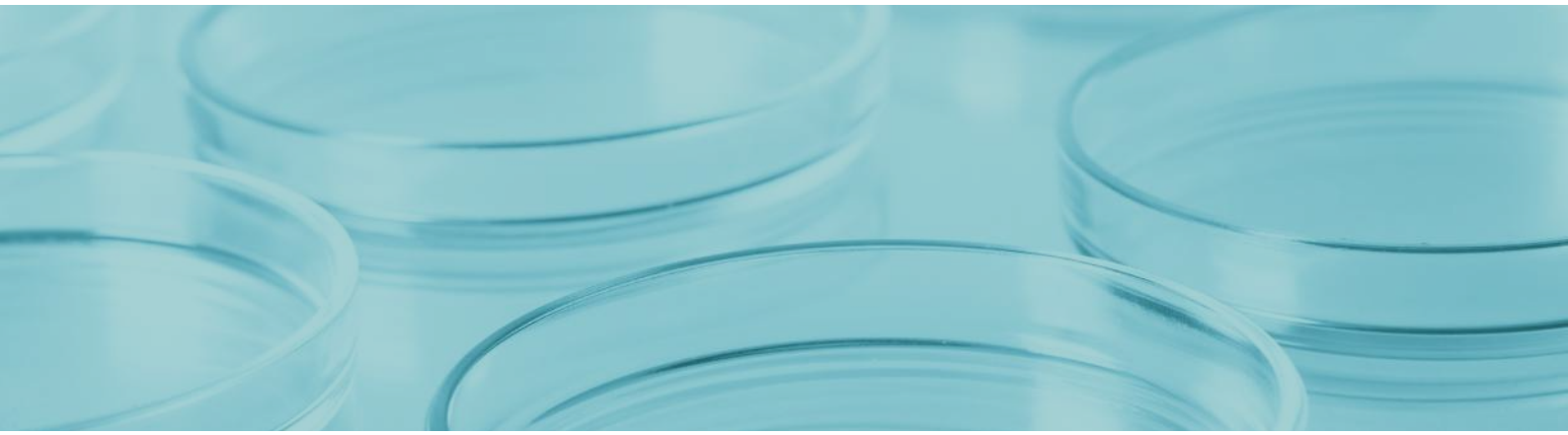
The **shape** of the RTD reflects the degree of axial dispersion or back mixing within that system, The RTD is dependent upon several factors such as input material attributes; mass flow rates, process parameters, equipment design and operation.

It is important to understand how the RTD varies over both the control and design space for each unit operation. This information serves as a basis for material traceability and for defining the RTD. While both batch and continuous processes are dependent upon the characteristics of the material, continuous manufacturing characterization is significantly more complex since the output of one unit operation has the potential to be the input material for the next process without the benefit of sampling and testing.

Characterization data can be used to develop in-silico models that describe the materials behavior within the unit operation. Often this is the first glimpse into how the material characteristics and process parameters interact.

The RTD characterizes the material as it moves through the process. It is a probability distribution that describes the amount of time a mass or fluid component remains in a process step.

We have stated that adoption of continuous manufacturing will be bolstered by strong government support as part of the reshoring effort to secure supply chain resiliency for medicines that are essential to national security and the wellbeing of the nation. Yet, the characterization and analysis techniques we describe have value for today's hybrid batch processes. The enhanced process efficiency and commensurately lower cost of goods will be a boon to drug sponsors and the national agenda as we set about establishing lower cost healthcare.



Automation

The capacity to realize reductions in cost of goods, increased product quality and flexible manufacturing response capability is a direct by-product of a firm's automation strategy. With downward pricing pressures an omnipresent reality, automation is likely to be at the heart of identifying cost centers that negatively impact the cost of goods or a firm's ability to meet market demand. Looking at the industry today, we note several trends that are likely to grow in importance in terms of automating manufacturing operations:

Robots and Cobots

Industrial robots have been deployed as islands of automation for decades. Operations that require manual human intervention, such as material loading and unloading, palletizing post-packaging or other repetitive tasks have long utilized robotic solutions. Robots are deployed successfully in the laboratory to provide 24-hour processing capability for highly repetitive and time-consuming testing, such as chromatographic and dissolution testing. Collaborative robots, or "cobots," are improving efficiency in pharmaceutical research, drug production, and quality control. Cobots can be programmed for a variety of tasks, relocated easily, and can start working quickly. They can be mounted above workspaces to save valuable floor space for humans and equipment in small labs. Cobots free human operators and analysts from fatiguing repetitive tasks and allow them to focus on higher complexity work.

Cloud Computing

Adopting cloud-hosted over server-based solutions has had a large impact on manufacturing operations. Because it is encrypted, cloud-hosted data is extremely secure and enables pharma companies to meet relevant compliance and regulatory requirements by providing enhanced visibility and control over their business processes. The cloud computing or software as a service (SaaS) model has many other advantages: lower capital investment, significantly smaller GxP IT infrastructure support requirements, and greater flexibility in addressing data management requirements. Moving to a cloud platform allows manufacturers to use new types of production systems, from 3D printing and high-performance computing (HPC) to the Internet of Things (IoT) and industrial robots. With well defined qualification and architecture frameworks to address data integrity and security considerations, cloud computing will continue to be a backbone of the manufacturing framework for many years to come.

21st Century Supply Chain Management

Adding automation to supply chain applications affects efficiency, capacity, and overall cost of goods for a drug sponsor. Typically, optimized supply chains are characterized as having less than 50 percent inventory holdings, and three times faster cash-to-cash cycle compared to under-optimized supply chains.[6]

Automated storage and retrieval systems (ASRS) can increase the accuracy of picking and staging material for processing to 99 percent. Studies have shown that having a human pick an order is more than 50 percent of the total picking time.

Blockchain technologies have the potential for faster delivery of safe medications while meeting government reporting requirements at the same time and are key to critical, effective traceability through better data sharing. Optimizing the total value chain will become a core component of any business strategy, by leveraging a combination of automation and cloud computing solutions.

Digital Integration

The factory of the future will control a number of digital solutions to provide information quickly and accurately wherever it is needed throughout the operation. The use of extended reality (XR) is already demonstrating its value in modern manufacturing operations. Extended reality subsumes virtual reality, augmented reality and mixed reality. Put simply, the focus is merging the physical with the virtual world. Virtual reality (VR) is a fully immersive simulated experience that replaces the real world with a virtual environment at a 1:1 scale. Augmented reality (AR) adds a digital layer of information onto real surroundings, providing new ways of interacting with reality. And finally, mixed reality (MR) is just as it sounds – a combination of these, where real world and digital objects interact.

Digital Twins
Pharma is using VR to make full-scale digital facility environments that allow people to walk through a facility before it exists in reality, to spot any flow errors, to test equipment, or examine critical and difficult design tasks.

Training and Operational Support
Our industry has long grappled with achieving more effective training of personnel. Virtual reality allows people to review procedures and execute them through simulation in a realistic virtual environment, without the need for physical equipment. VR training can also allow personnel to understand the consequences of incorrect behavior by simulating changes in airflow and contamination in a safe, virtual environment.

This is advantageous because many pharma companies have global operations. Duplicating staff in multiple sites can be costly when the quality and experience of staff varies based upon the facility location. Augmented reality allows remote staff to direct and participate in critical support activities by live streaming with subject matter experts (SMEs) in multiple locations— without having to travel—saving time and money while assuring valuable training to all site personnel.

Artificial Intelligence (AI)

Slowly but surely, AI is making its way into the pharmaceutical sector, opening new possibilities and breaking new competitive ground for ingenious pharmaceutical companies ready to leverage leading -edge technologies.

AI is a broad term that covers areas that include replicating human cognitive processes (i.e., symbolic logic) and machine learning (ML). Using machine learning allows for accurate predictions, classifications, and identification of patterns – in the same way as the human neural network, but much more efficiently and on a much bigger scale.

AI Model Training
One area that is frequently cited is that the amount of data required to train a machine-learning or deep-learning model is extremely high, and pharma doesn't typically generate the same levels of data as the telecom or semiconductor industries do. In reality the amount of data required depends both on the complexity of the problem to solve and on the complexity of the chosen algorithm. For solutions that are data constrained there are data augmentation techniques that can be used to refine and optimize a model.

Virtual reality allows people to review procedures and execute them through simulation in a realistic virtual environment, without the need for physical equipment.

Manufacturing Applications of AI
Equipment maintenance is one area in pharmaceutical manufacturing that is not data constrained. AI has been very successfully applied to equipment monitoring to build predictive models that predict equipment failure, in part because it is very easy to gather millions of data points when continuously measuring equipment vibrations. AI is used to develop equipment duty cycles and proactive preventative maintenance procedures that increase the overall equipment effectiveness (OEE) of manufacturing operations, avoid catastrophic equipment failures and reduce waste and discrepant material.

An area where machine learning has been very effective is in supply chain management and inventory management, to improve forecast accuracy, demand management, inventory management and manufacturing scheduling. Look for ML applications to be more broadly deployed across the supply chain as organizations look to drive business performance amid continued pricing pressure.

Cost of Poor Quality (COPQ)

The cost of poor quality, or COPQ, is an important theme that will likely play a much bigger role in pharma's evaluation of the effectiveness of operational improvements. COPQ covers both the direct and indirect costs associated with defects generated by a process. Such costs vary depending on how far the product or service goes along the process before being detected. If one can address a defect or process excursion *early* in a process, the cost is diminished. If one has to remediate a quality event at the customer level, it is much more expensive and, in our industry, the regulatory governance can dramatically raise the financial exposure if it results in a recall or enforcement action. Every time there is an excursion to the normal process that results in discrepant material, or in additional sampling, testing and evaluation, an organization's quality management system is engaged and that has a cascade effect upon the bottom line due to the associated additional inventory, investigation, and lost revenue costs.

COPQ consists of three basic cost categories: appraisal costs, internal failure costs, and external failure costs. **Appraisal costs** are the costs associated with sampling and testing material for conformance to a predefined specification. **Internal failure costs** pertain to defects identified within an operation before shipping to the customer. **External costs** are associated with defects found by the customer. PAT represents a forward-thinking solution to minimize appraisal costs by measuring product in-line or at-line within the process and not incurring addition labor and risk by sampling and testing after processing. Layered on top of these three is **cost of prevention**. These are the costs incurred in the management and execution of your Quality Management System (QMS). Organizations that track and manage to COPQ will realize significant acceleration in both cost reduction and overall business performance.

COPQ covers both the direct and indirect costs associated with defects generated by a process. Such costs vary depending on how far the product or service goes along the process before being detected.

Conclusion

Whether continuous manufacturing is to become a major development within the overall pharmaceutical manufacturing market in the future is difficult to predict. It is more certain that initiatives such as reshoring, and a sharpened focus on ensuring the integrity of the strategic national stockpile (SNS) will be a springboard for the development and refinement of advanced manufacturing technologies. For industry, the chief benefit from broader adoption of such approaches is to take advantage of lower cost of goods by reducing waste and the cost of poor quality (COPQ), and that in itself may increase the industry's comfort with principles such as real time release (RTR). Integrating machine learning into advanced manufacturing programs has the potential to drive the efficiency of individual unit operations and boost overall business operations. This will result in more stable supply chains and potentially lower costs all around. In a market likely to continue to encounter consistent downward pricing pressures, the adoption of these elements will allow manufacturers to lower their costs and still manage a profit as they provide improved, higher quality drug therapies to patients— this is a win-win in anyone's book.

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Part 2.4

The world in 2030 and its impact on Pharma

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The world in 2030 and its impact on Pharma

Introduction

Capturing sector-changing opportunities in the prudently cautious pharmaceutical industry is a game of providence and preparedness. Significant milestones can be best measured over the span of decades, taking a panoramic view on innovations within the industry. In 1996, the FDA approved Lipitor, a small molecule cardiovascular drug that dominated the best-selling sales rankings during the 2000's. Six years later in 2002, the FDA went on to approve Humira, a drug that became pharma's most valuable brand, eclipsing even Lipitor in annual sales. Humira's growth, fuelled by rising indications and popularity in the US, marked the new reign of biologics throughout the 2010's.

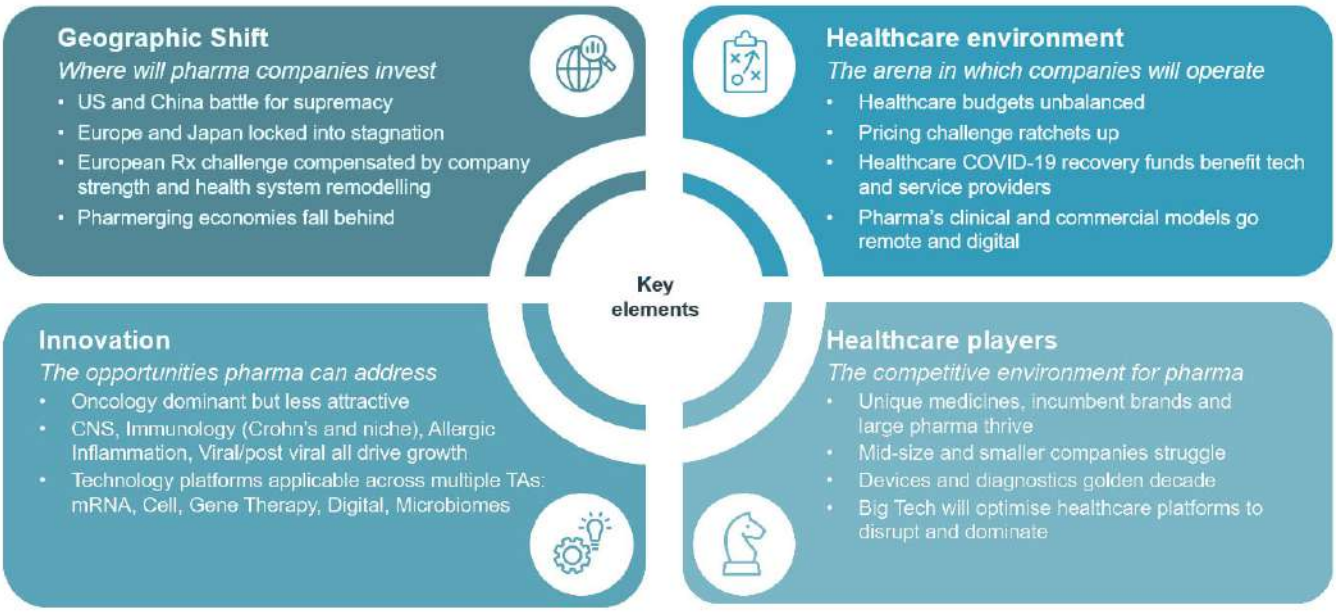
This same decade also matured the notion that provision of health from protected innovative medicines had shifted from large patient populations to more defined, most often specialty patient cohorts as generics took hold of major disease areas. It became increasingly important for patients to be identified and categorised precisely, driven by the need to deliver the right medicines to the right people. This led to the development of advanced classification techniques such as pharmacogenomic biomarkers and whole genome sequencing, sparking nations to invest heavily into building these capabilities.

As the infrastructure of patient classification developed, so did the drugs that successfully made it through the approval pathway. The 2010's ushered in the first advanced therapies medicinal products, most notably cell and gene therapies.

As we set our gaze on the coming decade to 2030, there are four overarching elements to consider that will be top of mind for pharma companies that want to navigate the next decade successfully (Figure 1):

- **Geographic shift:** where they will invest
- **The healthcare environment:** the arena in which they will operate
- **Innovation:** the opportunities they can address
- **Healthcare players:** their competitive environment

Figure 1. Key Elements for Pharma to Consider Through 2030



Source: IQVIA European Thought Leadership Analysis

Geographic shift: Where pharma companies will invest

Key points:

- US and China battle for supremacy
- Europe and Japan locked into stagnation
- European Rx challenge compensated by company strength and health system remodelling
- Pharmerging economies fall behind

Combined, the US and China will continue to exert influence through the coming decade as a consequence of their sheer market size. The US share of global market is forecast to continue shrinking slowly, having done so continuously for over the past decade (IQVIA Market Prognosis Q1 2021). The FDA will continue to be the pace-setter and most influential regulator because of innovation in bold important issues and the importance of its domestic market. It will lead the path with regards to decentralised and adaptive trials, use of real world evidence and other novel sources of data (for example digital biomarkers) in order to bring earlier conditional approvals that blur the boundaries between clinical and the real-world. On the other hand, China's NMPA is adapting rapidly to becoming a globally competitive regulator, which is key to a huge market for both domestic and international innovation. This will help provide new fuel to China's continued growth.

Combined, both the US and China will comfortably hold over half of pharma sales, having reached that milestone in 2014 (IQVIA Market Prognosis Q3 2017). The size and economic interests of these countries will generate intense international rivalry in innovation and regulation to attract outside investment and provide the best medicines for their citizens. The domestic scale of these markets and nationalist policies could split the pharmaceutical market and make it less global if multinational companies decide to refocus their intensity solely on one country or the other.

The US share of global market is forecast to continue shrinking slowly, having done so continuously for over the past decade

The EU and Japan will continue to stagnate as stringent payer requirements for greater evidence increase through instruments such as value-based commissioning and greater emphasis on robust HEOR data. We already see the first inklings of these effects as recently a prominent

biotech firm announced they are winding down their operations in the European market. The UK's exit from the EU has given the MHRA the opportunity to differentiate itself from EMA and it will do so by being an early adopter of regulatory innovation; this will not compensate for the UK's total share being ~3% of total market however.

All other countries will each contribute a small amount (under 4%) of total market share and so will likely be a lower priority for pharma due to their size. It not all bad, within these rest-of-world countries, there will be numerous bright spots of growth, albeit lacking scale at an international level.

Healthcare environment: The arena in which pharma companies will operate

Key points:

- Healthcare budgets unbalanced
- Pricing challenge ratchets up
- Healthcare COVID-19 recovery funds benefit tech and service providers
- Pharma's clinical and commercial models go remote and digital

The path to 2030 will bring about an increasingly challenging environment. Major new uncertainties affect payer budget planning through to 2025, these include (figures from the IQVIA Institute Global Medicine Spending and Usage Trends, Outlook to 2025):

- $187bn on new brand spend to 2025
- $157bn 2021-25 COVID-19 vaccine incremental spending
- $166bn of Loss of Exclusivity (LOE) cost relief potential
- $68bn of COVID disruption impact relating to lost spend
- An unknown quantity relating to the cost of incremental treatments for long COVID and pandemic impacts on non-COVID patients

The huge costs facing healthcare will force payers to prioritise high unmet need areas and products with strong outcome evidence. Novel treatments with significant upfront costs and an evolving outcomes story, such as advance therapies, may struggle. The healthcare system will look for savings in areas where they know they can access them, such as driving an efficient off-patent sector.

The amount of value that is exposed to LOE events over the next decade is just over $500bn at list price and 90% of these stemming from the US and EU (see Figure 2). Importantly, 65% of this potential is derived from specialty medicines, such as oncology, immunology. This means that generics companies will be required to operate within the specialty domain, targeting smaller patient populations with medicines that require complex engagement with stakeholders. Currently, specialty medicines are growing but still represent under 10% of all Generics value; this will have to change.

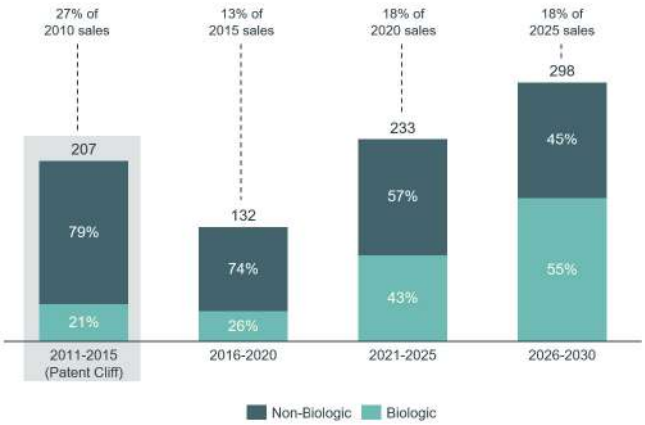
The striking difference over the next decade compared to the last however, is that Biologics now make up a much larger proportion of the LOE potential, from 20% in 2015 to 55% by 2030. Countries wishing to maximise savings from their drugs budget will need to expand the use of biosimilars throughout their healthcare systems by introducing policies and purchasing frameworks that incentivise the adoption and uptake of biosimilars to their maximum potential.

The potential savings that could be generated over the next 5 years following the pandemic is approximately 18% of total drug spend for 2020. If we contrast this to the 5 years following another global catastrophic event, the Great Recession, where savings represented 27% of 2010 sales, we will clearly have to do more with less. This opens up the room to opportunities that could potentially drive efficiencies, most promisingly through digital technologies and services.

The digital maturity of health systems will be a strong enabler of digital health services. Most developed countries have robust digital policies in place but they universally suffer from integrating fragmented legacy systems across different hospitals and integrating standards across different regions. The largest challenge over the next five years for most health systems will be to introduce greater interoperability and build a strong electronic health record network from which to utilise to make real evidence-backed decisions. The tech sector has an important part to play in this puzzle, where they are able to collect data on people before they become patients on their mass-market

smart devices. To further the value from their data, tech companies must find ways of working with the healthcare sector that leverages their strong consumer focus and unique platforms in a way that works within the existing regulations and ethical frameworks of healthcare.

Figure 2. Global Loss of Exclusivity Potential (bn USD)



Note: LOE Potential calculated using peak forcast sales, assumed to be year LOE-1
Source: IQVIA European Thought Leadership; IQVIA ForcastLink 2022-2030; IQVIA MIDAS MAT Q1 2020; IQVIA Market Prognosis; CER

Of course, the healthcare environment will also be affected by a greater challenge, that of environmental sustainability. Historically, the pharmaceutical industry has been no stranger to environmental regulation, often controlling emissions of air and water pollutants in order to minimise damage to local ecosystems from toxic and pharmaceutically active chemicals. More needs to be done however on being a proactive industry in reducing its impact on the environment. There is a strong argument that health systems as a whole should be frontrunners in limiting the impact of climate change, as it strikes at the heart of healthcare, for example a changing climate will affect the ecology of disease vectors, increase allergens, catastrophic natural events and geopolitical conflicts (see Figure 3).

With the absence of standardised regulation across nations that make up pharma's supply chain, companies must take the initiative and form a collective response. So far, large pharma have adopted Environmental, Social and Corporate Governance (ESG) practices, but this has seen little spill-over into smaller and private pharma companies and supply partners. One can imagine that generic companies who supply the bulk of medicines globally must be held accountable for the sheer scale of their operations, yet these are some of the most opaque. This will change however, as mounting pressure over the coming decade from investors will force all players to rethink their organisation's green credentials. The top 5 areas that we have identified as key challenges that pharmaceutical companies need to address in the coming decade are:

1. **Environmental, Social, and Corporate Governance.** A greater shareholder expectation of accountability. There needs to be increased awareness and incentives to engage smaller companies and generics manufacturers
2. **Water Use and Quality.** A Reduction in use of fresh water and greater scrutiny on toxic and active effluents
3. **Circular Economy.** Reduce waste and design products that are greener and more benign
4. **Reforming the Supply Chain.** Introduce greater transparency to track emissions and improve procurement
5. **Increased Environmental Regulation.** Enforcement of regulations will likely increase, and pharma must be ready to proactively engage regulators

Figure 3. Environmental Factors Threatening to Affect Health

Corporate Social Responsibility	Circular Economy	Reforming the Supply Chain	Increased Environmental Regulation	Hotter Climates
Severe Weather	Polluted Air	More Allergens	Ecology of Disease Vectors	Conflict
Access to Water and Food	Shifting Operating Models	Antimicrobial Resistance	Effluents in Water	Cultural Shifts towards Health

Innovation: The opportunities pharma companies can address

Key points:

- Oncology dominant but less attractive
- CNS, Immunology (Crohn's and niche), Allergic Inflammation, Viral/post viral all drive growth
- Technology platforms applicable across multiple TAs: mRNA, Cell, Gene Therapy, Digital, Microbiomes

By 2030, Oncology will continue to be the most valuable therapy area. However, it will have matured and become more competitive pushing large innovative pharma to look elsewhere for opportunities. The increasing segmentation of oncology is already affecting the TA. For example, between 2015-20, over 80 New Active Substances (NASs, the first time an innovative molecule is recorded in the global pharma market) were launched and the pipeline is bursting with candidates – over 12,000 molecules in the late-stage pipeline from over 500 companies.

This increasing fragmentation is challenging the return on investment on the normally lucrative oncology TA. A decade ago, the median oncology NAS launch would garner around $130mn in its first year sales (IQVIA MIDAS QTR, NAS analysis); this has steadily declined to around $50mn for launches in the past five years. If this trend continues through to 2030, pharma companies will have to rethink their costly trial development and go-to-market strategies or altogether look elsewhere for blockbuster launches.

Competition has been fierce in this space, with many companies chasing the same biomarker-driven targets with me-too products, hoping for some advantageous data that will allow them to be heard amongst the crowd. Biosimilars have also joined this space, threatening to erode the incumbent giants and by 2030; additionally, development of pembrolizumab and nivolumab biosimilars will see intense competition for these checkpoint inhibitors.

By 2030 we expect the leading TAs accompanying oncology to be in crossover areas like inflammation and cancer vaccines. Growth potential will be sourced from rare diseases and niche immunology areas. Some therapies will experience a revival, like cardiovascular, liver disease, and CNS – with or without Alzheimer's – already showing huge potential to be treated using digital therapeutics.

The modalities in which we can tackle these disease areas will increase with the development of platform technologies, more specifically in RNA, Cell & Gene, Digital and Microbiome. Most promising of these are rapid treatments from mRNA, whose profile has skyrocketed as a rapid and viable way to develop COVID-19 vaccines. This time round, we could imagine a patient's cancer to be characterised through a liquid biopsy to identify distinct biomarkers that can be targeted by administering a custom mRNA vaccine. Therapeutic mRNA vaccines offer the promise of rapid, custom treatments with very low adverse events.

This increasing fragmentation is challenging the return on investment on the normally lucrative oncology TA.

Cell therapies are still in their infancy, and we have begun to see them more effective in blood cancers rather than solid tumours. Administering these cell therapies are a logistical challenge, but advancements in allogeneic therapies promise to reduce this burden. Gene therapies have also met some roadblocks, such as low viability in polygenic diseases, high costs, immune responses to viral vectors, and a theoretical but closely studied risk of cancer through genes being inserted into the wrong DNA site (insertional mutagenesis). Gene silencing, from CRISPR-Cas9 or siRNA, have shown promise in controlling gene expression, but problems delivering to the right target, degradation and off-site activity have broadly kept them from mainstream success. These novel therapies come at a high cost, and in 10 years of being on the market, cell and gene therapies have only brought in $2.2bn in revenue. Mass market adoption is required for sales acceleration and as we begin to understand their long-term effects on health, we will also build better frameworks to pay for them.

Digital Therapeutics and companion apps are being developed at a rapid pace, outstripping the ability for regulators and payers to evaluate them. As such, they often rely on licensing from individuals – but this is changing rapidly, with most developed countries ramping up their

health system's digital capabilities. By 2030, a health system will have a secure and rich network of personal health data from which stakeholders will be able to make informed and personalised decisions. They will also be able to recognise the value of digital therapeutics as in the care pathway, especially in CNS areas of depression, anxiety, ADHD, ASD, PTSD, addiction amongst others. Digital innovations will diagnose, track, augment, support and in some cases be standalone therapeutics. This is blurring the boundary between devices, diagnostics and therapeutics and potentially spark a revolution in generation of data.

Microbiome therapeutics have already shown efficacy in treating potentially fatal clostridium difficile infections, colitis, constipation and IBS. Their future depends on successfully mapping the different strains of the billions of bacteria in the gut and making sense of this data to find causal links between microbiome and disease. This could offer life-changing treatments in autoimmune disorders, obesity, neurology, infections, and other chronic health conditions.

Healthcare players: The competitive environment for pharma companies

Key points:

- Unique medicines, incumbent brands and large pharma thrive
- Mid-size and smaller companies struggle
- Devices and diagnostics golden decade
- Big Tech will optimise healthcare platforms to disrupt and dominate

Despite blockbuster launches and large LOE events over the past decade, large pharma has remained stable through M&A activity and large product lifecycle management. We are entering a disruptive period however, fuelled by a combination of pressures on generics prices, extensive biosimilar uptake, and an influx of cash for COVID-19 vaccine developers. There are four challenges to shape large pharma beyond 2025, these are:

- **Stagnant Prices**. Over 50% growth of drug prices 2010 v 2015 (list price, IQVIA MIDAS) will not be sustainable in the coming decade. Pushback from a payer and political perspective means that increasing prices is not sustainable. This will accelerate the shift from a product to a service mindset that is increasingly patient-centric.
- **Flat SG&A**. There has been an increase in SG&A budget 2020 vs 2010, but the next decade will likely see flat growth. Companies will need to do more with the same, rethinking their promotional model, both in content and channel mix.
- **Increasing R&D costs**. R&D spend continues to rise while productivity continues to fall. Large pharma experienced R&D spend equalling 20% of sales in 2020 for the first time ($123bn). Companies will focus on impact and speed of execution as drivers of differentiation.
- **Increasing number of launches.** Most companies will have more launches, albeit individually smaller in size. Speed and consistency of launch will be key, along with patient identification and market development.
- **Increasing LOE size.** There will be major LOE events to 2030, but they are not evenly distributed – with nearly 70% of LOE exposure from 10 companies alone. Making the right bets in the first half of the decade on innovation and M&A will be vital to success in the second half.

We are entering a disruptive period however, fuelled by a combination of pressures on generics prices, extensive biosimilar uptake, and an influx of cash for COVID-19 vaccine developers.

Despite these roadblocks, large pharma has four inherent advantages over midsize pharma (MSP) and emerging biopharma (EBP). These can be broadly summarised by four focal areas:

- **Communicating value.** Large pharma has the resource and experience to make the change in how they communicate value to stakeholders. However, EBP do not have legacy systems to dismantle and may thrive in a world prioritising medical affairs over promotion.
- **Sustaining evidence.** Large pharma understands RWE and has the scale and resources to make it happen. MSP and EBP need to begin their RWE journey in earnest or risk being left out in developing integrated evidence strategies. Mitigating this risk are the development of RWE support from service providers.
- **Commercial operations.** Large pharma own vast commercial networks and can convert promising clinical candidates into commercial success. With an increasing source of innovation from EBP, it may increase the demand for commercialisation partners.
- **Presence in the US and China.** China is attempting to introduce a greater level of innovation and ease of doing business. MSP and EBP will need to navigate the barriers to entry if they do not have existing presence.

Ultimately, MSPs are at an uncomfortable crossroads where they need to move from a focus on traditional therapy areas and commercial models to specialised, modern ones. The stability of strength in their domestic market could become a hindrance in a data driven future where scale is important. Lastly, MSPs are typically privately owned and may lack the outside pressure to take big risks and make outsize investments in future growth areas.

A decade of change

The coming decade will be marked by a shift towards personalisation using greater insights at scale, aided by data and technology. Companies will need to rebalance their books, diverting costs from traditional engagements in favour of a leaner, smarter ways of operating. Those who do not bridge the information gap will be left behind with old, mature brands and waning profitability. We have seen it in other industries, where data owners or service providers gather critical mass and become natural monopolies through first-mover advantages, network effects and economies of scale with handling large quantities of data and information.

The top pharma companies in 2030 will be those that can navigate this sea change by ruthlessly creating a path by prioritising investments in promising countries and disease areas. The challenges are diverse for pharma companies of all sizes as payers demand more value and new platform technologies emerge, but all have shining beacons of opportunity on the horizon and need to act decisively to succeed or risk the rocky waters of doing too-little-too-late.

Companies will need to rebalance their books, diverting costs from traditional engagements in favour of a leaner, smarter ways of operating.

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Part 2.5

Supply and Demand Trends: Mammalian Biomanufacturing Industry Overview

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Supply and Demand Trends: Mammalian Biomanufacturing Industry Overview

Trends Overview 2020-2025

- Demand for biologics manufacturing by volume is projected to reach nearly 3,900kL, a 5-year growth rate of nearly 8% per year (just over 2,700kL in 2020).
  - If additional Alzheimer's drugs and PDL/PDL-1 checkpoint inhibitors are approved and accepted by insurers, demand could be much higher resulting in capacity constraints from our typical forecast. If approved, COVID 19 therapies and monoclonal antibody-based infection preventatives could cause additional pressure on large-scale manufacturing networks.
- Global biologics manufacturing capacity will increase to nearly 7,500kL by 2025 from nearly 5,200kL in 2020
  - CMO/hybrid companies increase their control of capacity from 32% in 2020 to 44% in 2025 with capacity growth rates in Europe and Asia nearing double digits.
- Over half of the recombinant products in late phase development (Phase 2, Phase 3) can be met by a single 2,000 or 5,000L bioreactor.
- In the short term, we predict manufacturing capacity will not be constrained but may tighten after 2025. While the majority of capacity currently remains in-house, companies performing contract manufacturing are expanding their capacities which, in the coming years may lessen the difficulties companies without capacity may have experienced accessing capacity at the right time and under the right terms.

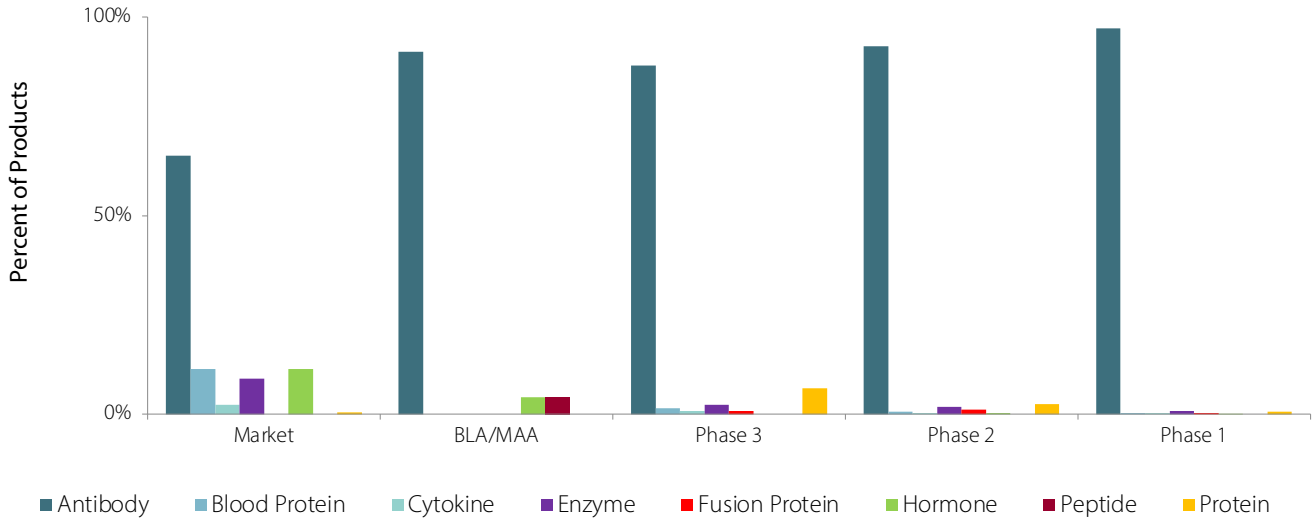
Abstract:
Biologic-based drugs are an increasingly important part of the portfolio growth strategies for pharmaceutical and biopharmaceutical companies. As the number of commercial products and pipeline candidates grow, including COVID 19 therapies and infection preventatives, key issues facing the industry include the current and future state of biomanufacturing capacity, the availability of that capacity, and technologies impacting upstream and downstream bioprocessing. BPTG provides a high-level overview of the current state of the supply of and demand for mammalian-based biopharmaceuticals, forecasting where the industry is heading and how manufacturers are keeping pace.

Article:

Since the approval of the first recombinant therapeutic antibody, OKT3, in 1986, mammalian-based biopharmaceutical product sales have continually increased and represent a driving sector in the overall growth of pharmaceutical company revenue. In 2020, the sales of the top five selling recombinant proteins (Humira, Keytruda, Eylea, Stelara, Opdivo), all antibody-based products, totaled nearly $57B. The compound annual growth rate for antibody product revenue, which include naked monoclonal antibodies, Fc-fusion proteins, antibody fragments, bispecific antibodies, antibody conjugates, and other antibody related products, was 16.9% from 2005 to 2015. Although this growth has remained in the mid-teens in the recent years due to the maturation of many products and emerging alternative therapeutic modalities, it far exceeds the 2.6% growth rate of traditional pharmaceutical (*i.e.*, small molecule) sales.

To provide context around this growing segment of the pharmaceutical market, BPTG's proprietary bioTRAK® database of biopharmaceutical products and manufacturing capacity estimates that there are over 1,500 biopharmaceutical products in some stage of clinical development in the United States or Europe. The majority, approximately 85%, produced in mammalian cell culture systems. We evaluated the distribution of mammalian products by product type and phase of development to further refine the biopharmaceutical manufacturing market. **Figure *1*** shows the distribution of product types, including antibody products, blood proteins, cytokines, enzymes, fusion proteins, hormones, and other recombinant proteins, by phase of development. Antibody products are the dominant commercially marketed product type at approximately 65% and are the largest product type for all phases of development, with the early-stage pipeline consisting of nearly all antibody products. It is important to note that many of the early commercial biopharmaceutical products, such as growth hormones, insulins, and interferons, are produced in microbial systems, and not included here.

Figure 1: Distribution of Mammalian Products by Product Type and Phase of Development



Whether commercially approved or in development, each of these products needs access to mammalian production capacity. For current commercially approved biopharmaceutical products, the future demand is estimated from each product's reported annual sales data, along with estimates of each product's future growth rates. Our future product growth estimations take into consideration a product's age, as sales growth typically slows as a product matures, while newly approved products often do not reach full market penetration for several years.

The projected treatment population size is estimated based on price per mg and sales. Combining the population with

the yearly per patient dosing, we forecast the kilogram quantities required to meet demand of each product for the next 5 years. These kilogram quantity forecasts can be converted to liter quantities for each product using cell line expression level and overall purification yield estimates. These estimates are based on industry benchmarks at the time the product was being developed and the maturity of the company developing the process. For example, the commercial process for a product launched more than ten years ago will likely have a lower expression level assigned in our forecast algorithm than a product currently in clinical development. For products in development, future commercial demand is estimated based on the market penetration of currently approved products or proxy products with similar indications. Additionally, for products in development, we employ a phase-based commercialization probability assumption when calculating future demand.

Figure *2* shows the projected kilogram quantities of product needed to meet annual commercial and clinical demand for all product types produced using mammalian production systems. In 2020, just over 32 metric tons of product were required. As more products enter the pipeline and products in development receive commercial approval each year, the overall kilogram requirements needed to meet product demand increase from nearly 32 metric tons in 2020 to nearly 64 metric tons in 2025. Demand for COVID-19 related products have a unique demand algorithm and are not included within the typical forecast which is shown below.

Figure 2: Estimated Quantity of Bulk Kilograms Needed to Meet Product Demand

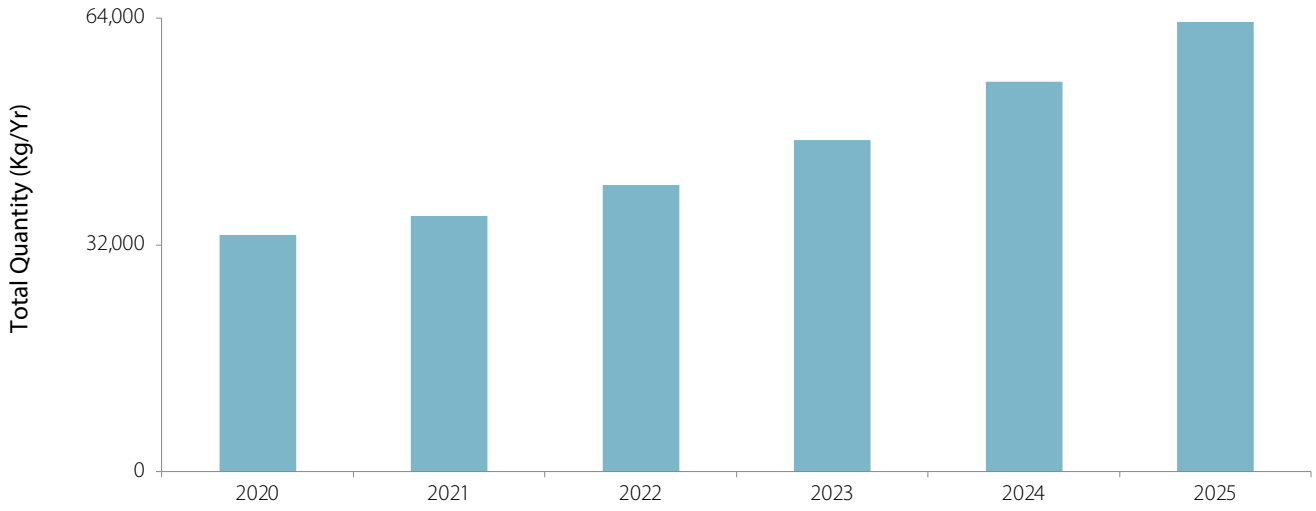
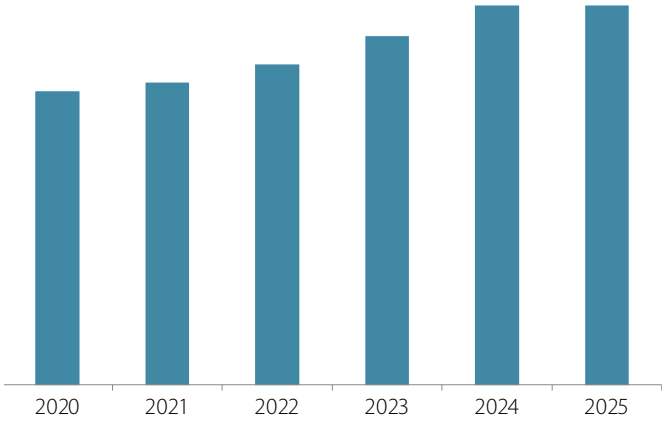


Figure 3: Estimated Volumetric Capacity Needed to Meet Product Demand

Figure *3* shows the projected volumetric capacity needed to meet annual commercial and clinical demand for all product types produced using mammalian production systems. In 2020, the annual volumetric requirements were nearly 2,700kL, while in 2025, the volumetric requirement is projected to be nearly 3,900kL, a 5-year growth rate of nearly 8%. Volumetric demand for COVID-19 related products is not included within the typical forecast which is shown right.



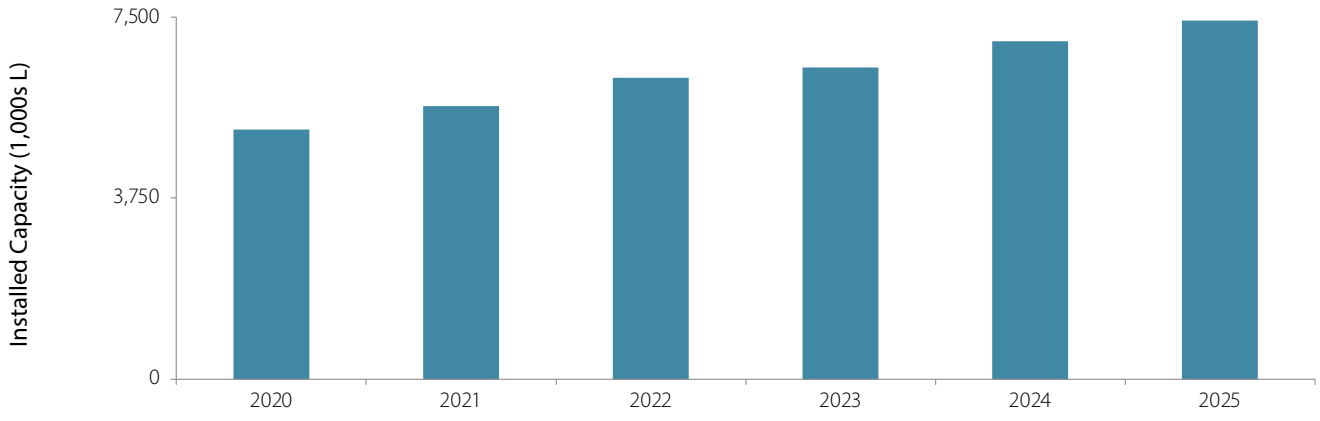
As with any forecasting model, our assumptions for a typical year are based on the most probable scenarios and include estimations for biopharmaceuticals which are being developed for certain large patient population indications such as Alzheimer's disease or broad cancer treatments like PDL/PDL-1 checkpoint inhibitors. Should several of these large-demand products obtain regulatory approval and adequate reimbursement by healthcare oversight organizations *(i.e.*, US Pharmacy Benefit Managers, the UK's National Institute for Healthcare and Excellence (NICE)) or become part of a managed entry agreement between a company and public payer of a social or national health insurance system, a significant increase in demand for manufacturing capacity could occur potentially leading to a capacity shortage.

In addition to the products being developed for typical indications, we again face the challenge of incorporating and determining the demand for recombinant products being developed to combat the COVID 19 pandemic. We are tracking both novel and repurposed products being developed to treat active cases of severe COVID 19 related symptoms, including several novel antibody-based products some of which have been granted Emergency Use Authorization (FDA) or Conditional Marketing Authorization (EMA) for post-exposure disease prevention.

Conversely, there are other manufacturing trends which could result in a decrease in demand for some biopharmaceutical manufacturing capacity. Among these are the industry's increased focus on orphan indications, a shift from full length naked antibodies to alternative antibody formats and more potent products *(e.g.*, antibody drug conjugates (ADCs) or bispecific antibodies) which would require lower doses and therefore less manufacturing capacity. Given the projected increase in volumetric demand over the next 5 years, the industry is cognizant of the inherent volatility of production capacity forecasts. There is always a degree of uncertainty in balancing the demand and supply equation due to production problems, market demand fluctuations over time, regulatory and reimbursement issues, and competitive factors.

To understand how the industry is positioned to meet these product demands, we estimated the 2020 mammalian cell culture supply to be nearly 5,200kL and predict it to grow to nearly 7,500kL by 2025, with a 5-year growth rate of approximately 7% per year (**Figure *4***). However, not all capacity is equally available throughout the industry. In 2021, Product companies, i.e., companies focused solely on product development, control nearly 70% of the installed mammalian cell culture capacity, while Hybrid companies, i.e., companies that are developing products, but also sell or make available any excess manufacturing capacity, and CMOs control significantly less capacity. The distribution of capacity changes slightly in 2025, with Product companies controlling nearly 56% of the installed capacity, while CMO capacity increases nearly 13%, with Hybrid companies remaining stable.

Figure 4: Mammalian Manufacturing Capacity



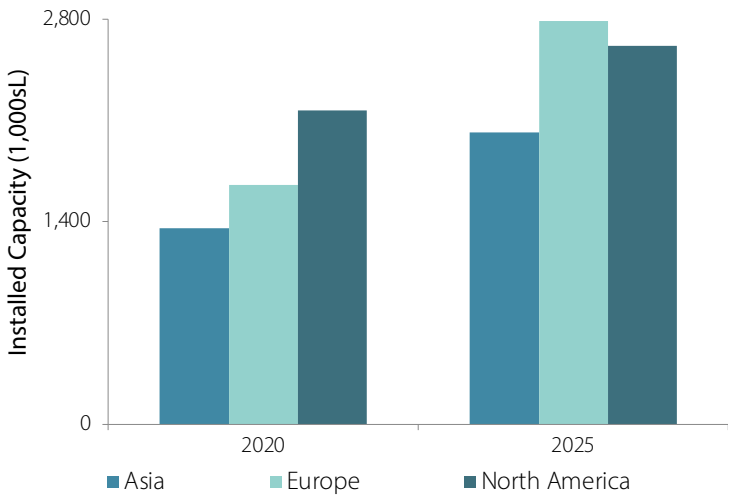
While Product companies control the majority of cell culture capacity, the distribution of this capacity is highly concentrated within ten companies, as shown in **Table *1***. Capacity for companies not ranked in the top ten is distributed among nearly 125 companies in 2021, and approximately 130 companies in 2025. Currently, nearly 60% of the capacity is controlled by ten companies remaining relatively unchanged in 2025. However, based on substantial capacity investments, WuXi Biologics, FujiFilm Diosynth Biotechnologies and Celltrion will displace Novartis, Sanofi, and Bristol Myers Squibb from the top ten.

Table 1: Control of Manufacturing Capacity

2021 Rank	2025 Rank	Company	Company Type
1	1	F. Hoffmann-La Roche	Product
2	2	Samsung Biologics	CMO
3	3	Lonza Group	CMO
4	6	Boehringer Ingelheim	Hybrid
5	10	Biogen	Product
6	-	Novartis	Hybrid
7	-	Sanofi	Product
8	7	Johnson & Johnson	Product
9	-	Bristol Myers Squibb	Product
10	9	Amgen	Product
-	4	WuXi Biologics	CMO
-	5	FujiFilm Diosynth Biotechnologies	CMO
-	8	Celltrion	Product

Figure *5* shows the geographic distribution of the manufacturing facilities. In 2020, just over 40% of all mammalian capacity is located in North America, followed by Europe and Asia. From 2015-2020, there has been minimal capacity growth in North America, modest growth in Europe, with significantly greater growth in Asia. By 2025, with growth rates projected in Asia and Europe of approximately 9% and North America at 4%, Europe will surpass North America in total liters of capacity.

Figure 5: Geographic Distribution of Capacity



As described earlier, different products require different capacity. For example, the 2020-kilogram demand for the top five selling antibody products totaled approximately 2.5 metric tons. The demand for the nearly 115 remaining marketed antibody products combined was nearly 25 metric tons (an average of ~215 kg each, the median 56 kg). For antibody products still in development, in a best-case commercial scenario where market success and maximum market penetration are assumed, projected demand for nearly 60% of these products in development is expected to be less than 100 kg per product per year. Just 10% of the products, such as those for Alzheimer's Disease, Parkinson's Disease, Diabetes, and possibly some coronary heart disease or atherosclerosis products, are projected to require over 750 kg per year.

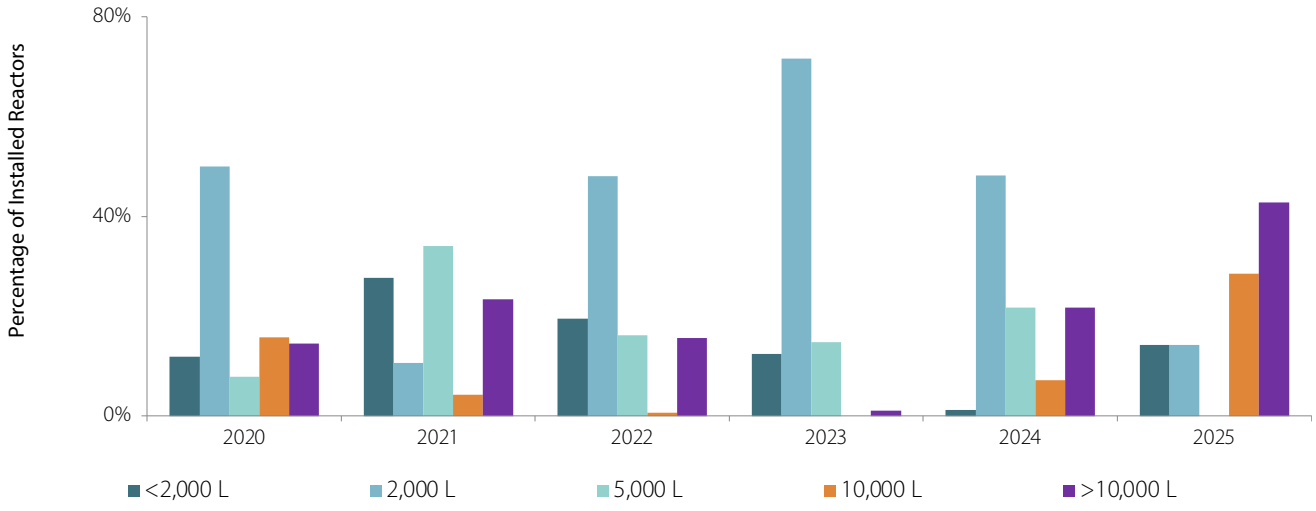
A closer review of future projected commercial manufacturing demands for products in Phase 2 and Phase 3 clinical development reveals 65% of the products in development can likely be met with a single 2,000 or 5,000L bioreactor assuming 18 batches per year per bioreactor with a 90% success rate for batch manufacturing (**Table *2***). However, this does not mean that large scale capacity is no longer needed. Our model predicts that the remaining products will need bioreactor capacity of 10,000L and greater to meet the forecasted demand. Increasing the number of bioreactors increases the manufacturing capacity and not surprisingly causes a shift in the percentage of products whose development can likely be met. As an example, a single 2,000L bioreactor is capable of manufacturing 48% of the products in Phase 2 and Phase 3 while a trio of bioreactors at this scale would be capable of manufacturing 70% of the products in development.

Table 2: Percentage of Product Demand Met by Bioreactor Scale

No. Bioreactors	2,000L Bioreactor	5,000L Bioreactor	10,000L Bioreactor	>10,000L Bioreactor
1	48%	17%	13%	22%
2	61%	17%	9%	13%
3	70%	14%	8%	8%

If we analyze the number and scale of bioreactors coming on line between 2020 and 2025 at the <2,000, 2,000, 5,000, 10,000 and >10,000L scale (**Figure *6***), it is evident that on average 40% of the bioreactors projected to come on line are 2,000L. Nearly 20% of the bioreactors are at a scale of 10,000 or greater. While manufacturers understand the capacity demand scenarios and are installing capacity to meet these anticipated demands, it is likely that the continued demand for certain COVID 19 treatments will continue to add pressure to manufacturing networks with large scale capacity.

Figure 6: Percentage and Scale of Future Bioreactors



While the majority of capacity is product based, rather than CMO based, contract manufacturers are expanding their capacities which, in the coming years may lessen the difficulties companies without capacity may have experienced accessing capacity at the right time and under the right terms.

Overall, the biopharmaceutical industry will continue to have strong growth for the foreseeable future, and antibody products continue to be the dominant driver of this growth. Installed capacity is currently able to meet the typical manufacturing demand for these products, but control and location of capacity can affect accessibility. While the majority of capacity is product based, rather than CMO based, contract manufacturers are expanding their capacities which, in the coming years may lessen the difficulties companies without capacity may have experienced accessing capacity at the right time and under the right terms.

While capacity will increase over the next five years, demand for capacity, pandemic aside, will increase at nearly equivalent rate allowing for some short-term loosening of capacity constraints, but after 2025, capacity tightening may occur. In recent years, we have noted that the industry was experiencing some capacity constraints at the clinical scales due to very high clinical demand and the industry has responded in kind with a wave of facility expansions.

The type and scale of capacity being installed will also be important as the demand for half of products in mid-to-late-stage development can be met with 5,000L of capacity or less, while the remaining half of products will need larger capacity to meet future demand. However, with the current pandemic, COVID 19 therapeutics and preventatives will likely require large-scale capacity if fully approved. With new bioreactor installations reflecting a pre-pandemic demand profile, we are watching how the industry is responding and rising to the challenge to meet the typical and additional demands for capacity as it is critically important to ensure current and future products are available to patients.

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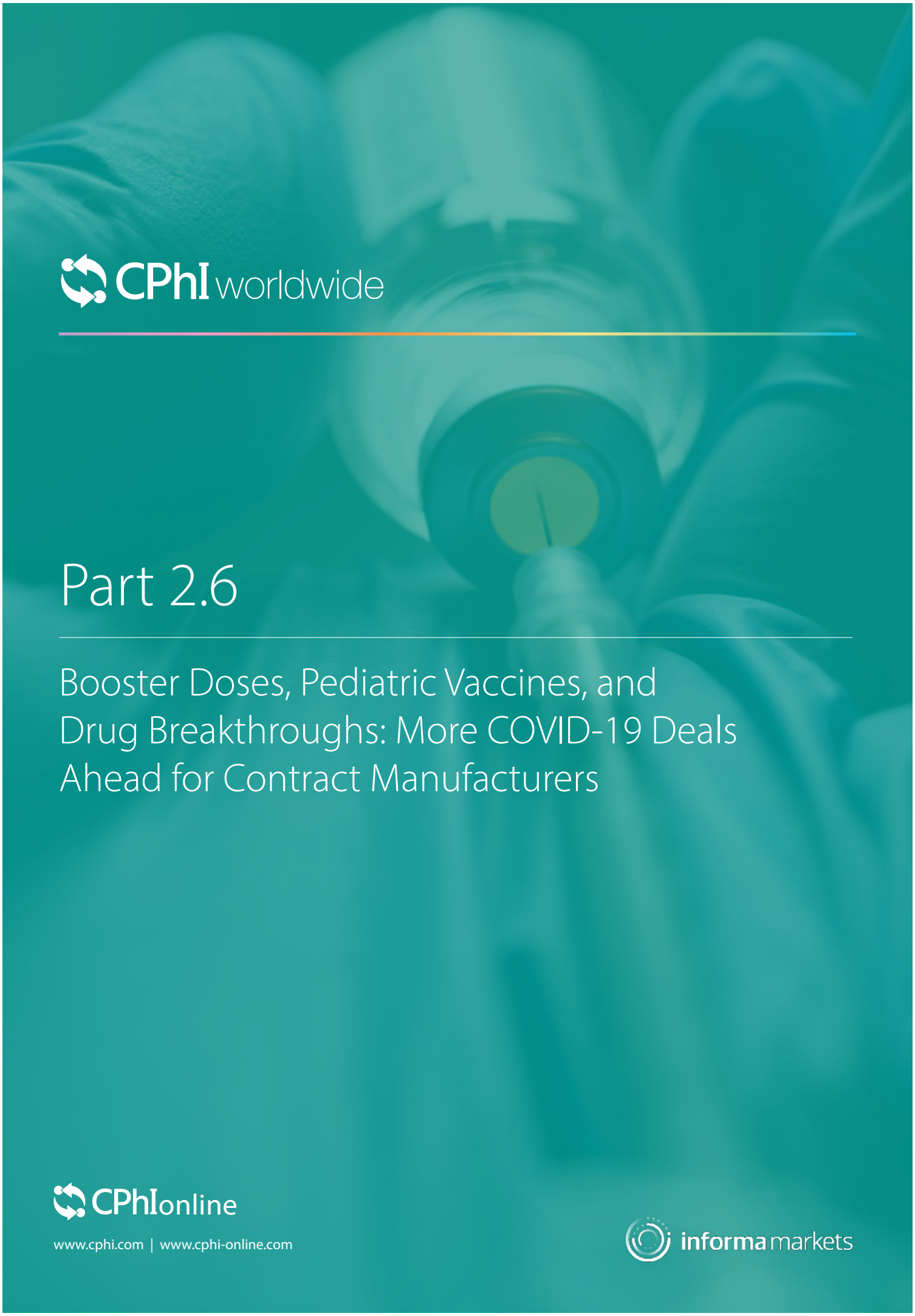

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Part 2.6

Booster Doses, Pediatric Vaccines, and Drug Breakthroughs: More COVID-19 Deals Ahead for Contract Manufacturers

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Author
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Booster Doses, Pediatric Vaccines, and Drug Breakthroughs: More COVID-19 Deals Ahead for Contract Manufacturers

There are more than 1,000 vaccines and therapies in development for COVID-19, and more than 30 have been approved (or granted Emergency Use Authorization) for COVID-19. The GlobalData Pharma Intelligence Center shows that 230 contract manufacturing agreements for COVID-19 vaccines and therapies have been publicly disclosed to date. This is just the tip of the iceberg, as many more exist and will be disclosed retrospectively.

The scale of COVID-19 vaccine doses needed means that sponsor companies are turning to contract manufacturing organizations (CMOs) to fulfil orders. This is true even for the largest multinationals, which ordinarily might have chosen to manufacture some of their innovative drugs in-house. At the beginning of the pandemic, slightly more than half of these agreements were for vaccines. According to GlobalData's *COVID-19: Contract Pharmaceutical Development and Manufacturing Relationships report*, this proportion has risen and continues to rise, as several vaccines have proven their safety and efficacy, received approval, and are being ordered in billions of doses by numerous governments (GlobalData, September 2021).

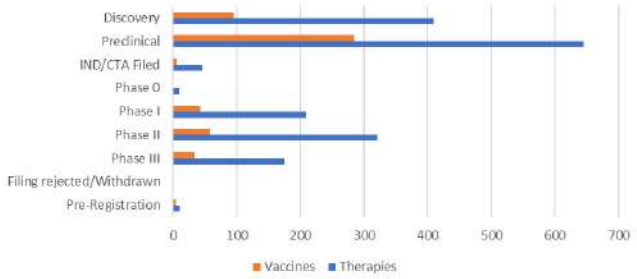
Some of these manufacturing contracts are for a huge number of doses and can span a decade. Nonetheless, COVID-19 manufacturing contracts are spread between a great number of CMOs. Specifically, more than 150 CMOs are involved in publicly disclosed contract manufacturing agreements. Many of these contracts are for messenger ribonucleic acid (mRNA)-based or recombinant vector vaccines, both of which are novel molecule types. Relatively few service providers are capable of certain steps in their production, such as viral vector production or mRNA production, which requires specialist equipment.

Near- and long-term developments will increase the size of existing vaccine manufacturing contracts and create new ones. The prospect of administering the vaccine in pediatric populations or administering one or more extra vaccine doses to all populations, both of which are currently under study, will further raise manufacturing volumes and bring CMOs more highly specialized work making these novel molecules. For more information about this issue, see GlobalData's *BIO 2021: mRNA Vaccine Booster Shots for COVID-19 and Increasing Uptake Will Offer CMOs Lucrative*

Opportunities report (Bio/Pharmaceutical Outsourcing Report, GlobalData, July 2021). On August 18, the US Centers for Disease Control and Prevention (CDC) and FDA announced a plan to offer the US general public a third shot of either Pfizer/BioNTech's or Moderna's COVID-19 vaccines, beginning on September 20 *(FDA OKs Third Dose for Pfizer and Moderna COVID-19 Vaccines: What Does It Mean for Manufacturing?*, Bio/Pharmaceutical Outsourcing Report, GlobalData, August 2021). The US is already administering a third dose to immunocompromised people, and Israel is also rolling out a third dose. Many European countries will offer a third dose to vulnerable groups. Under the FDA's plan, a third shot of the Pfizer/BioNTech or Moderna vaccines will be given eight months after the second dose. The agency says it is also likely that people who received the one-shot Johnson & Johnson vaccine will need a second shot. It is possible that these extra doses will not be the last. If future data support a regular, seasonal immunization program in response to the Delta COVID-19 variant or future variants, this will further increase manufacturing demand. However, the rate of manufacturing and distribution is limited. The World Health Organization (WHO) has called for a moratorium on "booster" shots until at least the end of September, so that at least 10% of the population of low-income countries can receive a first dose.

It is also probable that one or more vaccines currently in clinical development will be approved. These will require commercial-scale contract manufacturing. So far, vaccines have won over therapies in the fight against COVID-19. Several highly efficacious vaccines are now available, but significant room for improvement remains in COVID-19 treatments. The scale of COVID-19 vaccine production now dwarfs that of therapies, which are only indicated for sick patients, and then only in certain circumstances. There is still the possibility of a breakthrough in COVID-19 therapies.

Pipeline COVID 19 Vacines and Therapies



Source: GlobalData Pharmaceutical Intelligence Center, Drugs Database (Accessed June 28, 2021) © GlobalData.

If one such therapy is found to be safe and efficacious, there will likely be a flurry of contract manufacturing agreements. There are still unmet needs in this area, as vaccine distribution takes time, vaccine efficacy is not 100%, and certain parts of the population will not receive a vaccine or will not have a strong immune response. Many of the promising clinical-stage therapies and marketed therapies are monoclonal antibodies (often repurposed from development in other indications). Their manufacture requires CMOs with specialized biologic capabilities.

Top CMOs Strike Vaccine and Drug Deals

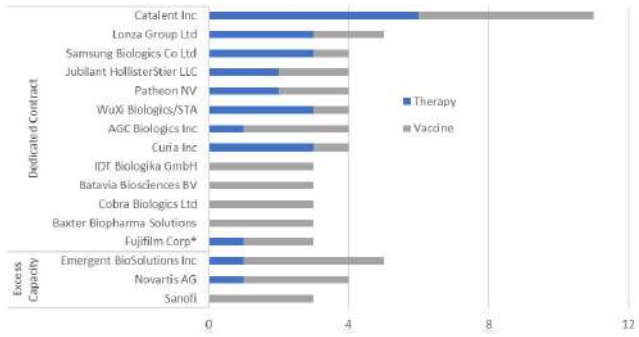
The CMOs benefiting most from COVID-19 vaccine development so far, by number of contracts that have been disclosed, are Catalent, Lonza, and Emergent BioSolutions. Other large contract development and manufacturing organizations (CDMOs) have also benefited. Emergent's contracts skew toward vaccine manufacture, whereas Catalent and Lonza's contracts are more evenly split between vaccines and therapies.

CMOs that only have outsourced contract services and are not the Marketing Authorization Holder (MAH) of a drug offer a dedicated contract manufacturing model. An excess capacity manufacturing model is offered by pharmaceutical companies that produce their own products and also offer contract services using their excess production capacity, but are also MAHs.

In the top three spots for disclosed contract manufacturing agreements, Catalent and Lonza are well known CMO industry leaders. Catalent's 11 publicly disclosed COVID-19 contracts to date are each for a different product, and are split between six therapies and five vaccines. The company

has one contract each for Moderna's, AstraZeneca's, and J&J's vaccines. Lonza's contracts include a 10-year active pharmaceutical ingredient (API) manufacturing contract with Moderna, which was signed in May 2020, and for which it is building commercial production lines in Portsmouth, New Hampshire, US; Visp, Switzerland; and Geleen, Netherlands.

Pipeline COVID 19 Vacines and Therapies



Source: GlobalData, Pharma Intelligence Center Drugs, Deals, and Companies Databases (Accessed July 30, 2021) © GlobalData

Notes: Fujifilm Corp has mixed excess capacity and dedicated contract business models because contracts are signed with different segments of the company

Emergent has been one of the largest winners from the contract manufacturing of COVID-19 vaccines and therapies, but that is poised to change following disasters at Emergent's Baltimore, Maryland, US plant, where the company ruined up to 30 million doses of COVID-19 vaccine. An FDA inspection found cross-contamination between AstraZeneca's and J&J's vaccines, as well as problems in the facility with cleanliness and overcrowding with materials. The company performs contract manufacturing and also markets and develops products for public health threats, including infectious diseases and chemical weapons. In June 2020, the company invested $75M in viral vector and gene therapy production up to 1,000L scale at its Canton, Massachusetts, US facility. It has nine manufacturing sites in total.

Most CMOs with contracts for COVID-19 vaccines and therapies are privately owned. This reflects the general make-up of the dedicated CMO industry, as more than 90% of dedicated CMOs are privately owned, although several of the largest are public. Private equity firms now own many of the world's leading CMOs, such as Recipharm, Cambrex, and PCI Pharma Services. Private CMOs are more likely to have vaccine contracts than therapies, but no single private company dominates; 120 different private CMOs have COVID-19 contracts.

Most CMOs with contracts for COVID-19 vaccines and therapies are privately owned.

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Part 2.7

Does China Need so Many Biologics CDMOs?

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Author
Vicky Xia, BioPlan Associates

Does China Need so Many Biologics CDMOs?

Growth of Chinese CMO segment may be creating over-capacity

The number and size of bioprocessing contract manufacturing organizations (CMOs) in China is expanding for four key reasons. These are outlined in detail in BioPlan's ***Growth of Biopharmaceutical Contract Manufacturing Organizations in China: An In-depth Study of Emerging Opportunities*** (1). However, according to our capacity analysis, balancing this current and future demand for capacity against the long lead times needed to build and commission facilities for future demand can be challenging – as predicting the growth requirement requires assessment of external factors that affect growth.

One primary driver for CDMO growth in China is the number of biosimilars and innovative drugs entering the clinical pipeline and reaching commercial scale. Secondly, because most early-stage biologics developers in China lack manufacturing facilities, the need for contract manufacturing services is growing. Third, the shift in regulatory policy allowing contract manufacturing in the first place (see below about the Marketing Authorization Holder (MAH) system reforms). The fourth reason is economic: China is demonstrating clear investment interest in participating in global markets for both innovative biologics and biosimilars produced at GMP quality levels, and many Chinese CMOs also perform work for Western companies. These factors are creating an extremely strong market environment for CMO services in China.

Background

Before 2016, domestic contracting for commercial pharmaceutical manufacturing did not exist in China. This is because the regulatory framework at the time demanded pharma developers be fully and directly in charge of the manufacturing of the drug products they developed. Meanwhile, manufacturing for certain developing overseas markets remained largely unregulated, and this is where most Chinese CMOs generated most of their export revenue (pre-2016). A few very well-known contract research organizations (CROs) with mostly scientific (vs. bioprocessing) backgrounds – such as WuXi AppTec and Chempartner – developed divisions devoted to contract bio-manufacturing for their overseas clients. Yet more often than not, these facilities were lab-scale or pilot-scale

producing biologicals for preclinical or clinical trial use. The Beijing-based Autekbio, founded in 2011, was the first, and one of the few CMOs fully devoted to contract manufacturing of biologicals.

However, the MAH (market authorization holder) reform, as well as the 2019 version of Drug Administration Law, gave the green light to outsource drug manufacturing, which opened the door for commercial scale contract bioprocessing and built the legal foundation of the biopharma CDMO industry we see today.

Though China's contract biomanufacturing is a relatively young business, in recent years we have seen a wave of opportunities. In fact, the extremely fast growth of China's biopharmaceutical markets has resulted in increased R&D investment in biotech start-ups and a higher demand for a variety of outsourcing options, including biologic products manufacturing.

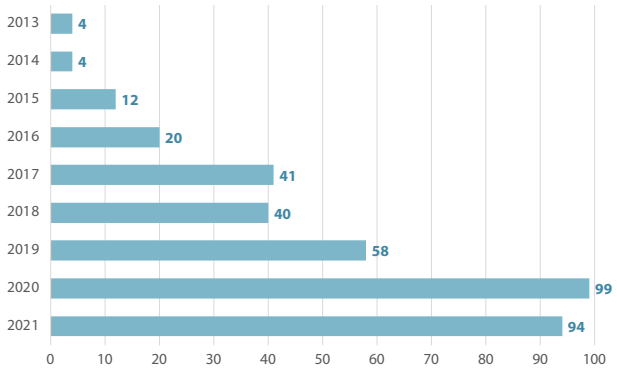
Yet a challenge remained in that the establishment of GMP bio-facilities requires tremendous time and technology, and there was not enough expertise in this field. For multinational pharmaceutical companies with their own GMP manufacturing facilities globally, collaboration with a manufacturing partner in China was one option, delivering cost advantages and smoothness in drug evaluation and approval processes in that country.

Another development is that increased venture capital has provided resources to biotech start-ups to purchase services from external suppliers so they can concentrate on their R&D efforts. As a result, outsourcing in China at clinical scales has grown very rapidly, and CMO services in China are expected to continue to expand.

Developing Domestic Biologics Pipelines

The development of the biologics pipeline by domestic companies is the primary driver of biopharmaceutical contract manufacturing in China, and this has been rapidly accelerated by the MAH system, which provided a legal foundation and industrial infrastructure for biopharmaceutical contract manufacturing. Looking deeper into the types of products manufactured. From our ***Top 100 China Facilities Directory***, dozens of domestic companies, both new and old, have started monoclonal antibody (mAb) development projects, most involving biogeneric/biosimilar versions of Western products. There are also a number of biotech start-ups working on innovative pipelines. China is now home to four PD-1 mAb therapeutics from domestic developers, with a further five PD-1 mAbs undergoing the NDA process. While some of the more established biotechs build their own production facilities, many of the newer biotech companies are or will be working with CMOs. For example, NASDAQ-listed BeiGene, a biotech company now has its own commercial scale facility in Guangzhou, but it also has contract manufacturing deals with Boehringer-Ingelheim Biologics in China. Additionally, the CMOs also often serve as a back up option, particularly when the biopharma companies are in the process of building up their own commercial scale facility.

Fig 1: IND Application of Bio-Therapeutics in China Since 2013 (2)



CMOs in China Adopting More Technology Platforms

Another interesting component of the CMOs in China is their wiliness to adopt newer technologies. For example, according to BioPlan's recent study they tend to be more open-minded in adopting single-use technology, compared to domestic biologics developers/ manufacturers. Most domestic biologics companies still consider single-use technologies as a relatively expensive

option and prefer stainless steel equipment for larger scale production. However, Chime Biologics has already kicked off operations at its single-use technology-based GE KuBio modular CMO facility. And, except for BeiGene, all other modular solution clients in China belong to the biologics CDMOs. Apart from single use bags and single use bioreactor systems, Chinese CDMOs are also the leader in adopting single use chromatography as well as Automation and Digitization in bioprocessing.

Biosimilar Nature of China's Biopharma Industry, Drug Price Control and the Future of Commercial Scale Contract bioprocessing in China

Despite the MAH reforms of 2016, overall, domestic developers still have strong preference for in-house commercial scale bioprocessing facilities, which is comparable to the general pattern in developed countries. The most important factor behind this preference is a cost concern. As most of the mAb pipelines under development by domestic companies are of biosimilar/me-too nature, the projected profit margin would be significantly less than that of innovative, fully novel mAb therapeutics generally originating from large Western companies. The below table shows that of all mAb therapeutics from domestic developers getting BLAs belong to the biosimilar and self-claimed bio-better class, and China is in fact still waiting for a first-in-class mAb therapeutics to come to market. IND application in China also shows a similar pattern, with almost all developers working on established targets including PD-1, PD-L1, EGFR, Her2, VEGF, etc.

Another factor is the fact that the majority of domestic developers are competing with each other for mAbs against known targets, and the volume-based government procurement program makes mAb developers even more cost-sensitive by significantly cutting the price of their products. Therefore, domestic developers are trying to control manufacturing costs in every way possible: shifting from single-use technology to stainless steel-based process lines for commercial scale production, shifting to bioprocessing supplies from MNC vendors to domestic vendors, as well as building their own commercial scale facilities instead of outsourcing to CDMOs.

There are also other factors at play which make outsourcing of commercial scale bioprocessing an unlikely decision for domestic developers. Until now, only the Chinese CMO industry leader, WuXi Biologics, has been widely accepted by the industry as fully capable of commercial scale bioprocessing. The current regulatory system puts the ***Market Authorization Holder*** as fully responsible for its products over the whole life cycle, so developers are cautious in outsourcing entire biomanufacturing work to CMOs due to quality concerns.

Table 1: mAb Therapeutics Launched onto China by Domestic Developers (2)

Name	Developer	Time of Launch
TNF-alpha receptor Fc	3S Guojian	2005
Nimotuzumab (anti-EGFR)	BioTech Pharma	2008
Daclizumab biosimilar	3S Guojian	2011
TNF-alpha receptor Fc	Celgen Pharma	2011
Conbercept	Kanghong Pharma	2014
TNF-alpha receptor Fc	Hisun Pharma	2015
Anti-PD1 mAb	Junshi Pharma	2018
Anti-PD1 mAb	Innovent Bio	2018
Rituximab biosimilar	Henlius Pharma	2019
Anti-PD1 mAb	Hengrui Pharma	2019
Adalimumab biosimilar	Bio-Thera	2019
Bevacizumab biosimilar	Qilu Pharma	2019
Adalimumab biosimilar	Hisun Pharma	2019
tislelizumab	BeiGene	2019
Rituximab biosimilar	Innovent Bio	2020
Bevacizumab biosimilar	Innovent Bio	2020
Adalimumab biosimilar	Innovent Bio	2020
Adalimumab biosimilar	Henlius Pharma	2020
Trastuzumab biosimilar	Henlius Pharma	2020
Trastuzumab biosimilar	3S Guojian	2020
Bevacizumab biosimilar	Hengrui Pharma	June 2021
Bevacizumab biosimilar	BoAn Pharma	May 2021
Disitamab	Rongchang Biopharma	July 2021
TACI-Fc	Rongchang Biopharma	March 2021
Infliximab biosimilar	MabTech	July 2021
Anti PD-1 mAb	Lepu Biotech	NDA in process
Anti PD-1 mAb	Genor Biotech	NDA in process
Anti PD-1 mAb	Chi Tai Tian Qing	NDA in process
Anti PD-1 mAb	Gloria Bio	NDA in process
Anti PD-1 mAb	Henlius Pharma	NDA in process

Table 2: mAb/protein Therapeutics from Domestic Developers Getting BLA (3)

Year	Number of Biosimilar mAb getting BLA	Number of Bio-better getting BLA
2014	1	0
2015	1	0
2016	0	0
2017	0	0
2018	0	2
2019	4	2
2020	6	0
2021H1	3	2

M&A preferences

Many of the venture capital groups behind the mAb developers in China are planning for their companies to go pubic as an exit route, and Chinese investors are known for their preference for fixed assets such as land & factories over intellectual property such as pipelines & patents. Such a preference has affected domestic developer perspectives and they view building an in-house production facility as a good strategy to get a higher valuation during IPO. And, up until 2020, it had also been relatively easy for mAb developers in China to get financing for building in-house facilities. This enthusiasm sees investors give high valuations to companies, while municipal governments have helped developers with access to bank loans and cheap land.

As a result, few domestic developers have turned to external partners for commercial scale biomanufacturing. In fact, BioPlan's internal studies reported only nine commercial scale contract manufacturing deals with China-based CMOs, among which the majority are for WuXi Biologics. Yet according to WuXi Biologic's financial statement, though the first half of 2020 saw the number of late-phase (phase III) projects increasing by 26.7% (from 15 last year to 19), commercial manufacturing deals showed no growth.

Table 3: Commercial Scale Contract Manufacturing Deals with China-based CMOs (1)

CMO	Developer	Developer Type	Bio-therapeutics	Status
JHL	Sanofi	MNC China Operation	Biosimilar mAb	MOU Announced 2016
Boehringer-Ingelheim Shanghai	BeiGene	China-based Nasdaq company	PD-1 mAb, launched in 2019	On-going since 2017
WuXi Biologics	GSK*	MNC China Operation	Vaccine	Announced 2019
WuXi Biologics	TaiMed	Taiwan-based Nasdaq company	Ibalizumab, launched in 2018	On-going since 20184
WuXi Biologics	Brii Bio	China-based innovative biopharma co.	bispecific antibodies discovered from the WuXiBody™ Platform.	MOU
WuXi Biologics	Amicus	US company	ATB200, current at Phase III	Announced on Feb, 2019
WuXi Biologics	I-Mab	China-based company	At least 1 mAb	Announced April, 2019
One Thousand Aks	ZelGen	China-based company	R18A	Announced Jan, 2019
One Thousand Aks	YiLing Pharma	China-based company	An innovative mAb	Announced Nov, 2019

Does China Need So Many Biologics CDMO?

The strong preference of domestic biologics developers for in-house manufacturing puts the future of China-based biologics CDMOs at particularly poignant moment. Many industry analysts doubt if China really needs so many biologics CDMOs and foresee a period of mergers and acquisitions in the near future. Already, we have seen WuXi Biologics acquire C-Mab on March 2021 and Chris Chen, WuXi Biologic's CEO, stated that 'cost control pressures will

certainly drive a wave of M&A in the sector'(4). Meanwhile the rapid growth of China's biologics CDMOs continues to attract interest from Western companies, many of who are following BI's steps. In October 2020 Thermo Fisher formed a JV with Hangzhou-based Innoforce with focus on contract bioprocessing(5). Merck Millipore also established a BioReliance center in Shanghai, with over 2,000L of capacity, and Lonza purchased a modular plant (Cytiva's KUBIO) in Guangzhou, which is put into operation in 2021(6).

The question now, of course, is whether these Western CDMOs can become significantly profitable in China - especially when volume-based government procurement programs threaten to cut the profit margins for mAb therapeutics by 70%. In 2016 Pfizer invested USD $350 million to build a 4,000L bio-facility with KUBIO. The facility was intended to manufacture biosimilars as well as provide contract bioprocessing services. But in March, Pfizer sold this facility to WuXi Biologics(7). Industry insiders suspect that domestic developers will become more price-sensitive, making the competition an uphill battle for Western CDMOs. It is well-known that Western biologics CDMOs have a different cost structure compared to that of domestic peers, as Western CDMOs typically stick to buying bioprocessing supplies from more expensive MNC vendors, while domestic CDMOs, including the industry leader, WuXi Biologics, have gradually shifted toward cheaper supplies from domestic vendors or even started to make certain supplies, including cell culture media themselves.

Appendix

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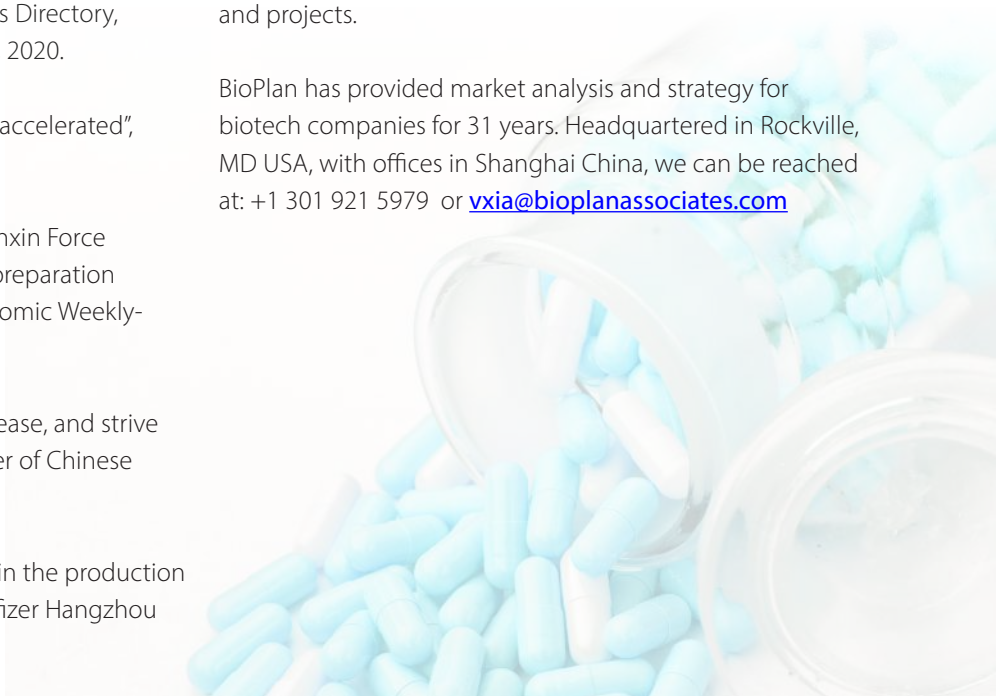
BioPlan has provided market analysis and strategy for biotech companies for 31 years. Headquartered in Rockville, MD USA, with offices in Shanghai China, we can be reached at: +1 301 921 5979 or vxia@bioplanassociates.com



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Part 2.8

SIRIO nutraceutical predictions looking ahead to 2025

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SIRIO nutraceutical predictions looking ahead to 2025

Bullet summary of predications

- **"Body and mind" formulations** that combine a number of potential benefits together will be a long-term trend for consumers over the next five years.
- **Consumers are likely to spend less time traveling to work** over the next five years than the preceding five, but they are spending more time digesting information via digital screens – with blue light and ocular formulations growing in popularity
- **Substantial increase in natural products coming to market** in the next two-three years that are plant-based trends and combine wellness and mood benefits – new natural actives and adaptogens to continue to rise in popularity: Ashwagandha, ginseng and saffron.
- **Consumer friendly dosage forms will lead the market**, with pharma introducing complementary wellness nutraceutical products – i.e. ingredients with EFSA approved health claims
- **Products that consumers can identify as beneficial** in the quest for 'proactive & pre-emptive health', using natural ingredients and in gummy to softgel form to see rapid growth for the next 2-3 years.
- **As more products and brands seek to enter** the nutra industry, CDMOs will become the guardians of entry, providing detailed development and strategy advice on the formulary possibilities
- **As the market expands,** we therefore may see bigger brands and potentially pharma companies align in strategic partnerships, especially as contingencies and robust supply chains are sought.

Background

Global industry has undergone significant changes in both 2020 and 2021 and nutraceuticals is of course no exception. In fact, demand has continued to increase throughout this period and many of the underlying trends behind this have been accelerated by the short-term challenges of the pandemic – significantly, these trends are also now translating into longer-term behavioural changes. For example, over the preceding 5-years we have seen a gradual move towards nutraceuticals that use plant-based ingredients, natural gummies and probiotics. All three have increased in popularity as consumers have sought natural ways to boost health and wellbeing.

In fact, never before has global consumer behaviour been altered so significantly and synchronously, with the challenges Covid-19 has brought to delivering similar experiences for consumers in United States, Europe and Asia. So, beyond the immediate needs this drove in terms of nutraceuticals for immunity, the longer-term implications for our industry are perhaps more profound. The demand it has created for wellness products and an overall awareness of how supplements can contribute to improved health and wellbeing is likely to be a long-lasting consumer behaviour shift. Consumers are likely to spend less time travelling to work over the next five years than the preceding five, but they are spending more time digesting information via digital screens. Additionally, both in response to the last year and due to the growing trend of preventative healthcare, consumers are increasingly focused on any ways they can improve their overall wellness and prevent or reduce the impact of disease and the aging process. With these trends in mind, we will look ahead to 2022 and beyond to envisage what types of products and ingredients will be popular and profitable in the near and medium term and, crucially, what type of development and manufacturing outsourcing will be needed to support these trends.

Before we dive deeper into future trends, we should first look at the current data and the overall market – which is anticipated to grow at CAGR of over 8.5% until 2025 according to new research from Technavio[1]. Looking deeper, what we also see from FMCG Gurus research is that a remarkable 79% of global consumers are trying to improve their diet. This trend is mirrored by a desire to live healthier, with the data suggesting that globally 26% of consumers identify as flexitarian - with environmental concerns shared by the majority of consumers. Emphasising the shifting perspectives of global consumers, research from a 2021 McKinsey report shows that 'in every market researched there was a substantial increase in the prioritization of wellness over the past two to three years'[2]. Significantly these demographic behavioural changes are emerging at the same time as we are seeing increases in consumer spending post pandemic.

Never before has global consumer behaviour been altered so significantly and synchronously, with the challenges Covid-19 has brought to delivering similar experiences for consumers in United States, Europe and Asia.

Furthermore, the consumer perception of what being 'healthy' entails is also evolving. Most consumers now associate this not just with physical health, but also mental and even social aspects that contribute to their overall wellness. There is an increasing consumer perspective that to stay 'healthy' and 'well' means taking a more holistic approach to lifestyle, nutrition and supplement choices.

Running in parallel to this, there has been well-documented trends towards plant-based diets alongside sustainable food supplies and organic certification[3]. What is interesting is that as these trends have significant crossover themes and are now converging around the idea of 'proactive living' and using natural ways to boost wellness and health.

For nutraceutical brands this means that we are seeing shifts in both the way products are marketed, but also the ingredients they contain. If brands can combine natural ingredients with proven benefits and enjoyable dosage forms, they are likely to have a winning product, which is why in particular we continue to anticipate an accelerated rise of nutraceutical gummies as they are able to perfectly intersect these three factors together.

The other interesting aspect is that in an age of new trends and behaviours you naturally see a lot of innovation from companies and new product launches as consumers re-examine their priorities. The Mckinsey report broke this down into 6 segments with – 'better': health, fitness, nutrition, appearance, sleep and mindfulness – with the goal of personal improvement the driving theme of consumer changes. Significantly, for both nutraceutical and pharma companies, 'better health' constantly appears as the most important category and the one with the highest levels of consumer spending across every major market surveyed.

The convergence of big pharma and nutraceuticals

The growth in preventative medicine and health as a consumer trend has not gone unnoticed by pharma companies, which are looking to use their often highly trusted and valuable brands to open-up new potential parallel markets. This means looking at non pharmaceutical or alternative pharmaceutical methods that can be sold as part of the overall package to improve health – everything from applications, and dietary advice to supplements.

Coinciding with this consumer nutraceutical trend, pharma has been pursuing 'patient centric' treatments, reimagining its approach to communications with patients and perhaps, most significantly, looking at how it can improve 'patient experiences'. One common problem that has been often reduced patient adherence to pharmaceutical interventions is dissatisfaction with API delivery options and dosages. In particular, the conventional solid dose delivery form most commonly used often delivers an unpleasant taste and, in the case of the very old and young, can be difficult to swallow. Dosage flexibility and experiential aspects of active delivery is of course an area where nutraceuticals have shone in recent years, providing a diversity of options and consumer innovations that remain unmatched in pharmaceutical products.

How will pharma, a historically conservative industry, look to enter?

We believe initially through the innovate delivery forms of existing supplements that have evidence based and clinically supportable health claims (e.g. EFSA). For example, omega 3 in combination with vitamin B, D C and/or zinc. What is likely to appeal to pharma is also the possibility to introduce products that offer not only a more enjoyable experience but could also help chime with the increasing ethical considerations of the consumer (particularly those in wire income bands). For example, enjoyable dosage forms like gummies and softgels that consumers look forward to taking, made with natural and/or sustainable ingredients. A probiotic gummy with omega 3 and vitamins B6/12 could make for an ideal commentary product in IBS or dietary issues.

The most successful pharma entrants are likely to be those with well-developed marketing strategies and products that closely align with adjacent offerings. This is particularly important as the *McKinsey Wellness Research* showed that 'consumers don't want a single solution from brands and that targeted extensions will deliver greater engagement and potential sales breakthroughs'.

In terms of the contract partners pharma companies work with, they are clearly going to favour those CDMOs that operate higher GMP standards and are certified to manufacture pharmaceuticals as well as nutraceuticals [e.g. as SIRIO is in Europe).

For contract manufacturers there are also many opportunities as increasingly we are seeing clients looking for entirely new combinations, and there remains a strong desire to be first to market with products that can potentially appeal across a number of converging segments. For example, we see ingredient combinations that have 'dual health' benefits rise in popularity, particularly those than can transcend both body and mind.

These "body and mind" formulations are ones that combine a number of potential benefits together like mood enhancement, focus and/or sleep, but also additional "mind" benefits such as enhanced immunity, heart function or metabolism. This, we believe, will be a long-term trend for consumers over the next five years.

For example, probiotic formulations, which help stabilize the microbiome – an essential regulator of equilibrium in immunity, diet, and more recently research continues to emerge on its vital role in the nervous system – are potentially another big trend and products with multi supportable health claims are likely to see strong growth.

At SIRIO, we have seen this first-hand in the last year, with the continued demand for our patented *probiotic/omega 3* softgels. In fact, we anticipate nutraceutical customers in both the United States and especially in Europe coming to us to explore novel combinations over the next 12-24 months as consumers become more aware of this innovation.

Significantly, the trend for mood formulations is proving universal and, the differences we see are in regional preferences for dosage forms, ingredient types, and most importantly flavour profiles.

Another 'trendy' ingredients class we have seen substantial increase in popularity is adaptogens – led in the United States by formulations containing popularity of ashwagandha and in Europe by ingredients like ginseng and saffron. These ingredients are increasingly in demand in response to increased incidence of stress and sleeping problems – both in response to anxiety and increased digital screen time.

For example, saffron due to the antioxidant and anti-inflammatory effects of its two extracts, crocin and safranal, is used not only to improve mood and combat depression, but its efficacy is also now being explored for preventing age-related ocular diseases. We anticipate an increasing number of contract manufacturers will be using saffron in their mood formulations in the next 12 months as demand grows.

Significantly, the trend for mood formulations is proving universal and, the differences we see are in regional preferences for dosage forms, ingredient types, and most importantly flavour profiles. For example, in China we have introduced a center-filled, plant-based and sugar-free gummy product containing the active ingredients GABA (γ-aminobutyric acid) and theanine. This product is used to promote relaxation and calm before sleep and is combined with a regional flavour profile and scientific design. Consumers here are looking for multidimensional experiences and so the product combines peach and oolong tea in the filling and jasmine and lavender in the outer layer. This personalisation of ingredients and flavours will continue to drive forward innovation, new dosages and ultimately products with greatest growth potential and margins for nutraceutical brands.

This is very much where the market is heading, with the development research and new products design now emerging from contract partners. It is why earlier this year we launched a global nutra-innovation team that empowers customers not only with constant innovation in ingredient combinations, but also trends and learning from different preferences across the globe.

In fact, more widely, development services and R&D teams are becoming a vital part of how we work with nutraceutical brands, and, in the future, we imagine CDMOs will become much more influential in the selection and development of formulations for clients – using formulary experience to help guide them to a better understanding of what is likely to work well together.

Another area we believe we will now see lasting changes from the pandemic are in the nutraceutical manufacturing plants themselves. The last year has drawn specific focus on the importance of supply chain resilience, management and remote resources. So, over the next few years, we will see a tremendous amount of digitisation in manufacturing, both allowing remote reporting and predictive supply and manufacturing – so important as brands compete for the best manufacturing resources at contract partners.

The most advanced contract partners are adopting smart factories and real-time process controls for customers to have reassurance. The biggest lesson from the pandemic is that you need to look closely at supply robustness and capability of any of your partners. How much capacity they have, do they deliver in time and how much flexibility they can build into planning. We have seen in the last 6-months many logistics challenges across all markets – and particularly in Europe – with a shortage of containers, drivers and suitable transport conditions.

Consequentially, nutraceutical companies will want to ensure they work with contract players with large and robust facilities. There will be a preference for those that can offer multiple contingencies while maintaining high production quality and service. And that may well be a longer lasting change as bigger brands look for more strategic partners and global resources in case of any facility down time.

Conclusion

Overall, by 2025 we anticipate a far larger number of nutraceuticals will be taken in more novel delivery forms, notably softgels and gummies. Nutraceuticals will also be a key part of new lifestyle-based consumer approaches and form an integral part of their preventative health and wellness-based choices. Increasingly, we will see parallel trends merging into a far greater brand narrative - with plant-based, wellness and ethical considerations a perfect example where brands have the potential to deliver to broad based consumer appeal with multiple sales angles. In terms of contract manufacturing, we therefore expect the biggest growth among CDMOs that have the expertise to help customers develop new formulations, but also the ability to deliver in multiple markets.

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Part 2.9

Want A Regulatory Crystal Ball? All You Might Need Is A Mirror

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Want A Regulatory Crystal Ball? All You Might Need Is A Mirror

Covid notwithstanding, the next five years will likely be governed by the same factors that drove changes during the last five: Brexit, China's growing influence, and political instability in the US.

The pharma industry is about to find itself in an unrepentantly vulnerable position: Baring any deaths or defections, for the first time ever, the user fee legislation that finances speedy drug reviews by the US Food & Drug Administration will be renewed while Democrats hold the House, Senate and Presidency.

The threat of Medicare drug price negotiation legislation remains very real too, but the alignment of the five-year user fee cycle with complete Democratic control of the legislating process illustrates that industry could face both pricing and policy fallout from the 2020 elections.

Of course, the Democrats' razor-thin majorities and the disposition of the Biden administration suggest that the user fee process, acronymically know as PDUFA, won't be as bad as industry might fear under a different scenario of Democratic control.

Instead, industry's regulatory and policy challenges over the next five years will likely be driven by the same factors that have marked that last half-decade: Brexit, China's growing influence, and political instability in the United States.

Getting Anything Done In The US

"Instability" may seem an odd description of the political situation in the US, given that a major complaint of most stakeholders regardless of affiliation is that it's nearly impossible to change anything. But this rigidity is a large cause of the political problems in the first place.

If current policy reflected public opinion on everything from taxes to immigration to (unfortunately for industry) drug pricing, there would likely be less public rage, more productive discourse, and fewer attempted putsches.

What this means for the user fee debate is that there will be a lot of anti-industry vitriol when the legislation is up for renewal next year, but not much in the way of business-harming policy riders in the bill. Of course, as anyone who has had to deal with a REMS can attest, a determined committee chair can drive significant regulatory changes even if their party only controls one chamber of Congress.

And while big changes are not likely in the cards, sponsors would be wise to expect new restrictions on accelerated approval (both in terms of when the confirmatory trials need to start and when they need to finish) as well as new requirements to enroll a more diverse population of patients in any trials.

Working Through Brexit, And Reimagining Europe

Europe's parliamentary systems are less sclerotic than the President and Congress structure in the US. There is, though, a brewing post-Brexit rivalry between the EU and UK, with each aiming to demonstrate they are the more supportive regulator.

Over the next few years, the EU expects to overhaul its pharmaceutical legislative framework and the UK MHRA plans to implement a new Great Britain approval pathway for innovative medicines.

The European Commission has drafted a set of proposals for "future-proofing" the regulatory framework to support what it calls patient-centered and needs-driven innovation, including:

- Revising the current system of incentives to promote innovation in drug development;
- Greater transparency of R&D costs;
- Specific incentives to promote the development of new types of antimicrobials;
- Better tracking of drug supplies and shortages;
- More flexibility in data requirements;
- Shorter review timelines; and
- Providing for a single assessment process across the EU member states for active substances used in different generic medicines to facilitate life-cycle management.

And the European landscape will also see a revamped study environment when the Clinical Trials Information System (CTIS) goes live in the beginning of next year.

Among other things, the CTIS reforms will offer a harmonized electronic submission and assessment process for trials conducted in multiple EU member states, and greater transparency of trial results. A single application will include the submission to national competent authorities and to the ethics committees for all involved countries.

Numerous companies and industry bodies have highlighted the need for sponsors and CROs to start preparing and training for the introduction of the new system in January 2022. They recommend internal "readiness exercises" to synchronize their processes with the CTIS portal requirements and to find out how the portal interacts with various existing master databases.

Organizations will also have to consider the impact of the CTR on their clinical operations, such as anticipating differences in site activation ramp-ups and possible reduction of time between first and last site activations.

The end of the Brexit transition period saw a permanent split between the EMA and the UK Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA is now a freestanding regulatory agency with the ability to set its own regulatory standards. It is no longer a part of the EU drug regulatory network, and its experts no longer attend meetings of the EMA committees. (EU centralized approvals remain valid in Northern Ireland, which is still part of the EU single market for goods.)

Temporary provisions have been put in place to allow Great Britain to recognize EU centralized approval recommendations by the EMA's drug evaluation committee, the CHMP, and marketing authorizations issued by the European Commission. This is known as the "Reliance Route."

After the reliance route expires at the end of next year, the Innovative Licensing and Access Pathway (ILAP) is expected to become the main route for filing new innovative medicines in Great Britain over the next few years.

A key part of the ILAP is the award of an "innovation passport" to products judged to be eligible for the pathway. Generally speaking, the product should be intended to treat a life-threatening or seriously debilitating condition, and there should be a significant patient or public health need. It should be an innovative medicine such as a new active substance or biological entity, or a novel drug-device combination, and be under development for a clinically significant new indication or for a rare disease or other special patient population.

A key part of the ILAP is the award of an "innovation passport" to products judged to be eligible for the pathway.

The innovation passport opens the way to the "Target Development Profile," a living document that will set out a roadmap for the development of, and patient access to, the new product. The TDP will make use of tools such as continuous benefit-risk assessment and more patient engagement in the development process.

Japan's Identity Crises Continues

Like the UK, Japan finds itself a smaller country with a keen interest in remaining a premier destination for pharmaceutical companies. Unlike the UK, though, it can't claim a Covid vaccine as among its recent achievements, a disappointment helping to fuel the drive to shake up Japan's pharmaceutical regulation and reimbursement.

In many ways, though, industry is looking for a rollback rather than a revolution, especially a restoration of the original price maintenance premium system. Introduced on a trial basis in April 2010, this originally exempted all new drugs from Japan's regular biennial price cuts until patent expiry, effectively maintaining initial reimbursement prices.

However, changes made in April 2018 significantly narrowed the scope for eligibility, limited the premium to only the first three best- or first-in-class products or similar products launched within three years, and adopted a new "company scoring" system to decide eligibility.

In addition, there was a shift towards annual (rather than the regular biennial) regular price revisions based on actual market prices, expanded repricing of big-selling drugs, and the adoption of a trial cost-effectiveness assessment scheme. The first of the "off-year" reductions was implemented this April.

In many ways, though, industry is looking for a rollback rather than a revolution, especially a restoration of the original price maintenance premium system.

Japan's clinical data requirements and regulatory processes have also come under a renewed spotlight because of the slow approval and roll-out of Covid vaccines, due in part to the need to conduct local studies and go through standard (albeit expedited) regulatory procedures.

China's Big Regulatory Moves Match Its Growing Market

Japan's neighbor China developed multiple Covid vaccines (though many have questioned their effectiveness), and those product successes are among the factors contributing to Japan's crisis of Rx conscious. China is no longer an improvised if colossal rival; the country is a full-fledged pharmaceutical ecosystem, featuring complex

financing, development, and now approval systems that complement its earlier strengths in manufacturing.

That transformation is perhaps illustrated best by the country's first approval of a cell therapy: Fosun Kite Biotechnology Co Ltd's CD-19-targeting chimeric antigen receptor T-cell (CAR-T) therapy FKC876, marketed globally as Yescarta (axicabtagene ciloleucel), which was cleared in June as a third-line treatment for adult patients with diffuse B-cell lymphoma or relapsed and recurrent B-cell lymphoma.

Yescarta's approval relied heavily on foreign data and is expected to open the door for more CAR-Ts at a time when the area is fast gaining traction. China is ranked second globally in terms of number of cell therapy studies after only the US, and emerging technologies such as universal CAR-T "off-the-shelf" allogeneic products continue to draw large investment inflow.

To gain its new approval for Yescarta, Fosun-Kite – a joint venture between Kite Pharma (now part of Gilead Sciences) and China's diversified Fosun group – conducted a bridging study in 2019 in a local patient population in China, although the majority of the data to support regulatory nod, including three-year follow-up study results, came from Kite.The US firm's pivotal ZUMA-1 trial enrolled 101 patients with refractory large B-cell lymphoma showed that, after three years, 47% of patients were still alive with a median overall survival of 25.8 months.

One of the key considerations for cell therapy approvals in general is durability of response, which is no different in China. The national regulatory agency recently released follow-up study guidelines on gene and cell therapies, under which a five-year study following administration of gene therapies delivered via virus vectors (such as adeno-associated virus) is required.

Manufacturing: Redundancies Wanted

China has of course been known more as a manufacturing hub than an innovation center, but the pandemic threatens to upend that status as well. The supply disruptions that accompanied the beginning of the global lockdowns in early 2020 helped fuel nationalist concerns in many countries worried about their reliance on foreign production.

Manufacturing has long been the backwater of the pharmaceutical industry. When it gets high-level attention at all it is seen as the cause of embarrassing recalls, a place to save money, or a way to extend the lifespan of a product through patent litigation. Now, however, it's becoming more of a hot-button political issue.

But policy moves to encourage domestic manufacturing in the United States have been fitful at best, and any serious progress will likely be met by countervailing pressures from countries that would be at risk of losing manufacturing.

Of course, ending up with more manufacturing overall may not be the worst outcome, as the continued global shortage of Covid vaccine demonstrates. Building surge capacity is a manufacturing policy goal that is unlikely to encounter as much political resistance as re-shoring facilities, but the ultimate success of those efforts is no more certain.

There is clearer reason for optimism about the direction of global regulatory harmonization, though the pace is likely to remain turgid. The idea of a global regulatory dossier that exists in the "cloud" seems to be gaining some traction, and certainly could help keep countries on the same page with their drug approvals, at least for product quality.

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Further acceleration of various aspects of the regulatory review process could occur as a result of learnings from the

pandemic. In the CMC area, for example, there could be greater flexibility around stability testing.

As the nitrosamine issue unfolds, industry is finding it terribly difficult to assess and manage the risks; on the bright side, there could be learnings on how to establish specifications that are truly patient-relevant, which could free the industry from quality thresholds that grow ever tighter as analytical methods become increasingly discerning.

The biggest immediate challenge for manufacturers, however, will be seeing how well they have maintained compliance during an inspection hiatus that has lasted over a year but may soon be over as pandemic travel restrictions are expected to ease.

That challenge involves some of the questions many of us face in our own lives and jobs as we look towards a post-pandemic future: How well have we maintained what we need to keep, and how well positioned are we to make things better?

As the nitrosamine issue unfolds, industry is finding it terribly difficult to assess and manage the risks

and patients alike. To realize the long-term sustainability of many new drug modalities and therapies industry must rethink its approach to manufacturing, quality control, and the corresponding path to overall drug quality.

CPhI worldwide

Part 2.10

Developments in Global Pharmaceutical Excipients in the Next 3-5 Years

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Developments in Global Pharmaceutical Excipients in the Next 3-5 Years

Introduction

Excipients have always had a critical role in the safe and effective use of medicinal products. These can be as simple as a bulking agent to allow a tiny quantity of an active to be picked up by the patient right through to those responsible for forming the lipid nanoparticles that deliver the mRNA in several COVID-19 vaccines. Whereas they are pharmacologically inactive, in that they have no therapeutic effect on their own, the oversight applied to them in the drug product approval process can be as rigorous as the active substance.

In the developed world the ways of using and approving excipients are well established and there has been very little change in the past decade. But the newly emerging economies are now introducing new and more demanding ways of approving the manufacture and use of excipients and these developments are driving changes across the industry.

I expect there to be some key themes that will shape the excipient landscape in the 3 to 5 years, centred on:

- Regulations
- Innovation
- Economics
- Sustainability

Pharmacopoeia

Traditional excipients have been used for decades in many drug product formulations with a correspondingly large amount of information demonstrating their safe and effective use. This allows the quality of such excipients to be well defined in the various Pharmacopoeia monographs, simplifying the regulatory approval of new drug products that use these excipients. This comfortable arrangement has been in place for a long time, however, it makes the introduction of structural change extremely difficult, as exemplified by the low incidence of novel excipients and the poor progress in monograph harmonisation.

Previously, the slow pace of change allowed for economically motivated adulteration by unscrupulous actors in the early years of this century. As a result, there has been a drive to update pharmacopoeial monographs to make use of modern analytical techniques to allow for a much more precise definition of the quality and purity of the excipients. This trend must continue not least to ensure patient safety through analytical accuracy, improved understanding of the excipient composition, but also to stop using ancient test methods which require the use of environmentally damaging reagents.

The new economies are developing their own Pharmacopoeial monographs quickly, none more so than China. Whereas the monographs for the traditional excipients that are availably globally may include more modern analytical techniques, there has been further divergence from the established monographs. If the previous difficulties in achieving monograph harmonisation in the developed world were already exceptionally difficult then the introduction of more national pharmacopoeia with their own subtle differences will make that all but impossible. In this regard it is hard to see how the next few years are going to see much progress in the harmonisation of excipient monographs without a shift from the nationalistic viewpoint.

The oversight applied to excipients in the drug product approval process can be as rigorous as the active substance.

Impurities

It is becoming more and more important to have a better understanding of excipient composition as they can often contain several components, together which are critical to the overall function. It would be incorrect to consider these components as impurities. We can therefore expect to see more scrutiny about overall excipient composition with the objective of having a better definition of the intended composition.

However, excipients have been recognised as contributing to the overall level of impurities in a drug product and so are under increasing regulatory examination. Excipients were explicitly referenced in ICH Q3D guideline on Elemental Impurities, even though it was demonstrated that there was no systematic problem with excipients in this case. However, the same is not true in the current case of nitrosamine impurities, where the levels of patient concern are 3 orders of magnitude lower than what was previously an acceptable level for an impurity. It is now clear excipients may and can contribute to the formation of nitrosamines in susceptible drug products.

Thus, we can anticipate that as scientific knowledge advances, more details will be required to be shared about excipient composition profile, and this will require the excipient supplier to control the quality of their excipient accordingly. Whereas some impurity issues are clearly driven by demonstrable need to assure patient safety, other developments in the control of excipient quality will be driven by the need for sustainability. Microplastics and concerns about endocrine disruptors are two contemporary topics but we can expect more of this nature in the next few years. Some of these issues will be driven by the science, but unfortunately others will be placed on the agenda by political, social and other pressures.

Regulations

There have been few recent regulations in the developed economies concerning excipients. The most significant was the EU Ascertaining GMP for excipients Guidelines which required excipients users to perform a risk assessment to determine the appropriate GMP required for the manufacture of the excipient in their drug product. The fact this has been adopted by PIC/s now makes it global best practice. Of greatest significance in this document was

the approach away from telling industry "What to do" in a proscriptive set of rules and towards a position where the excipient user had to use logic and good science to justify their decision about the GMP required for the manufacture of the excipient. This is a significant milestone, and it is to be hoped that the approach can be utilised further in other aspects of the industry, especially as drug products become more and more complex. This document should also readily accommodate advanced manufacturing techniques, which are being developed in Industry 4.0 and may otherwise have been incompatible with traditional GMP definitions. In this respect, this will allow for more innovation in traditional excipient manufacturing.

The ascertaining GMP guide also specifically stipulated that excipient supplier certification (e.g. to a GMP standard like EXCiPACT) could be used to demonstrate they were applying the correct standard in their manufacturing operations. Such a development has been put to a lot of use during the pandemic, and there is no reason to suppose that when matters return to the "new normal" that there will be a return to widespread international auditing.

But there will also be another driver here to reduce travel, the need to reduce carbon emissions.

Of greatest significance in this document was the approach away from telling industry "What to do"

In the developed world this guide represents the definition of GMP for excipients, but in the developing world new specific guides are being introduced which set GMP standards that are much closer to ICH Q7 in principle and details. This may yet be counterproductive as it will deter some suppliers from making their excipients available in those countries because of the investment required to bring their existing GMP level up to that of full pharmaceutical standards. These pressures will mean more excipients will be expressly manufactured for use in pharmaceuticals and not be substances made for other purposes that "happen" to be sold for use in drug products.

Innovation

Despite the barriers to the introduction of truly novel excipients, some innovation has been possible with the introduction of co-processed excipients and excipient blends. These mixtures can offer new properties to the drug product, especially in solid dosage forms and thus aid the availability of the active. However, there has been a view by some regulatory authorities that any mixture of excipients which are not required to assure the stability of the excipient in the supply chain, is the first part of drug product formulation and therefore has to be performed under full drug product GMPs. Again, the investments needed for the excipient supplier to meet such standards are disproportionate to the risks to patient safety so these materials will become increasingly unavailable unless there is some adjustment of the regulatory position.

Novel Excipients

Truly novel chemical entities, which have been designed and manufactured as pharmaceutical excipients are exceptionally rare. The few examples in the recent past have incurred very large development costs, not least in the demonstration of patient safety, and have also been little utilised by the pharmaceutical industry. Why

would you formulate with a novel excipient knowing the regulatory scrutiny of the marketing authorisation dossier may trigger additional questions and delays when using a traditional excipient would not incur such questions even if it did not perform as well?

This is another block to the development of new therapeutic approaches, especially using biopharmaceuticals ("big molecules"), which often require new excipients with new properties. None better exemplified than the polar lipids used to encapsulate the mRNA in COVID-19 vaccines. Indeed, without these excipients there would have been no effective vaccine using mRNA. The acute need for a successful vaccine outweighed any reluctance to use novel excipients, and this allowed all parties, the excipient manufacturer, the vaccine maker and the regulatory authorities to take pragmatic steps to accelerate the use and approval of these substances.

The US FDA now acknowledges the lack of novel excipients is indeed a problem, noting the limitations of existing excipients in some drug product scenarios. On 7th September 2021 they announced the Novel Excipient Review Pilot Program. This will select and then review four novel excipients in the next two years using a new pathway. This will allow manufacturers to obtain an FDA review prior to the use of the novel excipient in a drug formulation. Note this is not an excipient approval process; the novel excipient would still be evaluated as part of the overall drug product approval.

In Europe the absence of an excipient master file system is a specific problem that means the only way to introduce a novel excipient is via the marketing authorisation dossier – and therefore, all information about the excipient has to be shared with the pharmaceutical manufacturer, including all the intellectual property invested in the new excipient. At least in the US, Canada, Japan and now China excipient master files exist which allow some protection of the excipient manufacturer's intellectual property. So, we can expect to see novel excipients used first in these regions at the expense of patients in Europe who may miss out on new novel therapies.

The US FDA now acknowledges the lack of novel excipients is indeed a problem

But for novel excipients one pathway is clear, as these are intended to be used in pharmaceutical drug products and have not been repurposed from other applications, the GMP to be applied may have to be more akin to ICH Q7 for actives than that for traditional excipients. This is in accordance with the ascertaining GMP risk assessment guide as there is less knowledge about the manufacture and use of the novel excipient, so higher standards may be required to mitigate the risks.

If there is one bright spot with regards novel excipients, then the new lipids used to encapsulate the mRNA vaccines can be repurposed to perform the same duty with other actives that require the same delivery mechanisms. But this multiple application of a novel excipient can be a blueprint for further introductions. Rather than designing one for a specific drug product, it is designed for a specific purpose and hence can be applied to multiple drug products. Consequently, some of the risks of developing and introducing the novel excipient can be mitigated. The success of this strategy has been proven, so we can expect others to follow.

Economics

The pandemic and perhaps more so its aftermath with the acute disruption of global supply chains has brought into sharp focus the risks of sourcing materials for drug products on a worldwide scale. The natural reaction will be to redress the risks by sourcing excipients more locally, with cost savings by sourcing more remotely being demoted in priority. How long this trend lasts will depend on how long lasting the pandemic and its aftermath will be, but the adjustments are likely to be permanent for the most critical drug products, and especially COVID-19 vaccines.

Many excipients were not designed for drug product use, being intended for use in other industries, e.g., food, cosmetics. This position is being eroded and we can expect

to see more and more of the traditional excipients being manufactured exclusively for pharmaceutical use. It is possible that a few suppliers will take the lead in this and that as a result the number of suppliers will decrease in the coming years.

As a result, closer collaborations between excipients suppliers and users will develop from what can currently be a very distant relationship.

Why would you formulate with a novel excipient knowing the regulatory scrutiny of the marketing authorisation dossier may trigger additional questions and delays?

Sustainability

The awful human tragedy associated with the COVID-19 pandemic is not the only global crisis of our times; that of global warming and its consequences will also have a damaging impact on human lives as the current news programmes continue to show. Other industries are taking the brunt of attention in decarbonising, but there is a slow groundswell within the pharmaceutical industry which will gain momentum in the next 3-5 years. Initial steps can come with small steps such as removing the use of environmentally hazardous and toxic substances in the manufacture and testing of drug products, and with more use of remote and 3rd party auditing. The next steps will involve the principles of the circular economy in all aspects of the industry, including excipients. Here substitutions from fossil-based substances to sustainably sourced ones will have to be found, and this will pose a number of scientific challenges not least ensuring the replacements have the same or better quality, purity and patient safety profiles. Such changes are going to be applied externally to the industry and are likely to be government led as well as by social influences.

Conclusions

The very nature of the industry puts patient safety first and foremost, and rightly so. This makes change in the developed world rather slow and measured. Yet the developing world, unencumbered of a well-oiled infrastructure is forging ahead with new standards and ways of dealing with excipients. The pandemic too has demonstrated that a much faster pace of change does not mean that patient safety has to be compromised.

In the next 3-5 years we can therefore expect to see the acceleration of the existing trends examining the composition and purity of excipients in ever more detail as well as the emergence of sustainability as an important factor. Supply chain perturbations due to the pandemic may turn out to be transitory unless political factors also weigh in as the economics of a low-cost supplier will usually win in the end. Additionally, there remains significant barriers to the introduction of novel excipients despite the success with those utilised in mRNA based COVID-19 vaccines. In this regard, Europe is at a distinct disadvantage in the protection of the excipient manufacturer's intellectual property, and so could well miss out on novel therapies using novel excipients, delaying patient access. Regardless of these changes and challenges we can be assured that excipients will continue to be a critical component of the success of drug products.

There remains significant barriers to the introduction of novel excipients despite the success with those utilised in mRNA based COVID-19 vaccines.

Appendix

Author Biography

Dr Iain Moore is Global Head of Quality Assurance Croda International plc, a manufacturer of speciality and performance chemicals based in the United Kingdom. Since joining Croda in 1987 in a technical role before moving to QA in 1995. This included applying Excipient and API GMP standards at two manufacturing sites and hosting two successful MHRA inspections. He has contributed to the publication of European and US National Standards. He is one of the co-authors of the IPEC-PQG GMP Guide for Pharmaceutical Excipients and the EFfCI GMP Guide and standard for Cosmetic Ingredients. He is chair of the EFFCI GMP Committee and is President of the Board of EXCIPACT asbl.

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