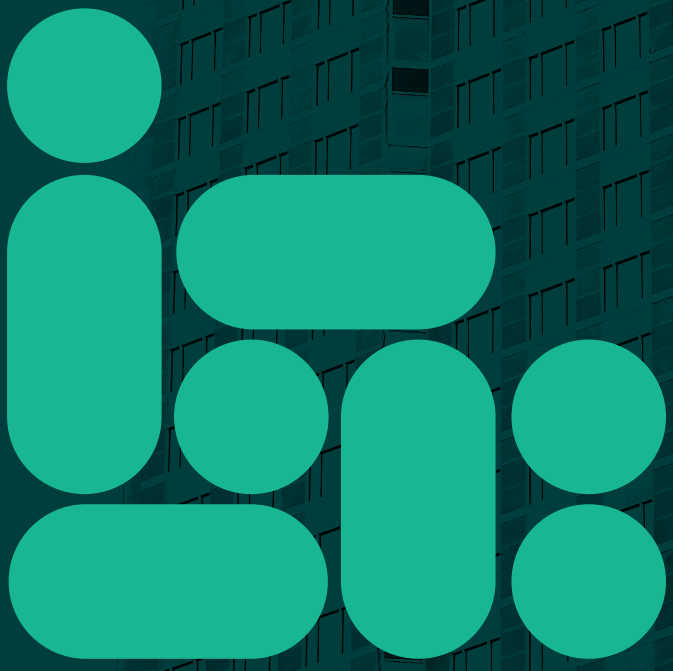
Annual Report

Psychedelic Approvals, VC Driven Contract Services Boom and Next Generation Manufacturing.

What's in store for global pharma in 2023 and beyond...

CPHI Frankfurt 2022



CPHI

Overview: CPHI Annual Industry Report and Survey
The sixth **CPHI Annual Survey** will explore the perspectives of some 400 pharma executives, evaluating the likely trends in 2023 and the reputations of all major pharma markets. The analysis spans insights from some 35 questions and is a key bellwether of industry prospects in the year ahead.

The second component of the **CPHI Annual Report** – now in its 10th edition – features the detailed analysis of 11 global experts who explore all facets of the industry today and look ahead to predict the major trends

Contents

Produced by defacto

Adam Andersen
Executive Vice President, Informa Markets

Introduction

CPHI Frankfurt – at the heart of pharma
We are releasing the CPHI Annual Industry Report at another key moment for the industry as the duality of a strong pharma industry and drug discovery pipeline is offset by wider macro-economic conditions around the globe.

Collectively, what we are seeing is that the value of partnerships and partnering has never been higher – whether that is to advance a new drug through development faster, to lower the cost of manufacturing processes, or to make supply chains more secure and resilient. And it's incredibly timely, that we address these issues in the Annual Report as we open the World's largest pharma event – CPHI Frankfurt.

Every company in the global manufacturing supply chain is looking for new technologies, additional capacity and to build contingencies into their business and that means building an even wider network of contacts and connections.

So while it is impossible to ignore the challenges of today, demand for pharma manufacturing is still extremely strong – and we see record scores all across the board for business confidence in our Annual Report surveys. The rankings of pharma executives across all metrics have improved from growth to quality scores for APIs, biologics and finished dosages.

In fact, our CPHI Annual Report experts all tell us that the growth we expect to see in next few years will be driven by the quality of partnering networks that the industry is building right now – which is why CPHI Frankfurt's return is so positive for industry.

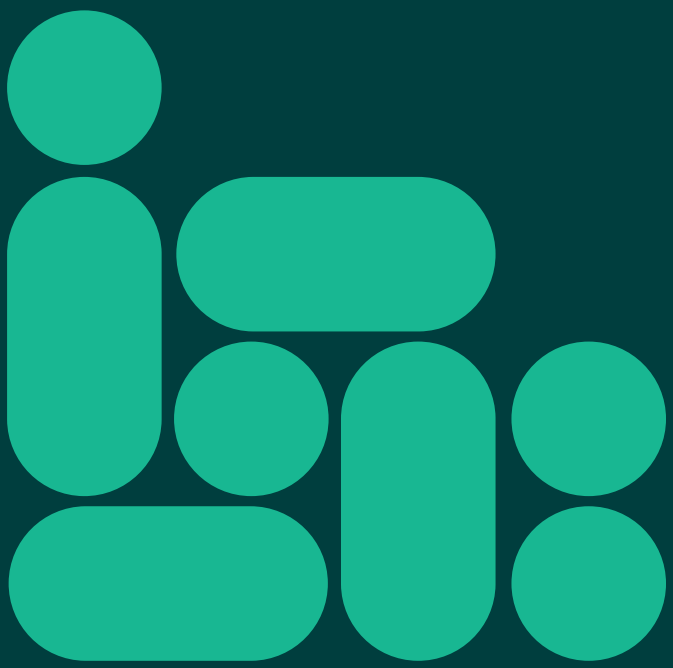
For those of you attending CPHI Frankfurt in person you will also see a number of significant changes, most notably, onsite conferences have returned, and we have rebranded to better reflect our place in the industry. Our new philosophy is to embrace our role 'at the heart of the pharma' – both facilitating partnering and connections, but also wider responsibilities of promoting good corporate ethics and driving progress on issues like sustainability. For our pharma attendees it means we are focussed on helping them meet partners faster and from wider networks - all year round.

Please take some time to study the report's findings. It's been written for the pharma industry and its supply partners so you can be better prepared; better informed and better able to meet and navigate the key challenges in 2023 and beyond.

Survey

The insights from 400 global pharma executives

CPHI Frankfurt 2022



The CPHI Annual Report 2022: Pharma Survey and Industry Rankings

Introduction

For the third consecutive year the findings of the CPHI Annual Report are announced as large macro forces are creating layers of economic uncertainty – except gone is the forced economic hibernation of Covid lockdowns to be replaced by surging inflation, variable growth prospects and an ongoing war in Europe. Yet running in parallel to this, pharma's innovation engine has maintained the successes of recent years, with new manufacturing hubs being created and several ground-breaking therapeutics edging toward commercial launch. Not least of which are Psychedelics and, potentially of even greater significance, MRN vaccines for use in certain oncological indications – both of which will be explored in greater detail in this report. The recent patent infringement lawsuit from Moderna against Pfizer and BioNTech[1] perhaps also hints at the potential these technologies have and the future battlegrounds ahead for supremacy – with RNA technology likely to have far wider uses in the next 5-10 years than the narrow field of Covid and infectious disease applications to date[2].

The wider economic conditions are continuing to exacerbate the pharma industry's two-tier market, with generic companies under sustained marginal pressure from inflationary causes, while innovators are better able to weather what is hoped are transient conditions. Uncertainly of course remains, not least in the form of global energy prices and the consequential implications this has for manufacturers – particularly as price rises are not yet globally uniform, which creates further market distortions. However, recent bailouts and Government interventions, coupled with analyst price predictions that the worst may now be over are mitigating these concerns somewhat[3].

The other notable and likely long-term trend occurring across major pharma economies is a focus on much greater supply chain resilience and localised supply networks. This is furthering a prosperous outlook for many manufactures with new government backed initiatives occurring from India to Europe and the USA.

Finally, after the sugar fuelled rush of the pandemic inspired innovation needs, biotech access to financing in the last 6-months has notably fallen – particularly as wider capital (private and public) seeks safer investment options in an inflationary and potentially even deflationary market.

However, a majority of analysts now think the bottom is in and that financing in the 12-months ahead will be more robust. Thus, once the worst of the inflationary pressure subside the biotech market could see a gradual rebound, with dramatic growth rates for CDMOs in 2023 (see Brian Scanlan's analysis later in this report). The slight caveat to this improved outlook is that CDMOs whose cycles operate by lagging behind the innovators – and are currently reporting record growths – may find a more restrained market

in 2024 unless new innovation contracts can be signed. However, with such a continued shortage of available capacity, we may find that the contract services sector is the one part of the industry to sale straight through all the economic headwinds of the next few years with growth continuing largely unabated.

Methodology

This is the sixth CPHI Annual Survey and will explore the insights of 400 industry executives from every region of the globe. The rankings evaluate the major pharmaceutical markets across key indicators including 'growth potential', 'quality of API manufacturing', 'competitiveness', and 'quality of finished product manufacturing' among many others survey questions – culminating in overall scores for each country. In addition, the rankings also provide detailed perception scores for biologics across three categories: 'quality of bioprocessing', 'growth' and 'innovation'.

This report is published annually and was released at CPHI Frankfurt 2022 – 1-3 November 2022 at the Frankfurt Messe, Germany.

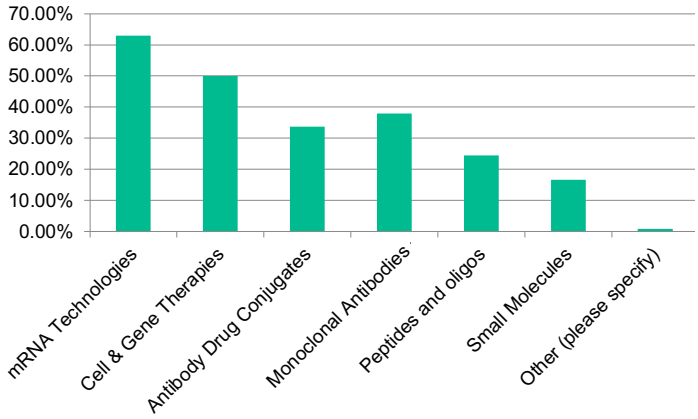
Biotech bottom?

The CPHI data on this area is a somewhat mixed, but with most executives hedging towards a more positive outlook in 2023 – in fact, only 19% believe the biotech market has a highly negative outlook for the next 12-months. Some 59% state the outlook is moderate, and the 'bottom has now come in for biotech valuations and funding' – with valuations reflecting a needed correction and funding paused for better conditions. In contrast, 22% of the market are taking a very bullish outlook and argue that biotech stocks now represent 'value investments'. Moreover, in terms of financing start-ups there is also less competition – with outside capital having exited the market – leaving only true biotech investors to pick up the best companies at relatively discount prices on previous years.

Biotech therapy prospects

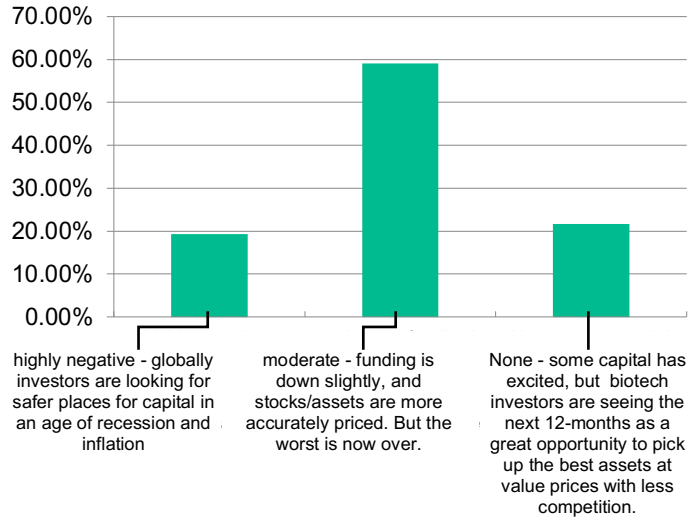
For the first time mRNA technologies have emerged as the toped ranked therapeutic class for early stages investments surpassing both cell and gene therapies and MAbs – historically the leading options. Small molecules picked up just 17% of votes, which despite the rise of advanced therapies and biologics, seems extremely surprising with so many still in development and the pipeline[4,5].

Figure 1. Which technology class will see the biggest preclinical investment in 2023? (Tick as many as appropriate).



"Overall, the biggest trend is the shift towards biologics and, while small molecules still dominate approvals and sales now, as soon as 2028 we are forecasting biologics will account for 55% of all drugs sales. Monoclonal antibodies (MAbs) being a key product class within biologics driving this growth, with 46% of total biologics sales attributed to MAbs. In fact, in 2028 biologics will have sales of 190bn over and above those of small molecule drugs." Quentin Horgan, Associate Director, Pharmaceutical Data & Analytics at GlobalData

Figure 2. Biotech stocks are hugely down on last year. What will be the impact on early stage funding in the next 12-months?



Psychedelic findings

One of the industry's biggest revolutions in terms of therapeutic indications is occurring in Psychedelics – with the metaphorical 'war on drugs' now seemingly from a different era we

are quickly seeing a shift in both consumer and research behaviour. For example, the recent rise of micro-dosing outside of therapeutic settings by large swathes – of often professional classes – in response to the pandemic is just one indicator of this shift[6]. But of more significance to the industry is the increased funding we see, as well as the more open-minded regulatory and government environment. Most importantly, results across a spate of trials in Europe and notably the USA are showing very welcome improvements in neurological indications as diverse as ADHD, addictive disorders (alcohol & drugs) to PTSD, chronic pain and depression.

Before we look deeper into the findings it's important to breakdown the different types of Psychedelics and their progress in trails. For example, dissociatives and amphetamines – like Katamine – having already received an approval, while hallucinogenic agents like Psilocybin, LSD and MDMA (midomafetamine) still in trials. The former are often taken as synthesised compounds in conjunction or in replace of a standard antidepressant (e.g. an SSRI). However, it's the latter group – which must be taken alongside a talking therapy course – that, should they be approved, seem to show the most dramatic rates of improvement.

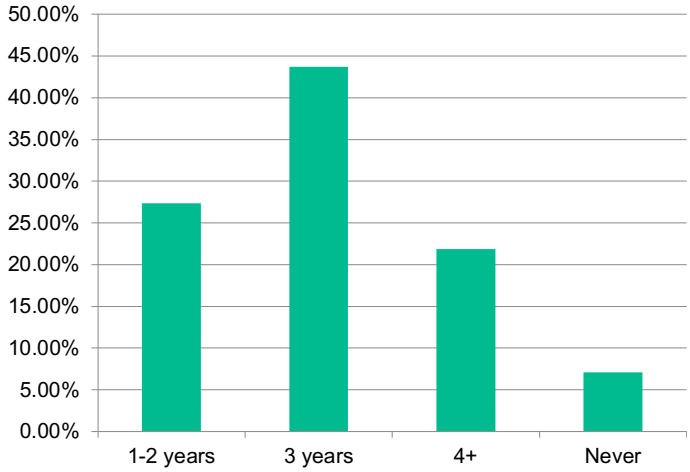
So while the FDA has already approved its first Psychedelic therapy back in 2019, namely, Johnson & Johnson's Spravato (Esketamine – a type of synthetic Ketamine), real world usage for this nasal spray has thus far been mixed[7].

The added complexity and cost, of course, of incorporating counselling and therapy sessions alongside a drug regimen is a critical problem still to be overcome. As unlike for Spravato – which just requires monitoring after administration – the majority of Psilocybin trials are required to be taken in special setting alongside a highly trained councillor to 'guide the patient through the experience'[8]. The FDA is also reportedly remaining extra vigilant on the potential for any of these compounds to be misused or to cause addiction. For an approval to be received the challenges around dosing, length of effectiveness and blinding will have to be overcome in a very cautious regulatory environment. And yet, when we asked the industry for their predictions on the likely approval of a hallucinogenic psychedelic like MDMA or Psilocybin some 93% believe this will occur, with more than 71% expecting it with the next three years.

And while it is forecast these initial approvals are likely to be expensive treatment options – potentially not available on the majority of health insurance schemes in the United States – the potential is enormous with some 40% of Americans reportedly struggling with either 'mental health or substance abuse disorders'[9]. Should we see even one approval many analysts are predicting the market will accelerate quickly, with pharma readying its considerable financial resources. At present the majority of these trials are funded through advocacy groups and not for profit organisations, but with limited to no resources to manufacturer these at scale there are clearly opportunities for pharma and pharma manufacturers. Especially, as these drugs will require Schedule 2 manufacturing facilities – downgraded from Schedule 1 on approval – limiting the number of contract manufacturing options available.

For example, looking at the trials in phase ii; 5 of the 26 current trials[10] are sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS), with a further MAPS sponsored trial using MDMA to treat post-traumatic stress disorder the only one presently in phase iii[11].

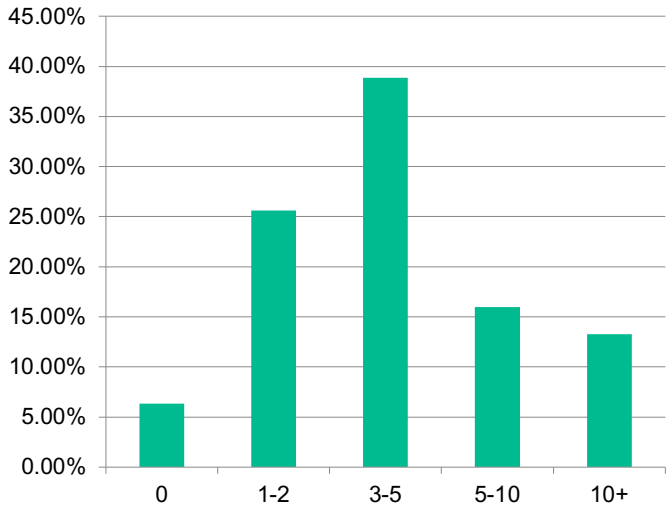
Figure 3. When will the FDA approve its first psychedelic drug/councilling combination? (e.g MDMA for PTSD / Psilocybin for depression etc)



In fact, looking 8-10 years ahead nearly 40% of the industry expects to see between 3 and 5 approvals, 16% anticipate between 5 and 10, with a further 13% believing the floodgates will truly have opened with 10+ approvals. All of which leaves the still unclear manufacturing *question open* to debate, as the scale at which these therapies can be operationally delivered again remains unclear.

Keynote speaker at CPHI Frankfurt and an expert on psychedelic trials, Dr David Erritzoe, Clinical Senior Lecturer and Consultant Psychiatrist, Department of Psychiatry at Imperial College London, added: *"Looking at the pipeline, five approvals in the ten-year timeframe seems very achievable and, I think if all goes well, we will see more than five. Again, my message here is that the approvals are only one part of a complex story and there is lots of promise outside of the current – often narrow – trial endpoints. As we get approvals, and the use of drug/therapy combinations matures we are likely to see even better outcomes and more innovative combinations and better personalisation of therapies."*

Figure 4. *How many FDA approved psychedelic drugs will be on the market in 2032?*

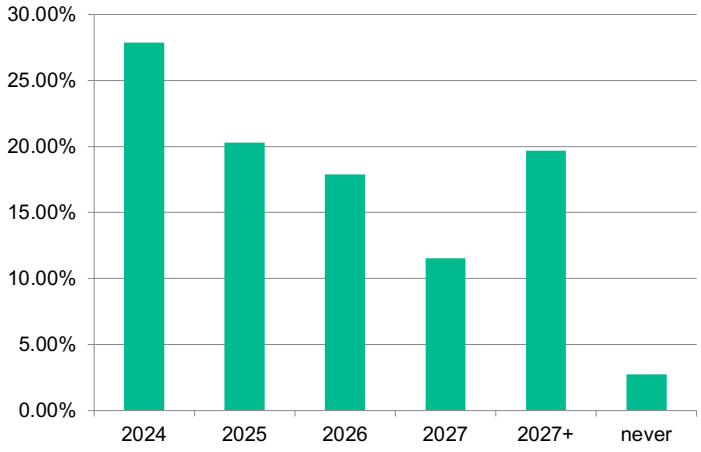


Yet not all experts are convinced approvals will be as plane sailing as the findings suggest, with Bikash Chatterjee CEO, Pharmatech Associates, forewarning that scheduling designation may be the drag factor on adoption: *"I do not think the FDA will approve a psychedelic in the next decade because most of these are classified as schedule 1 drugs, which are drugs that have no therapeutic benefit. DEA is notoriously conservative in changing their designations unless there is an overwhelming need to address. We have seen this with marijuana and CBD-based therapies today. Getting two federal agencies to collaborate and coordinate their programs is not quick nor easy".*

MRA vaccines

In contrast to the surge in excitement across psychedelics the response to the question around RNA cancer vaccine approvals has been much more subdued with 70% expecting a first approval in 2025 or thereafter, with some 20% expecting an approval to take to 2028 or longer. This perhaps reflects that, despite the whirlwind approvals we saw for Covid 19 mRNA vaccines, these therapies will be approved using standard oncological timelines and also the fact that only a limited number are now in early-stage trials. Yet despite these longer timelines, we do foresee a much more significant and profitable role for contract manufacturers. In fact, CDMOs and supply side partners for specialist ingredients like lipid-based excipients have been and remain integral to the global supply network for these innovative technologies. Therefore, it is anticipated will RNA be a highly lucrative therapeutic area for contract partners that invested early, with Covid production continuing for the next few years, and then gradually being replaced by the outsourced needs of oncological – and other target areas – as trials advance.

Figure 5. In your opinion, in what year will the FDA approve the first cancer immunotherapy mRNA vaccine



Analyst perspective mRNA oncology vaccines: *"We don't expect any sales next year and, despite the covid based interest, these trials are now running at the more standard oncology pace, with the most advanced candidates still only in early phase II. So right now, it's still very hard to get a clear picture on what their future sales potential is?"* Quentin Horgan, Associate Director, Pharmaceutical Data & Analytics at GlobalData.

Growth potential

Economists and analysts globally expect 2023 to be tough year for the majority of sectors – due to the tightening of long loosened monetary policy and energy supply disruption – with G7 nations raising interest rates quickly and a highly likely recession in many countries. Yet, despite this pessimistic outlook, pharma could potentially buck wider economic trends. Contract services in

particular remain in extremely high demand and with biotechs still sat on record level of cash [see Brian Scanlan's article in this report] – they cannot sit on this indefinitely – there is likely to be sudden rush of development inside the next 18-months.

So what do the results of the global survey point to in such a dichotomous and ambivalent business market?

Last year was the first year in the survey's history that the United States had topped the prospective 'growth potential' category, surpassing both India and, historically the surveys' fastest growing country, China. What is notable from the findings this year is that all countries have improved their growth potential scores – suggesting the industry is much more positive about its prospects in 2023. In fact, growth scores this year are by far and away the highest in the surveys' history – which many may find surprising.

The most notable changes are that the United States has cemented its surprise lead from last year and now has one of the highest growth scores in the survey's history. China by contrast, although posting a strong growth potential score, has a fallen a little behind the other two members (USA and India) of the big three. Significantly, the UK has improved its growth potential score again – to a pre-Brexit level – coming in narrowly behind Germany who are the other big mover in 2022. The UK currency Sterling has been progressively weakening in 2022 – even presenting a short-lived bond market crisis in late September[12] – and this may be contributing to an improved exports outlook for the country's pharma manufacturers. Political instability of course continues with, at the time of writing, the leader of the Country past October 28th unknown[13].

Overall, the growth potential scores – which are ultimately a measure of confidence – have increased dramatically and it may also perhaps hint to a globally inflationary market where values will almost certainly rise quickly, however, whether this also reflects inflation adjusted growth for pharma remains less clear.

Dollar strength question marks

One of the interesting economic side-effects of inflationary uncertainty is that the United States Dollar has strengthened against virtually all other major currencies – meaning manufacturing options in the country have become more expensive to overseas companies and potentially making manufacturing and contract services options outside the US more appealing to US-based companies (at least in the short term).

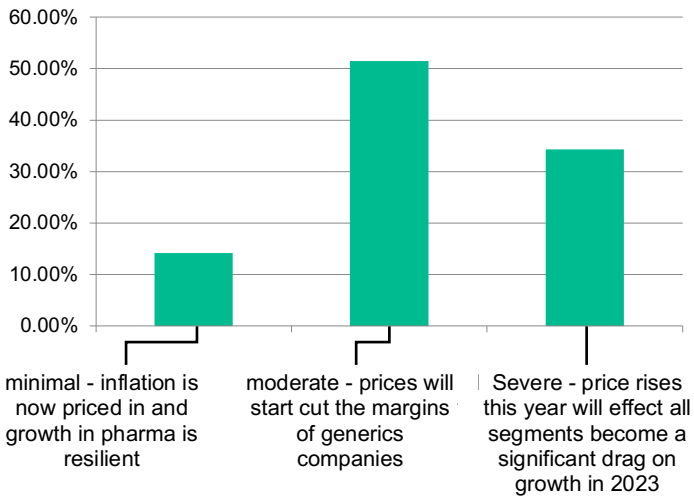
Figure 6. 2022 Changes in score and 2022 score (1-10) by region.

Country	2022 change in % score	2022 score (1-10)
USA	13.7%	8.5
India	9.9%	8.2
Germany	**32.1%**	8.1
China	11.7%	8.1
UK	**35.2%**	7.8
Italy	**30.1%**	7.0
France	**23.2%**	6.9
Japan	8.5%	6.9
Switzerland	16.4%	6.8
Korea	7.0%	6.6
Rest of Southeast Asia	18.0%	6.5
Rest of Middle East & Africa	**21.9%**	6.3
Spain	0.9%	5.6
Singapore	5.5%	5.6
Saudi Arabia	8.0%	5.4

Inflation concerns in 2023

The majority of the industry, while still struggling with higher costs globally, do predict that inflationary pressures will potentially ease in 2023, with 'moderate inflationary concerns' expected by 52%. However, perhaps reflecting the uneven nature in which it has hit markets and the uncertainty of war and growth, 34% still expect inflation to remain severe next year. In fact, just 14% believe inflation is now fully priced into markets, suggesting some severe marginal pains for cost sensitive manufacturing such as generics. The expectation then is that there will be further acquisitions for generic and low margin manufactures of ingredients, with countries in Eastern potentially very vulnerable and exposed to energy price rises. For innovative pharma, however, the expectation is that much of these prices rise can be absorbed and passed on in the case of contract manufacturers.

Figure 7. What will be the impact of global inflation on Pharma in 2023?



Overall competitiveness

Mirroring the findings in the growth potential category, the same top five remain at the head of the rankings for 'overall competitiveness' – with the UK seeing the biggest swing change in fortunes. The UK has risen from 8th place last year to a very credibly joint third, level with Germany and ahead, surprisingly, of China. As will be discussed in an article from BioPlan Associates later in the report, China is facing sizable drag factors on its economy from an overheated property sector that has built up into a slow-moving financial crash[14]. So we are potentially looking at lower investment, significantly lower biotech valuations and growth in the next year as its financial institutions look to adjust and cleanse the system of financial contagion. Looked at holistically, this means a slowing local biotech and innovation market, and stalled growth in pharma ingredients – it should be noted however, that the country still remains the world's largest ingredient production centre. The largest players in China targeting western markets may well be better able to weather the domestic storms. It is also notable that companies like Pharmaron, Asymchem and WuXi AppTec having reported truly staggering rates of growth[15,16,17] in the last few years and are investing in facilities globally.

Finished Product Manufacturing Quality

The top four countries in the ranking retained their positions but in a different order to 2021– albeit very close in terms of score. Notably, the USA continued with the strength it saw in other categories to once again move in front of Germany with a 7% rise to an all-time high score of 9. Perhaps more interesting, the UK continued its gains from 2021 and this year supplanted Japan as the 3rd place country for the first time. The UK, USA and Germany all increased their scores from 2021 – with the UK's reputation also improving by an impressive 7%. However, Japan's score fell slightly (4%) on 2021 and the country has now fallen back of the new 'big three'. The biggest rise in score was from India and China with the countries' reputations improving by nearly 8% and a massive 20.7%. Even accounting for the large relative number of Indian responses and China's subdued scores during the pandemic, these are very significant increases and could potentially mark the beginning of new era for the survey with India and China much more aligned to Western scores. Looked at collectively, it's clear, this year's executives are more positive in their outlook for pharmaceutical quality than in any previous year – suggesting as a whole the industry believes quality initiatives are improving standards globally.

Figure 8. Overall competitiness

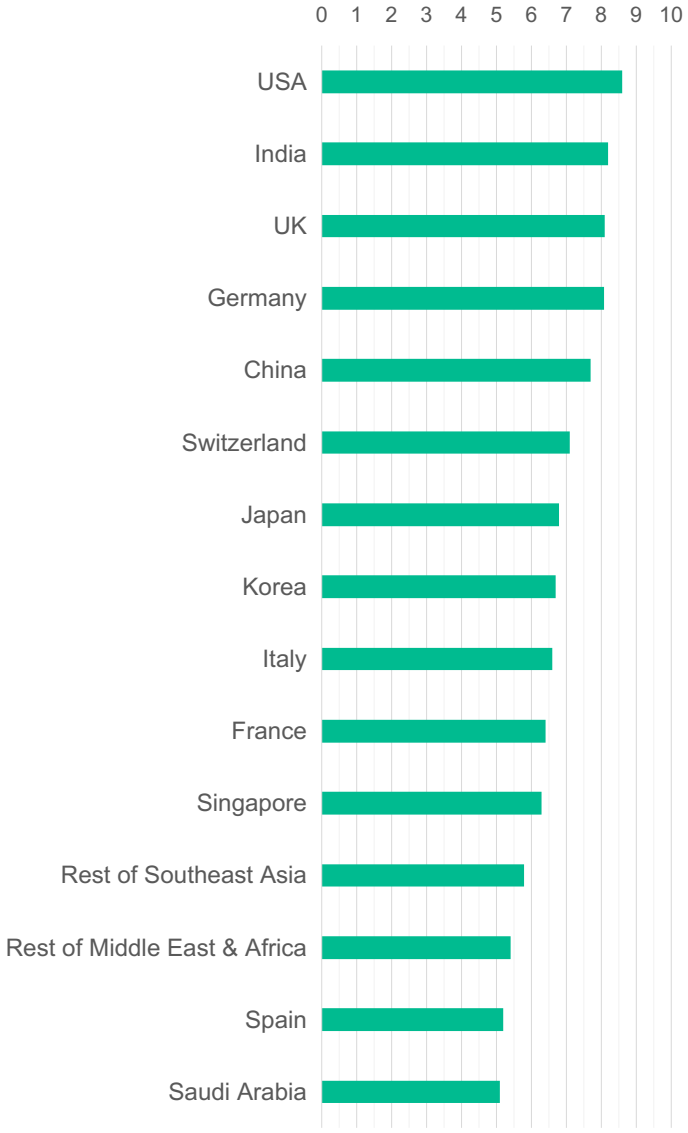
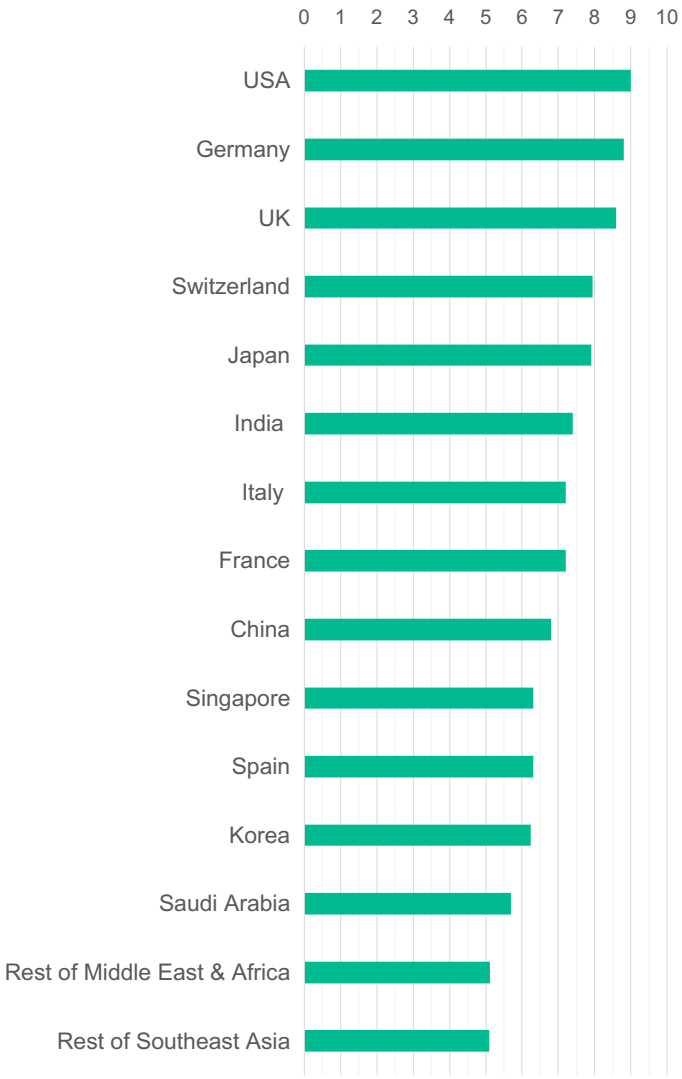


Figure 9. Finished Dosage Ranking



India is now exactly level with both Switzerland and Japan, placing only narrowly behind the United Kingdom. Even accounting for a large number of Indian responses (29%) this represents a huge shift in perceptions over the last two years, with a rise of around 25%.

API Manufacturing Quality

The scores across API manufacturing quality have remained consistent year-on-year with only a limited deviation from the 2021 score – with three notable exceptions.

Bucking the trend we see in other areas of the CPHI Annual Survey, Germany has once again retained its spot at the top of the rankings and has opened up a wider lead over the United States. Germany has seen a year-on-year rise of 6%.

The giant manufacturing hubs of India and China, however, have seen by far the biggest improvement in scores. India has further built on it gains in 2021, seeing a huge 15% year-on--year improvement. In fact, it is the first time in the surveys' history that an emerging pharma economy has drawn level with major Western pharma nations on quality of API manufacturing. India is now exactly level with both Switzerland and Japan, placing only narrowly behind the United Kingdom. Even accounting for a large number of Indian responses (29%) this represents a huge shift in perceptions over the last two years, with a rise of around 25%. The sudden increases in scores for API quality may be an indirect reflection of increased demand in the last two years as well, with Indian based API manufacturers quietly growing at 15% CAGR for the last few years[18]. Further, the United States Pharmacopeia reported this year that over 80% of APIs used in essential medicines are manufactured overseas, with Indian sites dominating. According to the USP, of the 342 manufacturing facilities worldwide with more than 10 active US-approved API products, more than half are based in India. Of those with more than 30 active US-approved API products, India accounts for 65%[19].

China, however, has seen an unprecedented surge in reputation for API manufacturing, seeing a massive 25% improvement in 2022 and bringing the country in line with quality scores of manufacturers in Italy and France. It is difficult to account for this shift or to pinpoint any specific indicators that might have led to such a turnaround. With 2021 being the notable exception, China has consistently seen steady and large increases in its scores over the last five years. It will therefore, be interesting to see in 2023, if this is indeed a landmark moment for pharma in China.

The other notable finding is that overall, all country confidence, has risen for a third successive year reaching its highest overall level – meaning the industry is now more confident in API manufacturing quality than at any point in the last 6 years.

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. What is extremely impressive this year is that with exceptions of moderate falls for Spain and Korea all countries have improved their scores – some dramatically so. India and China have fully recovered from the Covid slumps and are once again recording double digit improvements – most significantly they now rank alongside the majority of Western European nations for overall score. This year, is perhaps therefore, a watershed moment for both countries' rankings as major pharma economies – having now equalled the scores of most of Europe, with quality scores on average narrowly behind and growth ahead.

At the top of the table both the United States and Germany have also recorded double digit improvements, but the UK, has recovered its relative ranking to lofty highs not seen since pre-Brexit and, for the first time, has ranked higher Japan.

Most of the improvements seen in each countries scores relate to improved perception of quality across the industry, with growth prospects also holding up extremely well considering the wider macro-economic conditions.

In fact, the overall **CPHI Pharma Index** has risen by a remarkable **8.2% in 2022** – again the largest single year gain on record.

Figure 10. API Quality Ranking

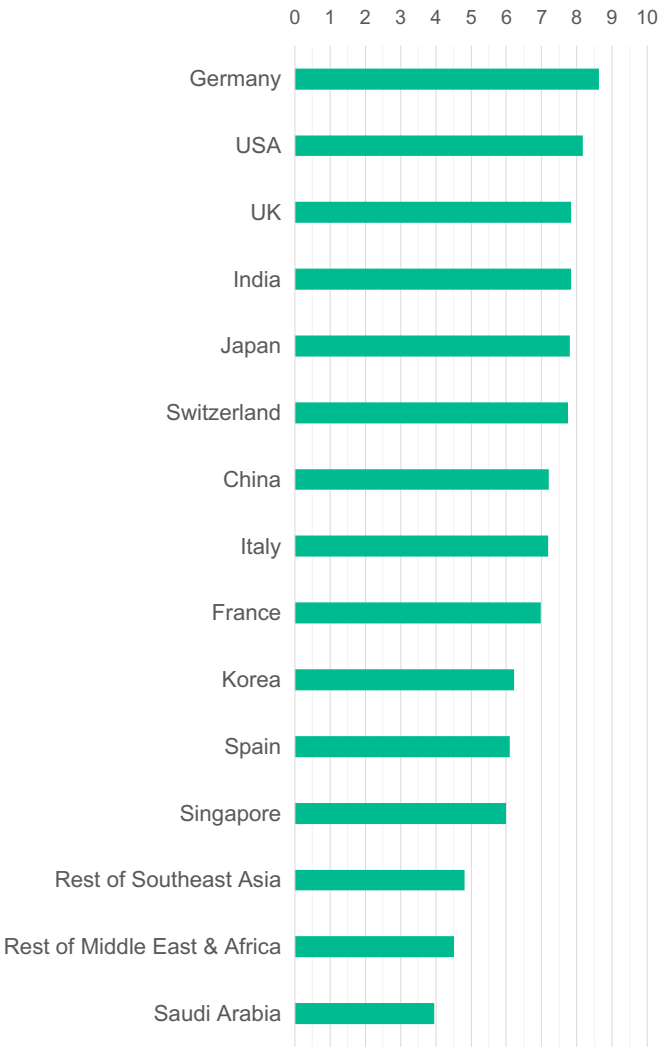


Figure 11. CPHI Pharma Index: average over 5 categories

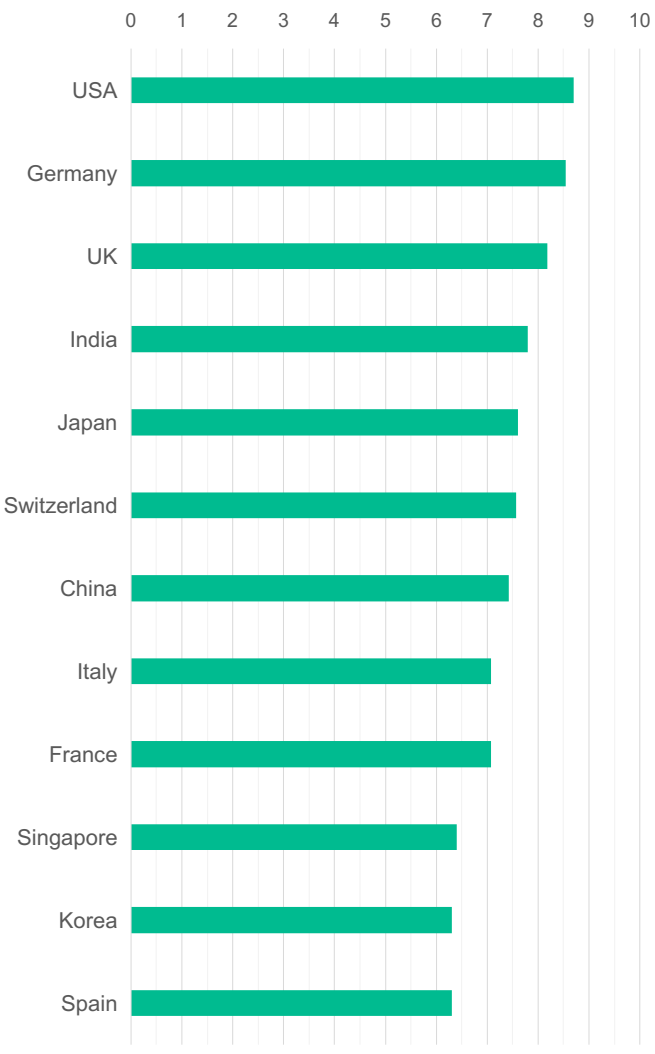


Figure 12. CPHI Pharma Index by category & year-on-year change

Country	Finished Dosage	API	Competitiveness	Knowledge of professionals	Growth Potential	2022 % change in score
USA	9	8.1	8.6	9.3	8.5	**11.82%**
Germany	8.8	8.6	8	9.2	8.1	**16.19%**
UK	8.6	7.8	8.1	8.6	7.8	**18.55%**
Switzerland	7.95	7.7	7.1	8.3	6.8	**8.29%**
Japan	7.91	7.8	6.8	8.6	6.9	**4.56%**
India	7.4	7.83	8.2	7.4	8.2	**13.62%**
Italy	7.2	7.1	6.6	7.5	7.0	**7.43%**
France	7.2	6.98	6.4	7.9	6.9	**7.37%**
China	6.8	7.2	7.7	7.3	8.1	**15.77%**
Singapore	6.31	6	6.3	7.8	5.6	**5.46%**
Korea	6.24	6.2	6.7	5.8	6.6	**-3.07%**
Spain	6.3	6.1	5.2	5.7	5.6	**-7.37%**

Contract Services section

2022 has been the year of contract manufacturing in many ways, with CDMOs greatly benefiting from Covid contracts, private equity renewing and strengthening its interests and predicted growth rates that seem to defy the present realities of global economies. In fact, Brian Scanlan will outline a case of significant growth for at least the next 24-months later in this report.

There is a question as to how CMOs focussed on generics or older drugs approaching their patent expiration will fair.

Figure 13. Will macro conditions create a two tier pharma manufacturing market in 2023: with high growth for companies focussed on innovation v generics

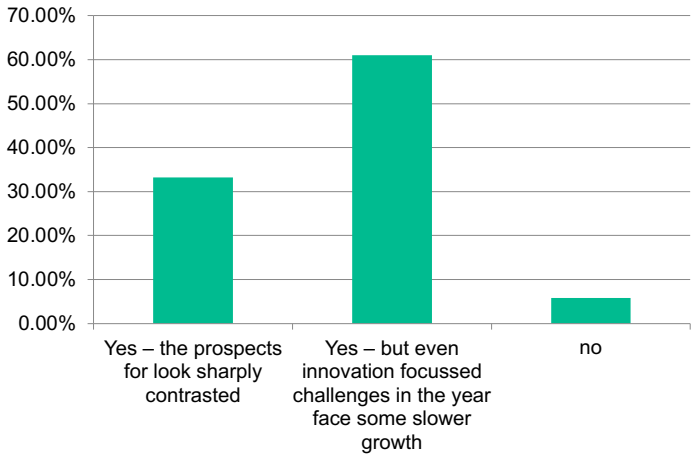
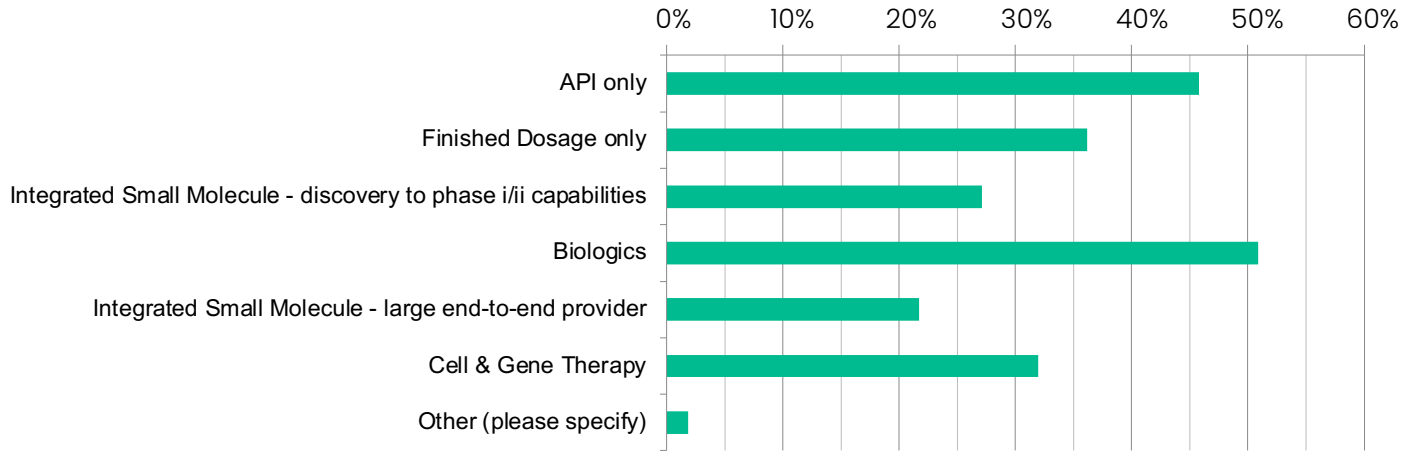
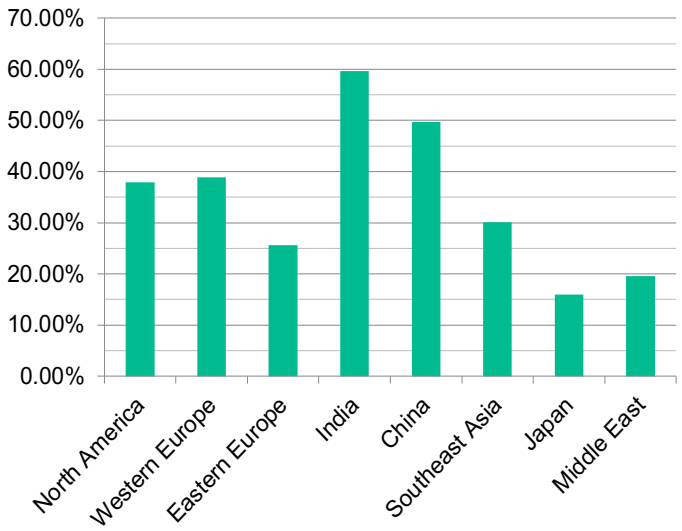


Figure 14. Which type of CDMOs will see capacity constraints in the next year i.e. demand exceeding available capacity? (tick as many as appropriate)



CDMO capacity, particularly with Covid contracts continuing, has remained an issue through the last 12-months – with access to commercial scale production most strained. Looking ahead for the next 12-month, the industry again identified biological CDMOs as those most likely to see the largest capacity constraints, with API CDMO resources also potentially strained. However, reversing the trend of recent years, Cell and gene therapy capacity constraints appear less of concern for executives – which may reflect both the building of increased capacity and also a slowing of the development pipeline.

Figure 15. Manufacturers hailing from which regions/countries will be the biggest beneficiaries of changes in supply chain/geo-sourcing strategies in next 3-years? (tick as many as appropriate)



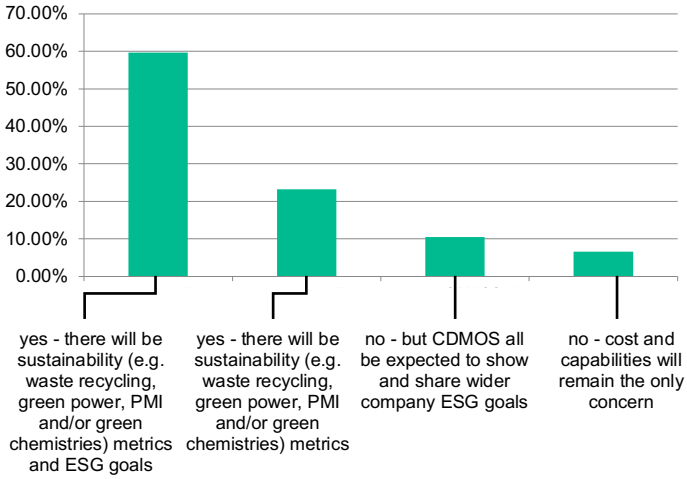
One of the most prominent and often highly politicised debates of the last 18-months have the discussions around global reshoring and geo-sourcing strategies. In last year's report, both the United States (58%) and Europe (60%) were identified as the biggest winners of macro changes in manufacturing strategies [over the next 12-months]. However, this year, when we asked for a slightly longer-term outlook – over the next 3-years – we saw a very different perspective. The scores the United States and Europe have both fallen by some 50% and India emerged as survey's clear winner. Executives believe India (60%) will see the greatest benefits from shifts in manufacturing supply chains, but surprisingly, China (50%) has also recovered much its Covid loses and, in the medium term, is once again seen as an extremely strong manufacturing hub. This perhaps poses the question as to whether the market will sustain and materialise ingredients manufacturing moving in the United States and Western markets. It perhaps points to a continuation of the global model we had seen pre-covid with only some essential medicines securing regional and national manufacturing arrangements.

The sustainability findings

The *CPHI sustainability sentiment index* points to almost universal consensus that environmental credentials are now integral to all supply chain decisions. 95% of industry executives suggest it is either 'important' or 'extremely important' (52%) to have visibility on supply chain partners. Looking further ahead, within the next five years, 83% believe specific 'sustainability metrics' (e.g. full waste recycling, green power percentage, low PMIs, and green chemistries) will be implemented within all CDMO contracts – suggesting the industry must accelerate its drive towards modern manufacturing and more efficient chemistries.

In fact, nearly 60% believe CDMOs will be required to provide their partners with both 'sustainability metrics' for projects and specific corporate 'ESG goals' within contracts.

Figure 16. Looking 5-years ahead, will innovators require CDMOs to implement sustainability goals as part of new contracts.



For an industry used to selling on 'the speed of development' and/or 'cost', this will have profound implications for how contract service providers go about marketing their services to innovators, as well as potential infrastructure planning. The consensus among the industry is that investments need to be made now in modern manufacturing to prepare for these shifts.

Figure 17. Is it important that you have visibility on supply chain partners' sustainability record?

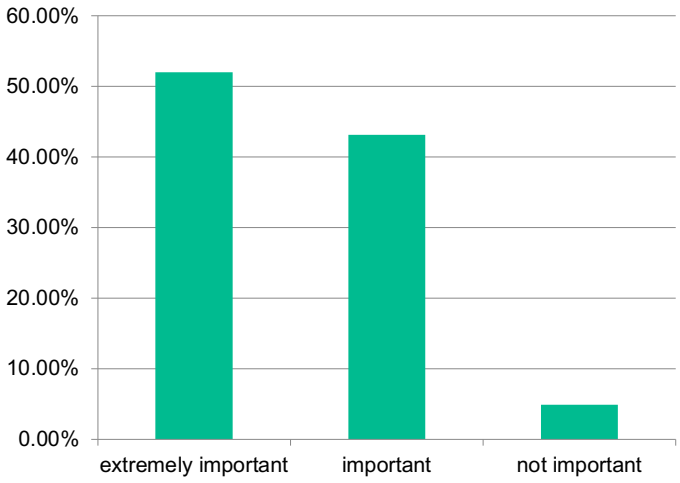
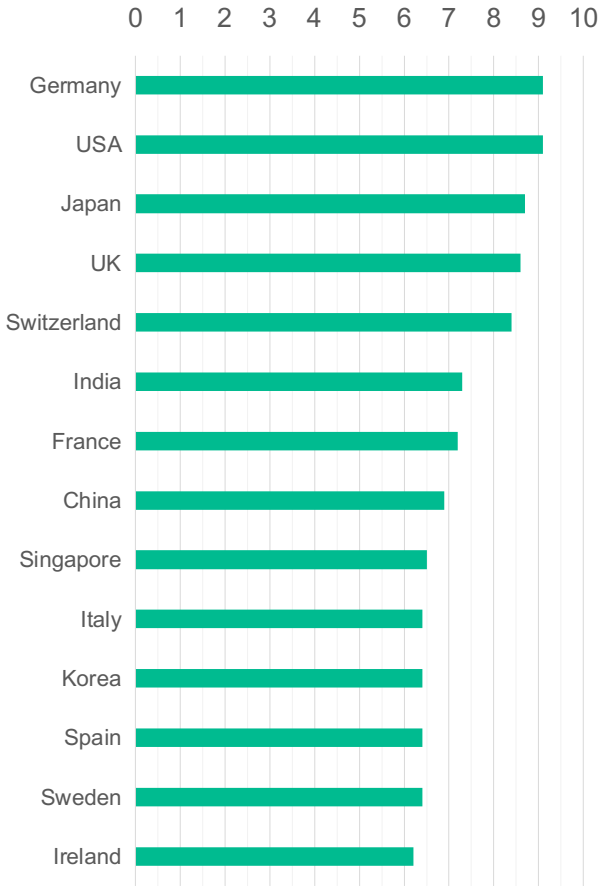


Figure 18. Biologics Quality



Biologics section

Biologics Manufacturing Quality

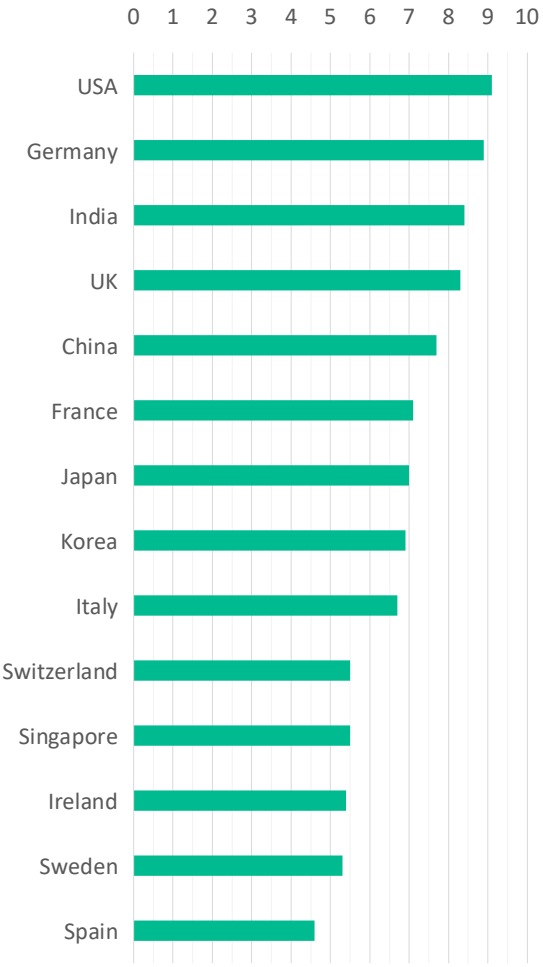
Biologics scores have increased across nearly all countries with the top two, Germany and the United States, now both scoring 9.1 – the highest quality score of any category in the surveys' history. The United Kingdom has also further improved on its gains in 2021 and is now ahead of Switzerland and closing on Japan – all of the top 5 nations scored extremely strongly. Yet despite these impressive improvements, the surges from India and China are by far the most significant changes. India has surprisingly overtaken France to lead 'the best of the rest', while China has seen a dramatic improvement rising from the foot of the table to a very respectable score of 6.9.

Biologics Manufacturing Growth

In terms of biologics growth potential, Germany and the United States have further improved their scores to circa 9, with India and China both showing robust growth potential – perhaps reflecting the demand for biological Covid vaccines produced in each nation alongside the emerging biopharma industries here. Of the other major nations, the

United Kingdom again saw significant improvements in its score, while for reasons unknown, Ireland's scores have collapsed from 7.0 to just above 5.

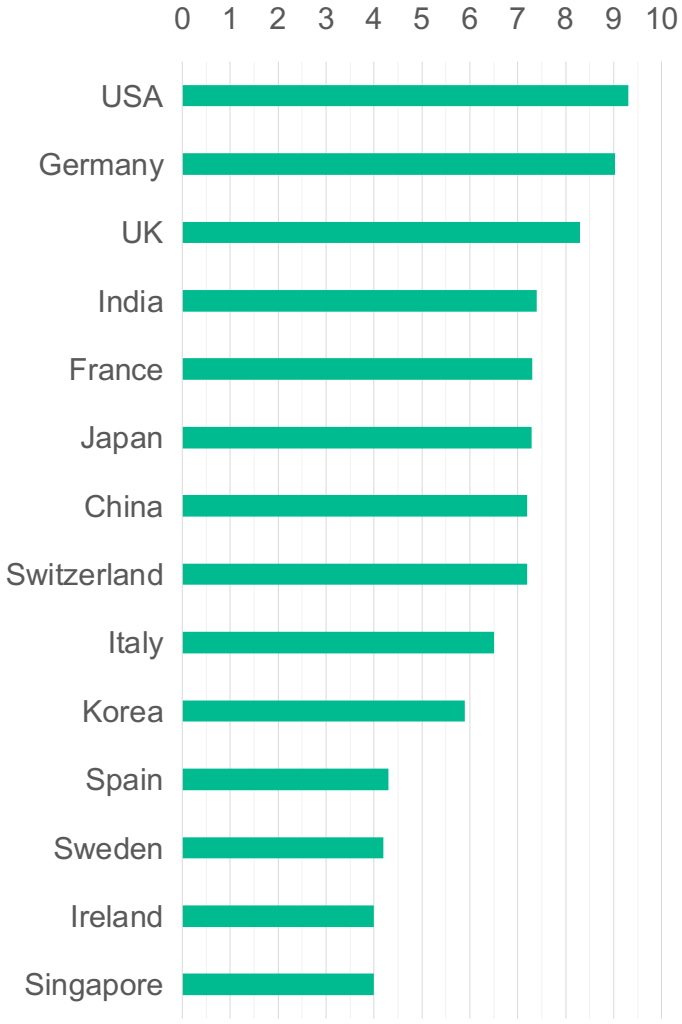
Figure 19. Biologics Growth Potential



Bio Innovation Index

There were several big and often surprising changes recorded in the scores for biologics innovation. The first big unsurprising, if impressive, change was to see the United States record again a new record score for innovation in its biologics market. What was surprising however, was that its impressive gains were matched by Germany with both countries scoring 9 or above. In another boon for UK biopharma the UK shot up the perception table and has replaced Switzerland – which has suffered another significant fall – in the big three. Once again, the other big emerging winners were India and China whose scores now all closely align with those of France, Japan, and Switzerland.

Figure 20. Bio Innovation Index



Additional findings

Figure 21. Will a shortage of experienced CMC personnel continue be a major challenge for the industry in the next 2-3 years - ?

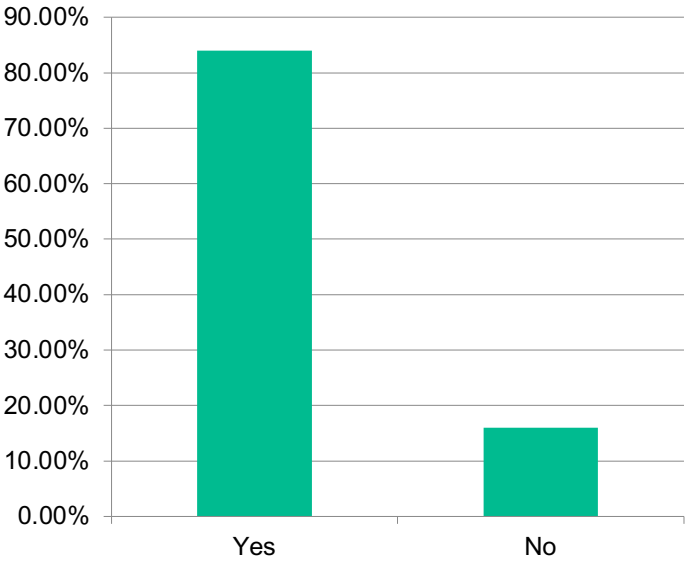


Figure 23. How many FDA drugs do you think will get approved in the calendar year 2023?

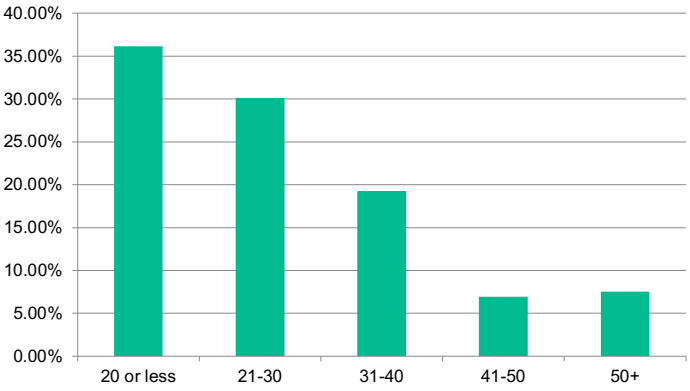
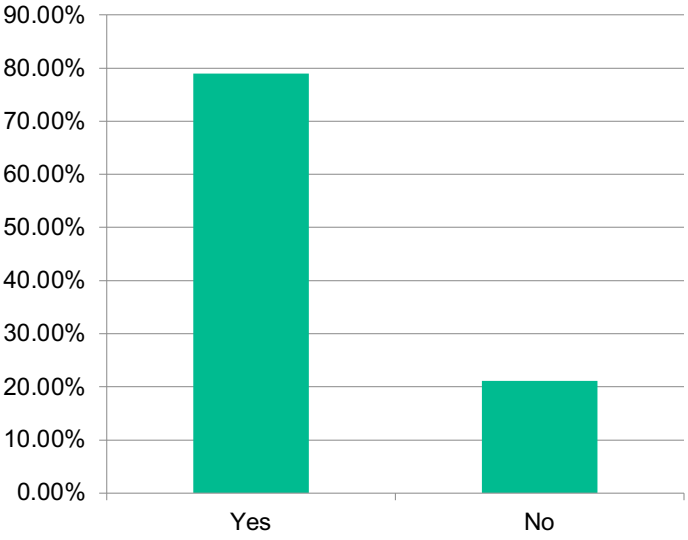


Figure 24. Will remote facilities monitoring be a standard requirement as part of client audits for CDMOs in 2027?



Additional findings Cont.

Figure 25. Which of the following digital technologies will deliver transformative change within pharma in the next 5-years?

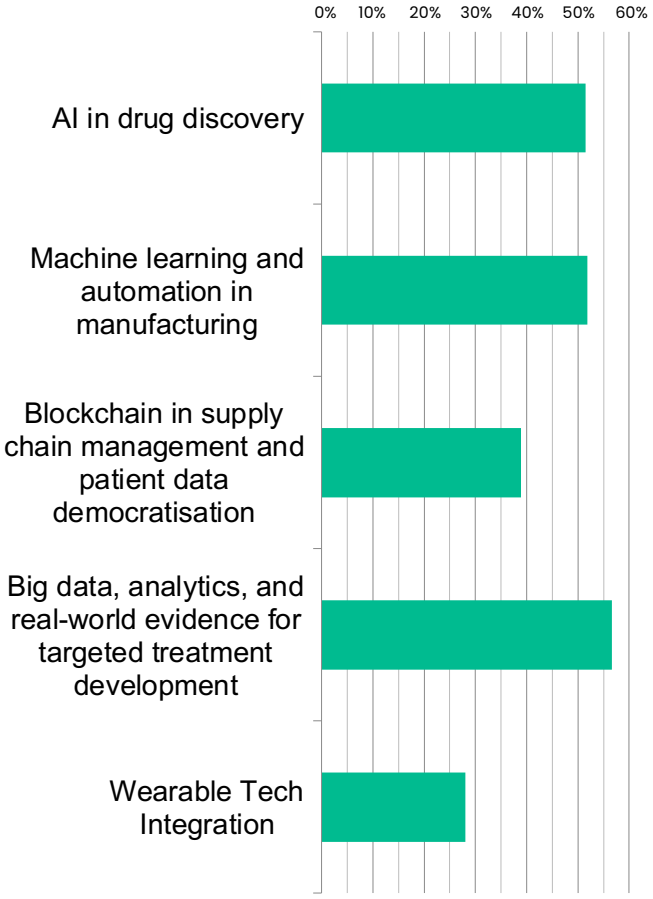


Figure 26. Sold Dose Innovation Rank

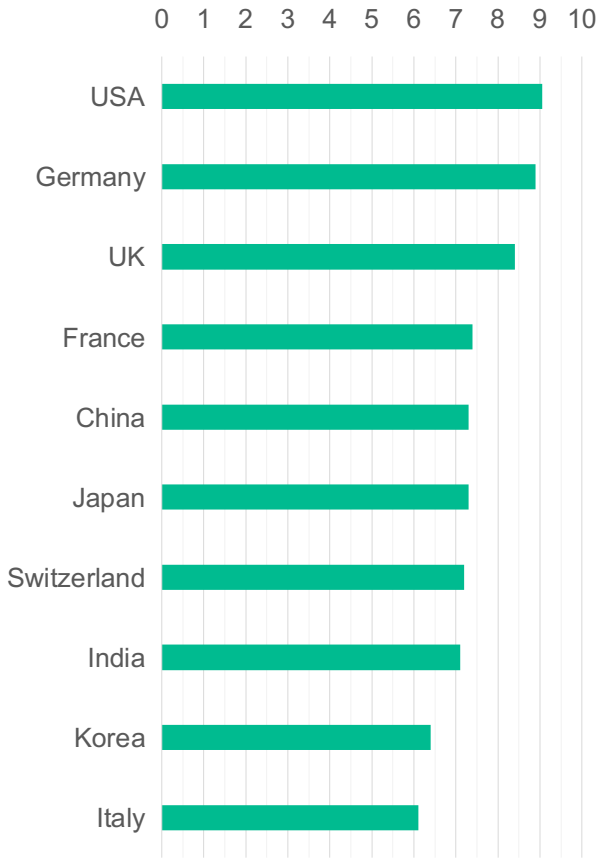


Figure 27. Drug Delivery Innovation Index

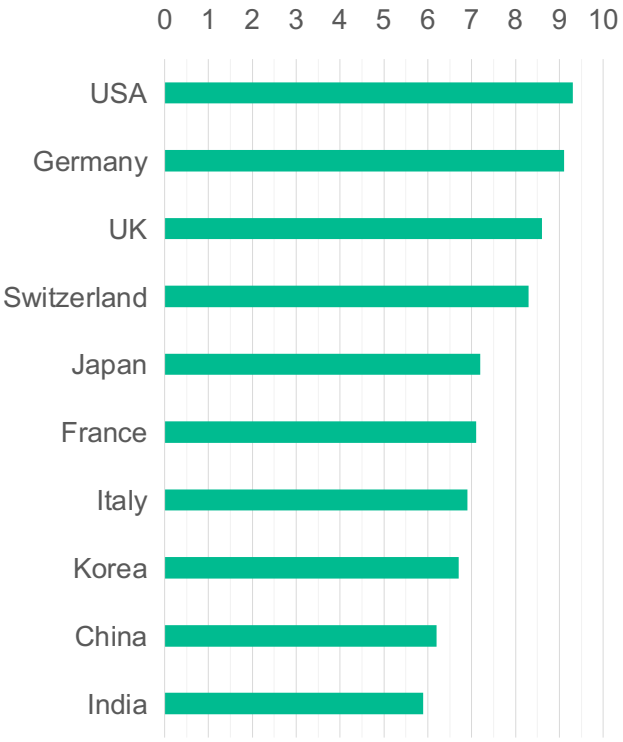


Figure 28. (question answred only by pharma/biotech, CMC consultants). Are you or supply your partners investing in next generation manufacturing - i.e continuous processing (bio or small molecule), flow chemistry, 3-D printed dosages or similar next

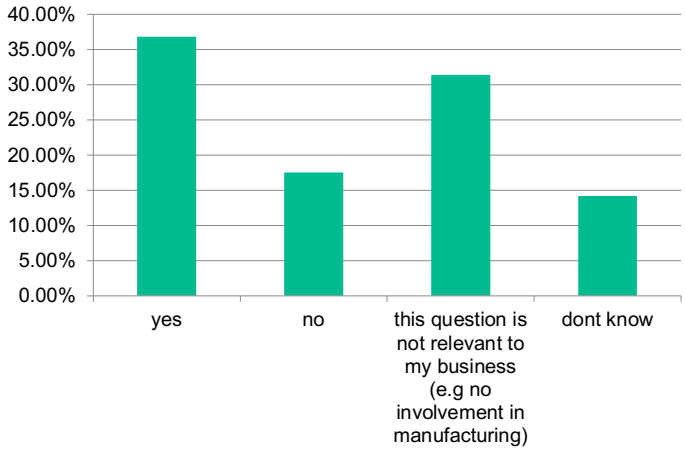


Figure 29. When do you think the next novel excipient will come to market?

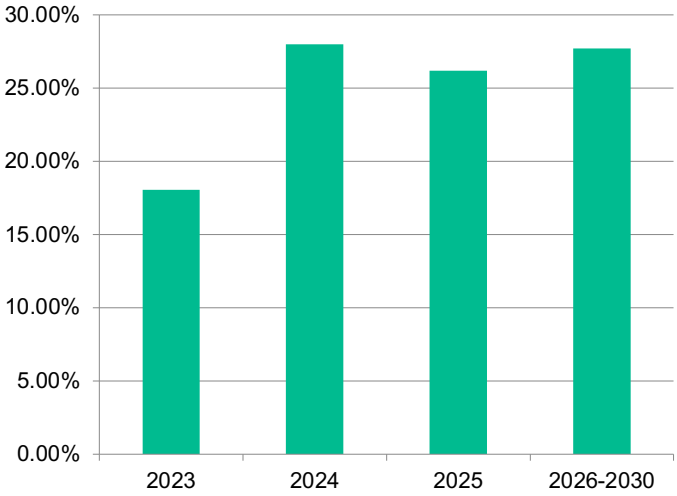
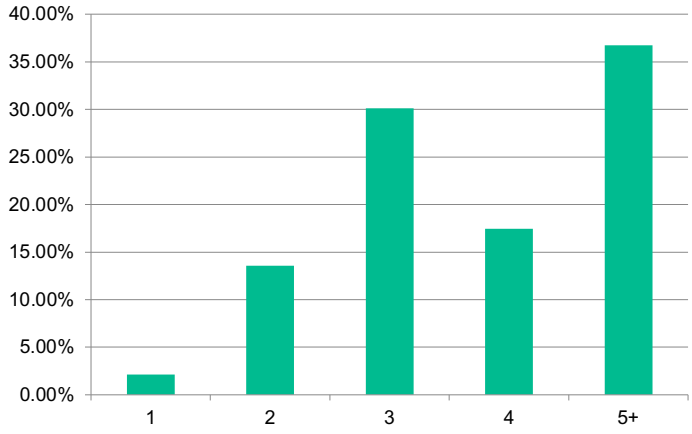


Figure 30. Now that the new FDA pilot programme has successfully launched (with 2 excipients available for review per year), how many novel excipients will have made it to market in five years time (2027)?



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Part 1

Biologics

CPHI Frankfurt 2022

Joel Ranck,
Market Analysis, BioPlan Associates

Key Bioprocessing and Biopharma Trends

Results from the BioPlan Associates Annual Report and Survey of Biopharmaceutical Manufacturing Production and Capacity

The biopharmaceutical industry continues to grow and shows remarkable resilience in adapting to supply chain challenges and improvements in efficiency as it recovers from the Covid-19 Pandemic. This year, suppliers reported an average growth of 24.5%, with some segments, such as single-use devices seeing annual growth exceeding 35%.

As part of the Annual Report and Survey on Biopharmaceutical Manufacturing Capacity and Production from BioPlan Associates, we surveyed more than 140 decision-makers within bioprocessing organizations, both developer and contract manufacturing organizations (CMOs), involved in bioprocessing activities in 25 countries. This article, produced exclusively for the **CPHI Annual Report**, presents a detailed analysis of the findings and predicts the key trends for the future of bio manufacturing.

The biopharmaceutical industry continues to grow and shows remarkable resilience in adapting to supply chain challenges

There were a number of notable trends in this year's research that stood out to us:

- **Industry growth** over the past 10 years has consistently pegged at ~12% - 13% annually, nearly doubling every ≥5 years. This year's growth during Covid-times has, for some segments more than doubled that growth.
- **Efficiency and productivity** improvements seen in bioprocessing as titers and yields continue to incrementally increase. 2021 showed the lowest average cost-per-gram on record.
- **Process automation** is now a critical element and is being built into bioprocessing equipment.
- **International biomanufacturing** and offshoring continue to grow worldwide, especially in major markets and Asia. This now includes an upcoming wave of facilities coming online for Covid-19 and other pandemic and biodefense product development and manufacturing.
- **Growth of contract manufacturing** facilities and capacity provide greater outsourced options.
- **More cell and gene therapy facilities** and products, including commercial manufacturing.
- **Increased reliance on single-use** vs. stainless steel-based processing including fewer new commercial scale stainless steel-based facilities.
- **Hiring challenges** in biopharmaceutical manufacturing continue to create significant bottlenecks. Finding qualified staff at global facilities continues to be a problem for over 50% of the industry.

Impact of Covid-19 on supply chain

COVID-19 changed the landscape of the industry and although we generally see an easing of supply problems, we continue to see challenges more than 2 years after the start of the pandemic. Overall, supply chain problems and sales are up, as are manufacturing costs.

With the increases in both demand and in supply chain problems, we see that manufacturers' fears of not having access to their supplies are impacting the entire pipeline. Overall, vendors are working to expand and improve customer relationships to reduce fears and address supply chain problems. Developing stronger relationships and improving supply chain security will likely improve the industry's supply processes, in the event of future.

Figure 1: Covid Impact on Suppliers: Bioprocessing Supply Chain Concerns

	2022	2021
Time Spent addressing customers' supply chain concerns	81.3%	70.8%

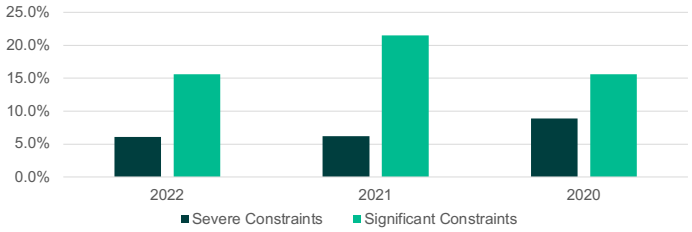
5 year predicted capacity constraints decrease

Despite Covid, we see a continuing trend toward *decreasing* expectations for future capacity constraints. Further, the expectation of 'No' capacity constraints over the next five years remains relatively the same as last year continuing an overall average of around 20% for the past five years.

The 5-year forward projected perception of fewer 'Severe' or 'Significant' constraints and overall continued lower perception in reporting of no constraints suggests that the industry does not see COVID-19 impacting capacity over this timeframe. With experience, the industry has proven it is able to effectively meet ever-increasing future capacity demands by using existing equipment and capacity, bringing more flexible single-use systems online, leveraging contract manufacturing capacity, and using modular construction to speed timelines.

Industry response to the COVID-19 pandemic is of course resulting in significant increases in related vaccines and biotherapeutics manufacturing. These needs for large expansions in capacity, combined with normal industry growth, could potentially result in a capacity glut at some larger scales in the coming years.

Figure 2: Projected Capacity Constraints, in 5 years, 2020 - 2022



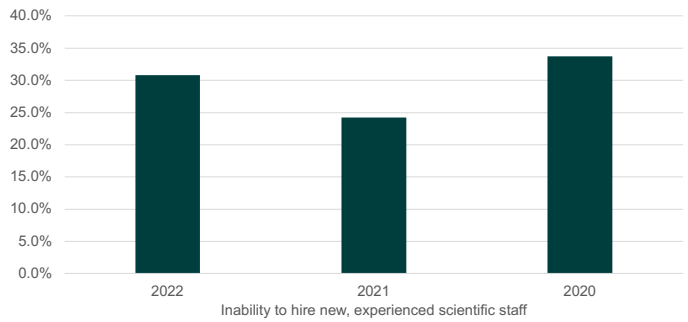
	2022	2021	2020
Severe Constraints	6.1%	6.2%	8.9%
Significant Constraints	15.6%	21.5%	15.6%

Inability to hire and retain experienced staff creates capacity constraints

The issue affecting the industry most acutely is the lack of experienced technical and production staff. An "Inability to hire new, experienced technical and production staff" was highly important to respondents with 34.2% of respondents indicating that this was a major constraining factor for growth, up from 2021. Further, the concern for retention of experienced technical and production staff also went up 10% this year.

The growth of new and existing facilities is making it difficult to retain experienced scientific and manufacturing staff. Some of this is due to experienced staff starting to retire and a shortage of available experienced bioprocessing professionals. Also, the rapidly growing cellular and gene therapy sectors and now industry responses to the COVID-19 pandemic are further increasing the demand for experienced staff.

Figure 3: Factors Likely to Create Capacity Constraints Over 5 Years



	2022	2021	2020
Inability to hire new, experienced scientific staff	30.8%	24.2%	33.7%

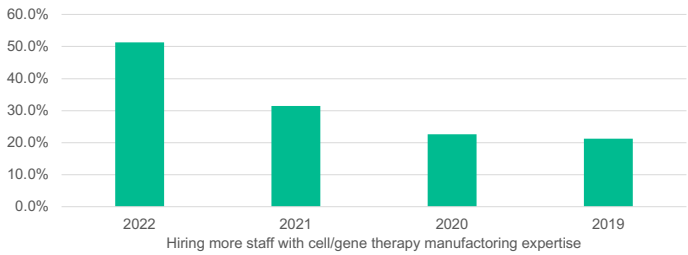
Demand for more cellular and gene therapy expertise

For 2022, we see a nearly *20-percentage point increase* in the percent of facilities having problems "Hiring more staff with cell/gene therapy manufacturing expertise" over 2021. This trend may be even more critical to larger operations, closer to a commercial scale, because as companies scale up capacity or take on larger projects, they need even more qualified individuals.

BioPlan has long noted progressively worsening staffing shortages in the cellular and gene therapies areas. Hiring staff with expertise is now the number one most needed improvement in the cellular and gene therapies areas. Due to worsening staff shortages, many companies

report that it takes 6-12 months to provide needed specialized training. Even CMOs may not be a viable alternative for some, due to a shortage of CMO's with cellular and gene therapy capacity experiencing the same staffing shortages.

Figure 4: Factors Likely to Create Capacity Constraints Over 5 Years (2020 - 2022)



	2022	2021	2020	2019
Hiring more staff with cell/gene therapy manufactoring expertise	51.3%	31.5%	22.6%	21.2%

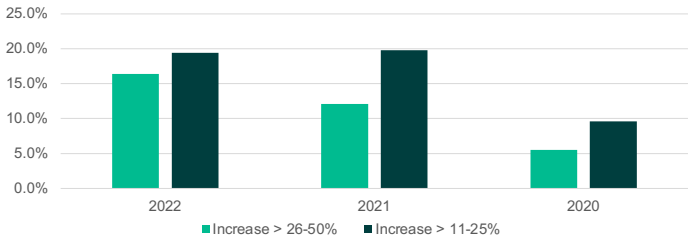
Spending on outsourcing to substantially increase

Many large biologics companies in China and India, as well as in other developing regions are preparing or developing commercial-scale biopharmaceutical manufacturing CMO facilities to serve domestic and regional needs. Some are targeting eventual full cGMP manufacture to supply Western markets or otherwise seeking Western clients.

We found that 35.8% of respondents will be *increasing* their spending on outsourced R&D or biomanufacturing over the next 12 months.

We estimate that, on average, budgets for outsourcing at individual facilities will remain relatively steady by a weighted average increase of 12.8% in 2022. These growth rates appear to show a continuing strong trend toward increasing outsourcing budgets. Although this general trend toward outsourcing has been evident over the past ~15 years, the Covid pandemic has solidified this shift.

Fig 5: Spending on Outsourcing Manufacturing or R&D, 2020 - 2022



	2022	2021	2020
Increase >26-50%	16.4%	12.1%	5.5%
Increase >11-25%	19.4%	19.8%	9.6%

Half of all vendors work to improve bioprocess automation

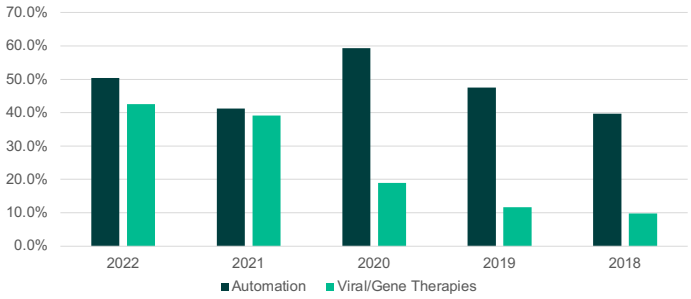
Automation is the hottest area of opportunity for vendors' new product development departments. Over half of suppliers to biopharma recognize that automation is critical if the biopharma industry is to continue maturing and optimizing bioprocesses.

Thus, when we asked suppliers and vendors about "NEW TECHNOLOGIES or NEW PRODUCT

DEVELOPMENT areas your company is working on today?" over half of vendors (50.4%) are working on "Automation" up by 9.2 percentage points from 2021.

Vendors are also focusing on creating new technologies or products related to "Viral/gene Therapies" with 42.6% of responding industry vendors signaling these are being addressed in R&D.

Figure 6: Top New Technologies or New Product Development Areas Vendors Working on in Biomanufacturing



	2022	2021	2020	2019	2018
Automation	50.4%	41.2%	59.3%	47.5%	39.7%
Viral/Gene Therapies	42.6%	39.3%	19.0%	11.7%	9.8%

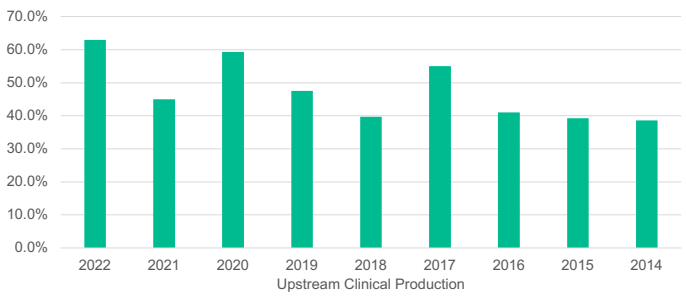
Nearly two-thirds of upstream clinical production uses single-use components

Single-use systems (disposable bioprocessing equipment) continue to gain acceptance in the industry due to their advantages for both CMOs and developers/manufacturers.

SUS devices can be implemented more efficiently, more rapidly, with fewer risks of quality problems, fewer up-front costs, and with much less required infrastructure, and smaller staff.

Across the board, we saw an increased rate of single-use products at all scales. Most notably the rate of single-use usage at 'Upstream Clinical Production' saw increased growth, with 62.9%, up from 45.0% in 2021. *This indicates that respondents expect that more than half of their upstream clinical production components and devices are single-use. Further, more than a fifth of respondents said that their facility only* used disposable devices for 'Upstream Clinical Production'.

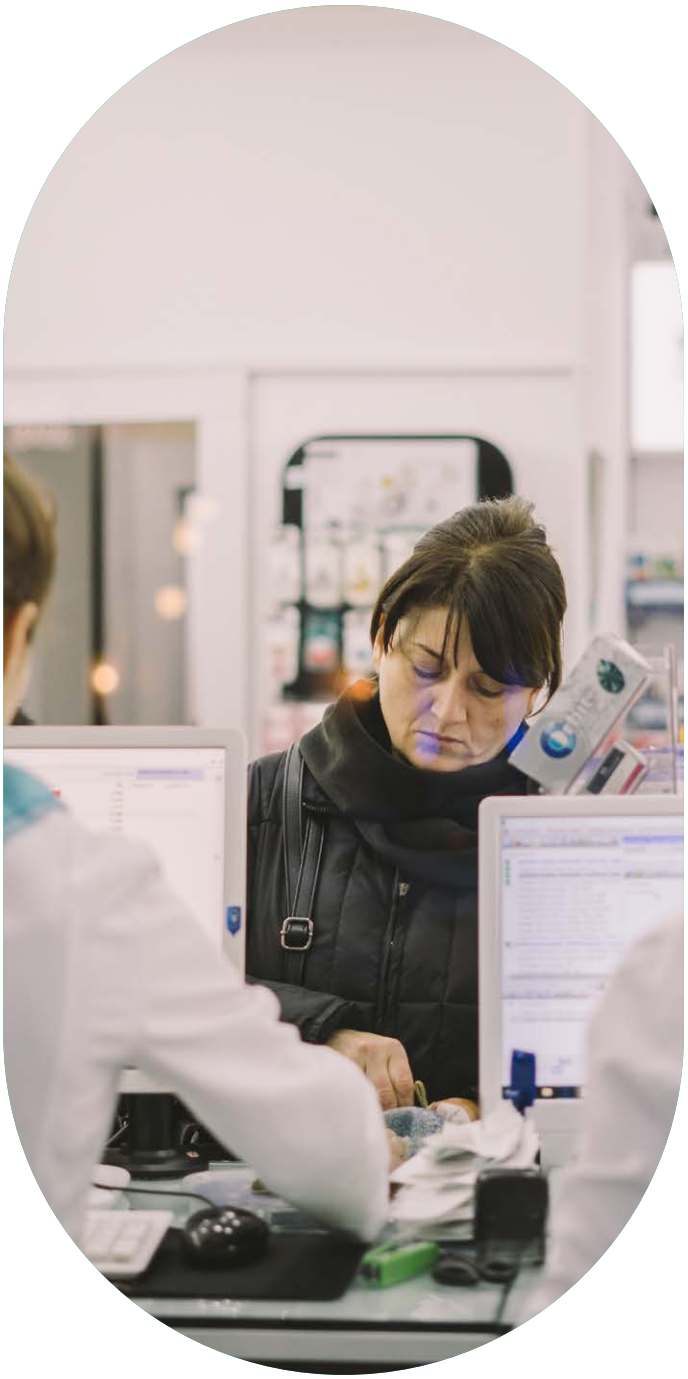
Figure 7: Average Estimated Percent of Manufacturing are Single-Use or Disposable



Upstream Clinical Production

2022	2021	2020	2019	2018	2017	2016	2015	2014
62.9%	45.0%	59.3%	47.5%	39.7%	55.0%	41.0%	39.3%	38.6%

Cited references Langer, E.S., et al. Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, April 2022, 500 pages see: www.bioplanassociates.com/19th



Trend insights Q&A with Eric Langer, Managing Partner at BioPlan Associates and CPHI Frankfurt team

CPHI: what is the implication for early phase innovators verses late phase innovators over the next two to three years (Note: we assume large and later stages projects wont struggle for future capacity but smaller earlier stage innovators will?)

EL: *"If you mean available capacity implications, there are likely sufficient bioprocess alternatives available at smaller (early) scale, including multiple CDMOs that are offering shorter wait times, strategies for using single-use technologies, especially at smaller scale, etc. Although sus devices have been in short supply during covid, this supply chain challenge is lightening up slowly. So over the next 3 years, we will be seeing a normalization of the supply chain, and additional build out of capacity."*

The real challenge will continue to be having access to human capital, trained and skilled staff with the quality expertise required to manufacture at GMP. Further, as demand for skills grow (with the growth of cell and gene therapy pipelines, and growth of Asia biopharma), the challenges of hiring and retaining good staff will become more acute.

Large-scale (late phase and commercial), will have similar challenges in terms of hiring, but there will still be options available for physical capacity for bioproduction, especially as covid challenges abate."

CPHI: Similarly, do we think development timelines will be slowed if innovators both struggle to access CMOs and they have limited in house resources (i.e. with bioprocess professionals in extremely short supply)? Could this slow approvals in the next two/ three years or will it just drive wages up and bring more people into the industry?

EL: *"The value and importance of novel therapies to healthcare and to investors cannot be overestimated. So when an innovative therapeutic is advancing in the pipeline, we will see increasing examples of flex capacity, as well as CDMO and in-house capacity coming online. It is unlikely that the pipeline will be stoppered as a result. Rather,*

efficiencies will be innovated, automation will be invested, and processes will be created to meet the capacity need. Some of the options may be more expensive than ideal, but even these will likely settle down over time."

CPHI: '2021 showed the lowest average cost-per-gram on record' what was the score for 2022? Are we in age of steady titre improvements continuing year after year – with increasing large improvements – could we see year-on-year improvements in the way we have seen for say processing power in computer chips?

EL: *"We were asking for 2021 cost estimates. So we're saying the data was for 2021, collected in 2021/2022… CPG is not just titer, but overall bioprocessing. Efficiency and productivity is the #1 focus—this has driven costs down. But yes, titer is a significant contributor, since doubling titer cuts bioreactor sizes dramatically. However, downstream costs still remain high, and will remain so until alternative chromatography/separation steps are adopted."*

CPHI: Are we at a critical point for cell and gene therapy innovators (i.e. the surge in staffing issues)– what are the implications for the next two to three years?

EL: *"Hard to say if today is 'critical' – ask the mAb manufacturers and innovators back in the 1990s. They would say that was a critical time. But we're only now, 20/30 years later seeing mAb's as a mainstream technology."*

CPHI: looking ahead what do you read into the implications of single-use tech and automation – what do you expect to see in the improvements do you expect to see in the next 2-3 years?

EL: *"Automation and Single Use Systems cut demand for trained staff, reduce costs, and enable both small and large scale bioprocessing. So yes, we'll see more, especially since so many suppliers are working to improve and integrate automation at so many steps. In the next 3 years, we'll see gradual adoption. But in this regulated industry, everything happens slower than many would prefer."*

CPHI: what is your outlook for biologics and cell and gene therapy outsourcing over the next year (should they be increasing capacity and investing to meet demand?) – do you foresee any regional trends or spikes in demand?

EL: *"With all the advanced therapies in clinical trials, and so much investment going on, certainly the pipeline will grow. Which ones will succeed and at what rate is speculation.*

Regionally, China has been working on cell therapies for decades, and could come in with some innovative therapies. However, US and EU have substantial investments and advanced technologies and trials. So again, it's speculation."

CPHI: can bio growth continue to buck macro trends and continue these high double digit rates for the next 5-years (i.e. the report said growth roughly doubles every 5-years) – what is you outlook for bio in 2027?

EL: *"Covid has created a bubble for suppliers in terms of revenue, and to some extent of volume, as buying and stockpiling continue. This will abate as supply factors related to covid diminish. Bio will continue to follow the underlying (healthy) 12-14% growth rate it has seen in terms of revenue from therapies, as well as derived revenue for supplies for bioproduction. The doubling of profits among suppliers will likely not continue as supply chains normalize, competition increases along with a return to discounting. Further, new suppliers in the industry, many of whom have seen rapid growth as a result of demand due to Covid shortages, will continue to provide alternatives to the major suppliers. Some of these suppliers are coming from Asia/China, where the domestic industry is growing even faster than in the US/EU, and where demand for consumables has created domestic competitive alternatives, where only multi-national suppliers had existed just 5 years ago."*

Vicky Xia
Senior Analyst, BioPlan Associates

Can China still become an innovation hub with drug prices under tight control?

1. Current situation: innovation in a 'fast-follow' fashion

China is a late comer to the innovative biopharma arena and the country began its journey with just bio-generics. However, In the past decade, the industry has been making steady improvements and gradually built up its infrastructure for true innovations to take place in China. At the macro level, the country has recruited thousands of talents with related research and industry experience from overseas (with many Chinese nationals gaining experience in the United States before returning to the country). Simultaneous to this, clinical trial reforms have helped increase the country's output and enabled biotech companies with no launched products to go public on both the Hong Kong and Shanghai Stock Exchanges. The reforms created a golden period for biotech start-ups in the country with a tremendous ability to raise funds, grow and become successful. Consequently, many more returnee scientists have seen the opportunities and returned to start their own biotech companies – with BeiGene, perhaps the most famous of these biotechs, having successfully launched an anti-cancer chemical drug into the US market, as well as a PD-1 mAb in China. In fact, China has seen dozens of mAb therapeutics launched over the past decade and the country's mAb capacity is now close to 1 million liters.

So the question now being asked, is whether China is already a biopharma innovation hub and if China-based biotechs like BeiGene can successfully bring down the cost of innovative drug development. To put the question into a wider global context, despite all the excitement China still lags behind US, EU and Japan in innovative drug development. According to a report from RDPAC released in March, 2021, China's innovative drug market (innovative drug according to Chinese standard) comprises only 9% of the total China market whereas the percentage is over 20% in other G20 countries and over 50% in countries like US, Germany or Japan. For example, the R&D expenditure of leading Chinese drug developers such as Hengrui Pharma is only $4.2 billion in 2020, less than 10% of MNC giants including Roche, Norvatis, J&J, etc. (Figure 1). The contrast in IP is also significant. Hengrui applied for 471 and 373 patents in 2020 and 2019 respectively, while Roche applied for 2122 and 2082 patents in 2020 and 2019 respectively.

China's relative weakness in innovation also becomes more evident when we take the nature of the innovation from domestic developers into consideration. Most, if not all innovation which has taken place in China's biopharma sector are 'fast-follow' or belong to ADC and bi-specific categories, instead of 'first-in-class' biotherapeutics. The mAb therapeutics and cell therapy from domestic developers are usually for established targets, and the biologics from domestic developers getting BLAs are either biosimilars, or bio-betters. More often than not, the more innovative pipelines currently under development by domestic

Figure 1. Leading Domestic Pharma R&D Expenditure vs. MNC Big Pharma[1]

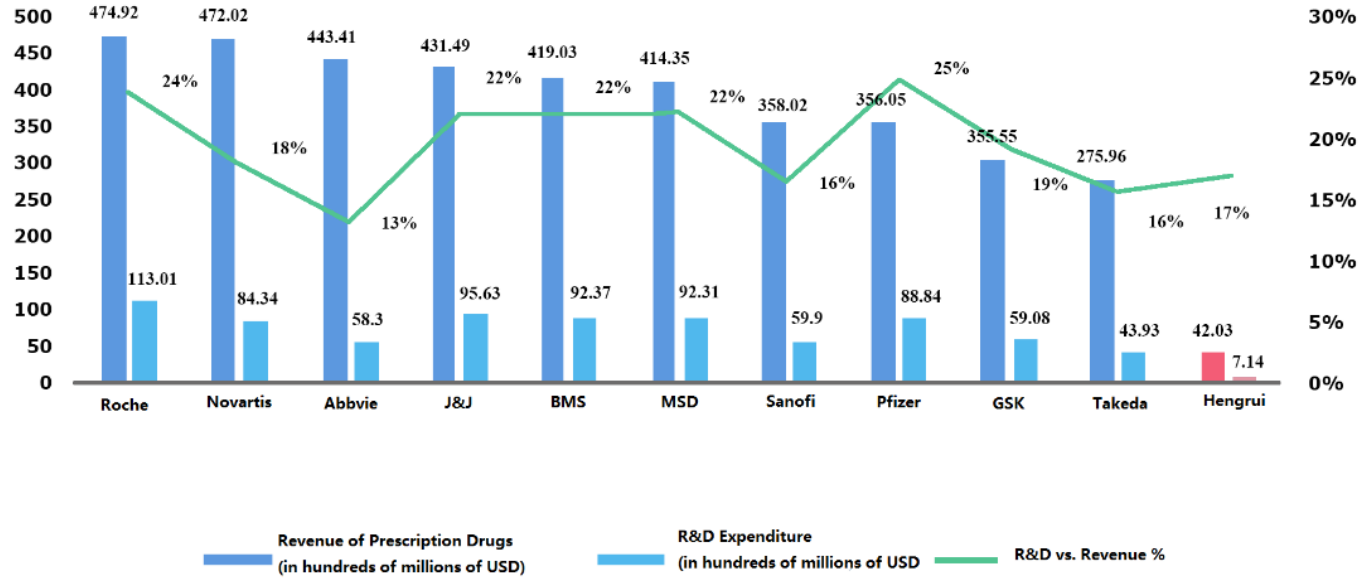
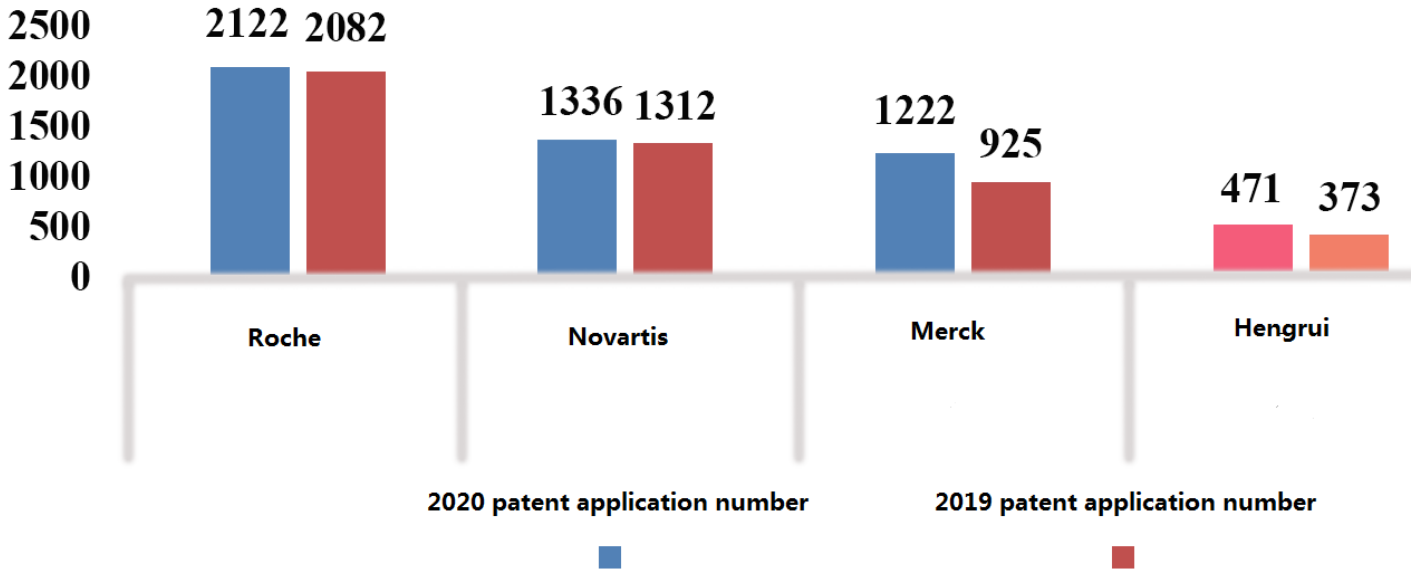


Figure 2 Leading Domestic Pharma Patents vs. MNC Big Pharma[1]



biopharma companies are in-licensed from overseas. Domestic developers see 'fast-follow' as a strategy which could minimize risks of pipeline while offering good market potential, whereas investors also tend to shy away from first-in-class projects. According to China Economics Review domestic VCs usually prefer 'bio-better' of biologics with FDA-granted BLAs, or at least those with existing publications in prestigious scientific journals[2].

But with such ready access to capital, China's fast follow 'innovative biotherapeutics' sector has become very crowded. For example, the country has granted 14 BLAs to PD-1 and PD-L1 mAbs, and dozens more have come into the clinical stage[3]. And although PD-1 is now often taken as a negative case for domestic developers, new targets and new routes (bi-specific, ADC, cell therapy, etc.) are still proliferating. Claudin 18.2, a relatively new target, is an example. Globally, Japanese company Astellas Pharma is the leader with claudiximab at phase III, but in China ~20 developers are working on the target, with some at phase I already[4].

The developers will often claim their projects as 'me-better', but most industry insiders say the majority of these projects are 'me-different' in nature. "Domestic developers have a mindset that it is ok as long as my project is not totally identical to those of my competitors", as one of them put it during a recent interview with BioPlan.

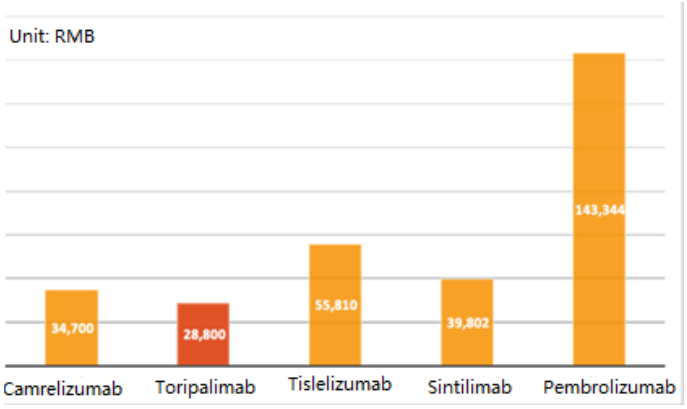
2. Recent trends put the future of China's innovation at risk

a. The policy on drug price control (VBP and NRDL negotiation) will hurt market prospect of fast-follow drugs.

China, unlike US, has a drug reimbursement system which is heavily dependent on the national healthcare insurance program, while only a very small portion of the population has commercial healthcare insurance coverage. In fact, before the wave of BLA to mAbs from domestic developers started in 2017, mAb therapeutics were widely regarded as 'luxury drugs' available only to the affluent population able to pay out of their own pockets. However, since 2019 the Bureau of National Healthcare Insurance has arranged multiple rounds of negotiation with developers, which has successfully added mAb therapeutics into drug reimbursement list, but only with steep price cuts. In 2022 the number of innovative drugs (according to Chinese standard) in the national reimbursement drug list has reached 119, and the majority of them enter the list with price reduction over 50%2. PD-1 has been a perfect example. In 2019, the first PD-1 from a domestic developer, Sintilimab, entered the national reimbursement drug list with a price of only RMB 2,843 (circa $400) per injection. In 2020-2021 other 3 PD-1 mAbs from domestic developers entered the NRDL with price cuts over 70%, with Hengrui's Camrelizumab (200mg/injection) having its price cut from RMB 19,800 (circa $3000) per injection to RMB 2,928 (circa $400) per injection. Consequently, after these rounds of price cuts, PD-1 mAbs from domestic developers are significantly cheaper than their MNC counterparts (Figure 3). Previously, China's PD-1 market was projected to be RMB 100 billion, but now, with the price cuts, even optimistic projections are for only RMB 20 billion (circa $3 billion)[5].

China, unlike US, has a drug reimbursement system which is heavily dependent on the national healthcare insurance program while only a very small portion of the population has commercial healthcare insurance coverage.

Figure 3 Price of PD-1 mAb Per Cycle from Domestic Developers vs. Keytruda[5]



*The first 4 are all from domestic developers, the last one is Keytruda from MSD

Besides the NRDL entry negotiation, regulatory authorities in China are also planning for a Volume-based Procurement Program (VBP) for biotherapeutics. The program would push for further price cuts from developers in exchange for large volume procurement by government. The current policy applies to generic drugs (drugs which have more than 2 manufacturers making the same drug) and the first round of VBP has already taken place for insulin at the end of 2021, which resulted in average price cuts of 48%[6].

Whether the VBP program will in the future incorporate mAb therapeutics is currently unknown. Policy makers have already made it clear that VBP will certainly be applied to biosimilar mAbs. The next question is to which products this will apply, as some predict that as 'me-better' mAb therapeutics targeting the same target (but not identical biosimilar) will be categorized as innovative drugs in China, VBP would not be applicable to them, while others are much more pessimistic. The latter group argues that with so many 'me-different' mAb drugs for the same target getting a BLA, regulatory authorities are likely to treat them as biosimilars sooner or later. For example, in the summer of 2021, China's CDE published Clinical Value Oriented Anti-Cancer Drug Clinical Development Guidelines. This required head-to-head comparative studies with the current best treatments, and it is widely regarded as a blow to 'me-too' drugs.

b. Domestic developers' export plans have not, thus far, had a smooth start

Analysts have lowered their expectations for China's market as price controls get more stringent and now many developers are changing strategy and looking to the US/EU markets for growth.

This is also likely to be a very challenging route as so far no biotech from China has achieved a BLA approval from the FDA. However, a number of mAb developers are currently applying for BLAs with mixed results.

For example, Innovent, had its joint BLA application with Eli Lilly for Sintilimab turned down by the FDA in March. The FDA cited a lack of international participants, with the trial solely dependent on clinical data from Chinese patients, as the reason for its failed approval. Junshi Pharma is also applying FDA approval for its PD-1 mAb and the FDA replied in May with a demand for a process change for quality control. Junshi is planning for a re-submission of the BLA application this year.

c. Market valuation of domestic biotech companies has plummeted

Domestic developers are starting to feel the pressure of price cuts. Regulatory authorities intend to expand the volume of mAb therapeutics via lower prices, and developers have found this causes not only a current steep reduction in profit margins, but also a cut in overall revenues. For example, Junshi's PD-1 mAb was launched in Dec 2018, but in 2021 its revenue from PD-1 mAb is only RMB 412 million, which is 60% lower than the RMB 1 billion revenue from the same mAb in 2020[7].

The net result is that biotechs may likely face more challenges than biopharma companies under the current pricing scheme, as they rely on external investment and the capital market is cooling down for China-based biotechs. In fact, the market valuations of domestic biotech companies has plummeted in 2022 (Table 1) even for the more prestigious ones such as BeiGene. According to China Economics Review, among the 34 biotech companies that went public on HK stock market in 2021, 24 fell on their first day of trading[2]. Meanwhile, capital markets interest for investing in in-licensing models is also on the decline. On Sep 22nd, 2021, Shanghai Stock Exchange (SSE) vetoed Haihe Pharma's bid for an IPO on SSE STAR market due to its 'heavy reliance on 3rd party technology'. Haihe Pharma is developing 7 out of its 8 pipeline projects via in-licensing or co-development. This decision is perceived by the industry as a signal that the golden age for biotech companies good at 'pseudo innovation and quick IPO exit' will soon become history.

Table 1 Stock Price of China-based Biotech Companies Went Down in 2022[8]

Company Name	All time high	Current Price
BeiGene	$426.56	$174.8
Zai Lab	$152.82	$42.82
Legend Bio	$58	$45.4
C-Stone	1.78	0.44
CNTB	$25.25	$1.37
HCM	$42.93	$13.02
I-Mab	$80.88	$6.01
Beyond Spring	$33	$1.56

While it is clear the above-mentioned policy moves are projected to hit biosimilars hardest or the self-claimed 'me-better' drugs, it will inevitably also hurt domestic developers' capability for future innovation. Chinese biopharma companies most often start from a biosimilar first model, before building the internal capability for mAb therapeutics development, including cell line development through to commercial production. They rely upon the profits generated from these projects – which are launched or close to getting a BLA – to provide the capital for more innovative and risky projects. This coupled with investors' waning interest in China's biopharma sector has led to industry insiders projecting many of these will cease trading within the next 5 years[9].

Chinese biopharma companies most often start from a biosimilar first model, before building the internal capability for mAb therapeutics development

3. The Industry is making adjustments, but not necessarily via large investment in first-in-class therapeutics

The industry is of course making adjustments as its market prospects change, and biotechs are now considering the out-licensing model for revenue – letting go of their ambitions to become full-fledged biopharmas. Alternatively, some biotechs, even those who have already gone through an IPO on Nasdaq, are looking for an acquisition exit route via a MNC big pharma. According to Bloomberg, I-Mab has held talks with other global drug makers about partnerships and investments, including clinical and

commercial agreements in China. It's also been seeking a partner to jointly develop its Ulilediimab, or TJD5, cancer treatment in the U.S. and Europe, as well as other pipeline assets[10]. Similarly, this August, Innovent Biologics and French pharma giant Sanofi announced a partnership to jointly develop clinical-stage oncology assets SAR408701 and SAR444245 in China. Per the terms, Sanofi (SNY) will invest €300M in Innovent (OTCPK:IVBIY) at HK$42.42 per share, implying a 20% premium to the 30-trading-day average share price as of Aug. 03. In addition, Sanofi (SNY) will have the right to make another €300M of equity investment in Innovent (OTCPK:IVBIY) subject to mutual agreement[11].

biotechs are now considering the out-licensing model for revenue – letting go of their ambitions to become full-fledged biopharmas

Another issue is that developers are also starting to have an overabundance of capacity, one that many had not expected. When market prospect boomed for mAb therapeutics, many developers built or expanded their capacity with government subsidiaries, resulting in total capacity for China's mAb sector quickly reaching up to one million liters[12]. Now with quite a few competitors selling very similar products, the ones lagging (in development and revenue) would have idle capacity. Some developers, including Innovent Biologics which has revenues from its PD-1 mAb – over RMB 3 billion in 2021 – have even started a side business in contract manufacturing to put idle capacity into operation[13]. Domestic substitution in bioprocessing supplies is another response that developers are trying to help reduce costs. Many domestic developers have incorporated supplies from domestic vendors, including single use bags (bioreactors excluded), cell culture media, or even resin, into their bioprocessing platforms.

Ultimately, despite the industry being fully aware of the necessary adjustment, its efforts toward first-in-class therapeutics is still relatively rare. So while some investors are turning to very early stage projects, due to relatively low valuations, there is still very few first-in-class pipelines in clinical stage in China. In the winter of 2021, Guangzhou-based Ming Med announced that its first-in-class HPK1 inhibitor PRJ1-3024 has kicked off a Phase I clinical study in US[14]. On June 2022, Innocare, a biotech startup founded by a prestigious returnee scientist Dr. Shi Yigong, announced that CM369, its first-in-class mAb against CCR8, is going to enter clinical studies soon having submitted an IND application to NMPA. The big question – a multimillion dollar one – is whether these efforts will turn into realized commercial successes.

4. When will first-in-class biotherapeutics arise and become mainstream in China?

China has clearly made significant incremental improvements to its biopharma industry. The country started with bio-generics (insulin, TPO, interferon, etc.) at the end of last century, turning to biosimilar mAb therapeutics in the first decade of this century, with the most recent decade witnessing a wave of 'fast-follow' mAbs. Domestic developers are now following relatively new targets, while first-in-class pipeline are starting to arise. However, China may still need to wait for a drug reimbursement system which gives strong support for innovative drugs to make commercial successes for innovative biotherapeutics possible. This could take place either via greater coverage of commercial healthcare insurance, or by reforms at the national healthcare insurance program which highly favors first-in-class drugs. China also needs to deliver improvements in target-related basic life science research and translational research, the latter being an especially weak link at current stage. Meanwhile, China may still need to recruit inter-disciplinary talents (clinical research, pharmacology, basic life sciences, etc.) from US/EU to properly empower the growth of its bio industry.

CPHI post review Q&A

CPHI: in your opinion, by when (year) will the first 'first-in-class' biopharmaceutical be approved from a China based biotech – and/or do you expect this to more likely be for a USFDA approval rather than NMPA (i.e. not enough revenue in domestic market yet)

VX: *"most biotech working on first-in-class would do US/China double application."*

CPHI: If you can, please make an optimistic and pessimistic prediction for the number of successful biopharmaceutical approvals from China in 5-year's time?

VX: *"I think new BLAs will be ~10 annually."*

CPHI: Could we see a splitting of the China bio research market with some(most) biotechs looking at me-too or me-different products and some using the growing research base in China to launch 'first-in-class' products for USA and China?

VX: *"There are several who claims that they focus on first-in-class (the two I mentioned); but i think the majority of biotech would claim that they work on both first-in-class and bio-betters."*

CPHI: In your opinion – a lot of analysts now think the bottom is in for global share prices and biotech funding shortages – can you see China's biotech industry rebounding quickly in 2023/24 (with big valuations) or do you only foresee a more restrained return as it is now a less attractive option?

VX: *"I personally do not think a quick rebound would take place in 2023/24 for China-based biotech. The evaluation of such biotech stocks has been a huge bubble in recent years. It may take a year or two for the cooling process and for the cycle to begin again on a more stable footing."*

CPHI: just a thought: with such access to scientists could China become a sort of early stage innovation hub before out-licensing this globally.

VX: *"I do not think China will become an early stage innovation hub imminently, however, it is catching up quickly."*

CPHI: Do you think the Government may realise innovation in biopharma is slowing and react to reinvigorate its biotechs with new policies? (i.e. like to did to start this with the MAH progamme)

VX: *"Presently, the government has more urgent things to consider, such as the real estate cooling down which is hurting the tax income of the government significantly. So for now, the cooling of life science innovation activity is not a priority."*

CPHI: any thoughts on Western Big Pharmas investing in research facilities in the region and/ or the impact that might have over the next few years?

VX: *"Western big pharmas have shifted to other strategies than just setting R&D centers in China – instead they are looking at co-development pipelines with domestic biopharma. For example, GSK closed its R&D center in Shanghai at the end of 2019.*

The other consideration is that setting up an R&D center in China is not as cost-effective as people might think. A lot of the talent requires to staff these facilities are now recruited from overseas."

Notes

1. https://baijiahao.baidu.com/s?id=1738651160097230659&wfr=spider&for=pc
2. 经济参考报/2022 年/3 月/23 日/ , 资本放大镜下的中国生物创新药产业, 曾亮亮 梁倩)
3. baijiahao.baidu.com/s?id=1738406700152008933&wfr=spider&for=p
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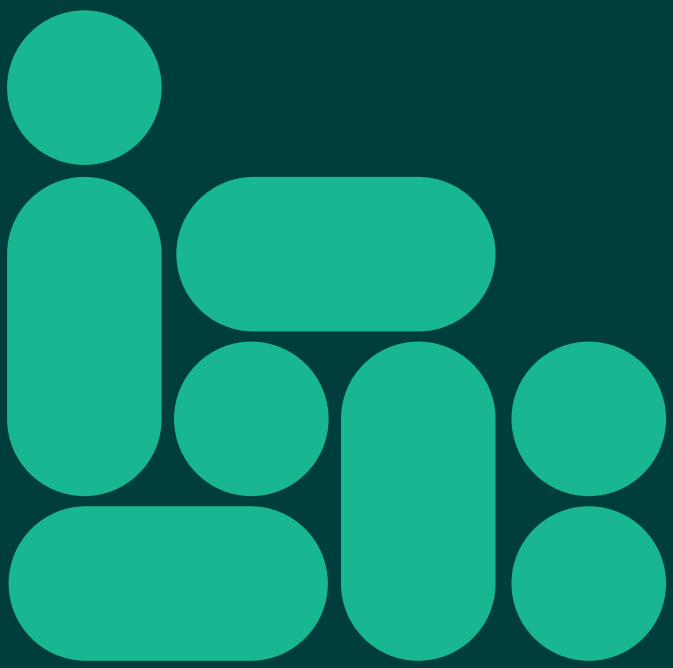
Part 2

CRO/CDMO prospects: funding overhang to drive growth?

CPHI Frankfurt 2022



Brian Scanlan
Operating Partner - Life Sciences, Edgewater Capital Partners

Predictions on the Health of the CRO/CDMO Sector in Uncertain Economic Times: When — or Will — the Bubble Burst?

Introduction

Public and private funding into the biotech and emerging pharma sector has created unprecedented demand for outsourced pharma services over the last several years, as the number of compounds in development has skyrocketed. Considering the current disruptions in public markets, global geopolitical concerns, and other economically impactful factors, important questions remain to be answered:

Can the CRO/CDMO sector expect a slowdown? And if so, when, and to what degree?

These are difficult questions to answer definitively, so we will explore the macro factors affecting the sector in order to provide our prognostications on the health of the pharma services space over the new few years.

Current VC Funding Into Biotech & Emerging Pharma

Demand for pharma services increased sharply in the wake of COVID-19, as some resources were globally focused on getting vaccines to the public, and others were focused on keeping up with demand for non-COVID therapeutic development and manufacturing. During this period, total biotech funding spiked from a little under $20B (~$70B TTM) in Q1 of 2020 to approximately $40B (~$140B TTM) in Q1 of 2021 (Figures 1 & 2). Despite a decline since Q2 of 2021, funding and the sector itself remain strong.

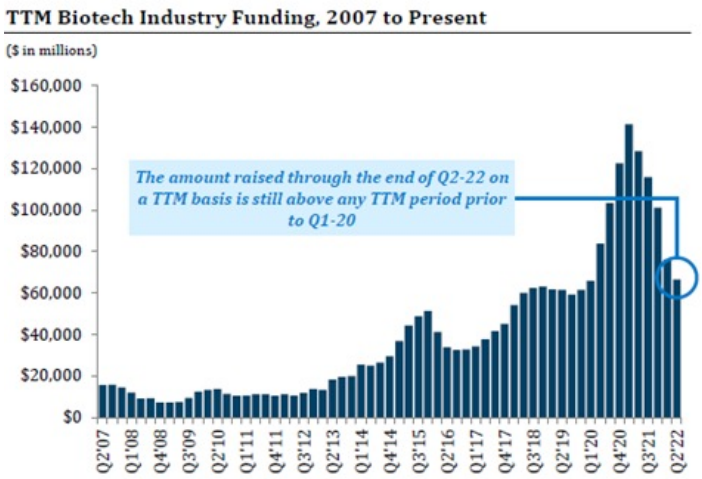


Figure 1. William Blair Equity Research. August 2022.

Putting pandemic-related factors aside, a significant portion of the heightened demand for CRO/CDMO services has been driven by VC-backed pharma and biopharma companies. While Q2 2022 follow-on and IPO funding have receded to Q2 2019 levels, post-pandemic VC funding remains above that of Q2 2019, even though we have seen a significant decline from its peak (Figure 2). The VC contribution to total funding places the current overall level essentially even with Q2 2019, though these comparisons are restricted to private funding, not public. The situation in public markets is dicey, to say the least. A model released by BlackRock on June 30, 2022, indicated that more than 80% of asset returns are attributable to macro risk factors — levels similar to those of 2008 and 2020.

Focusing on VC biotech funding levels, we can see that the growth from 2010 to today has been strong and relatively consistent (Figure 2). The increase in VC funding just from 2016 to 2021 was 161%, topping the overall growth rate of 116%. So, while biotech R&D spending is certainly lower than in 2021, the "decline" is mainly driven by the historical spike surrounding the global COVID-19 response. This appears to make for an unfavorable comparison, but only if we limit ourselves to a very short view.

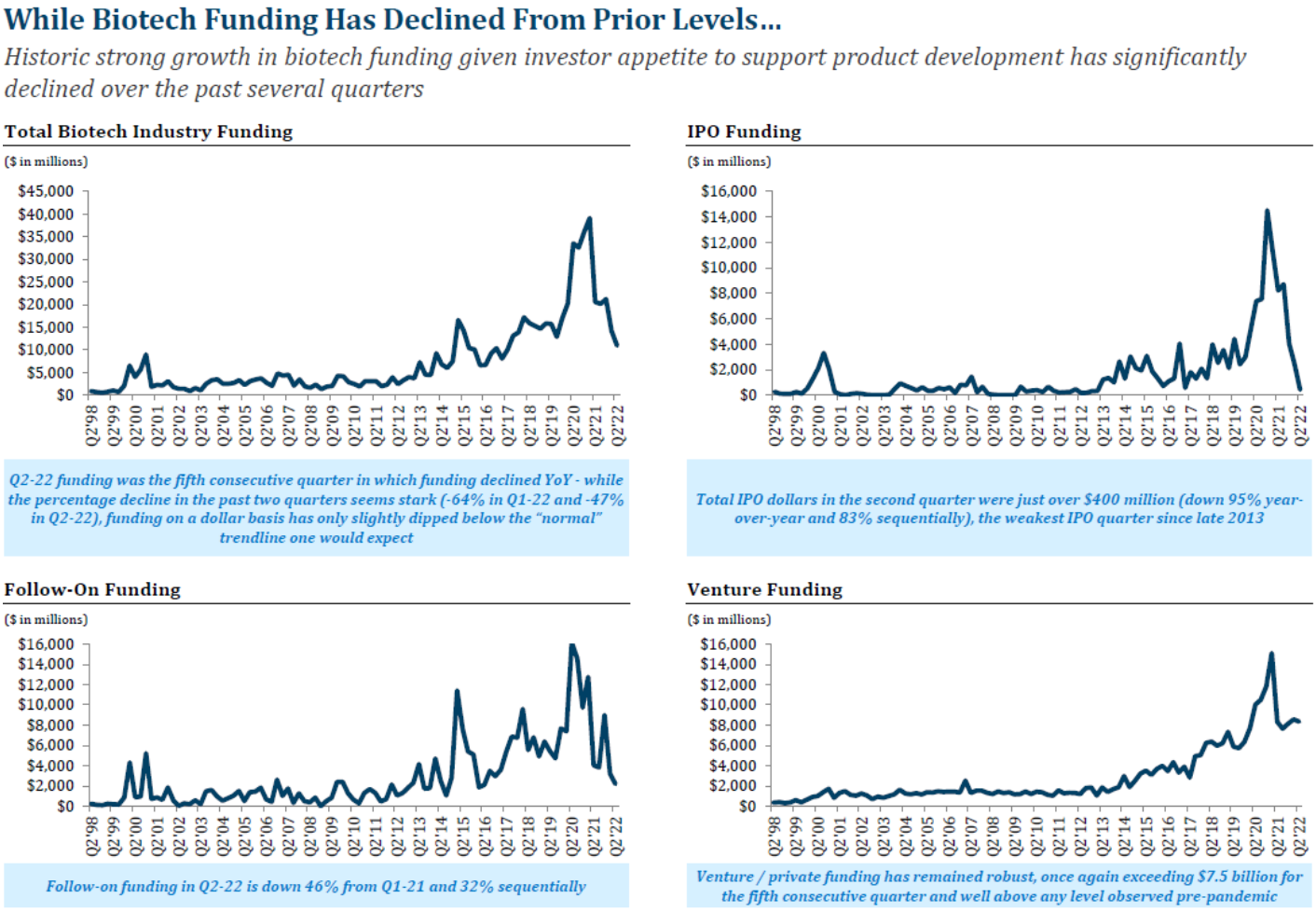


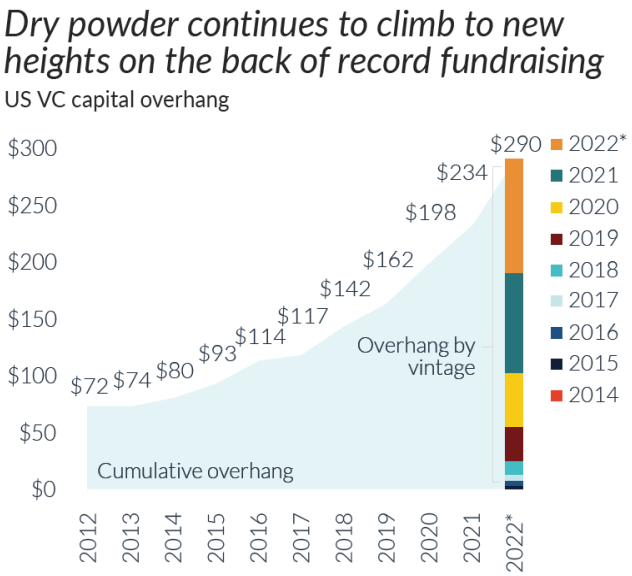
Figure 2. William Blair Equity Research. August 2022.

There is more than enough capital available to continue fueling innovation. Let us take a closer look at the numbers:

- **Q2 2022 —** $6B+ invested
  - Less than Q2 in 2021, nearly equal to 2020, but more than in any Q2 prior to 2020 (on record)
  - More VC funding than the entire year of 2013, which is viewed as a "boom" year for biotech backing
- **June 2022 —** Biggest month of Q2
  - ~$2.5B, more than any Q2 from 2019 or before
  - Occurred 18 months after the public market peaked (disentangled dynamics)

All of this funding into biotech and emerging pharma has created a turbocharged demand for pharma services, and the CRO/CDMO sector has seen almost no pullback in demand even during the current market disruptions. This is due, in part, to the VC-funded biotechs sitting on 2-3 years of cash reserves; critical programs remain funded. Further, biotech funding that has been raised over the last couple of years is likely to be deployed relatively soon because these closed-end investment vehicles must be used in deals within 4-5 years; VCs cannot sit on cash like hedge funds. The amount of dry powder set to be ignited in VC-backed biotech is enormous (Figure 3).

Figure 3. PitchBook-NVCA Venture Monitor. As of June 30, 2022.

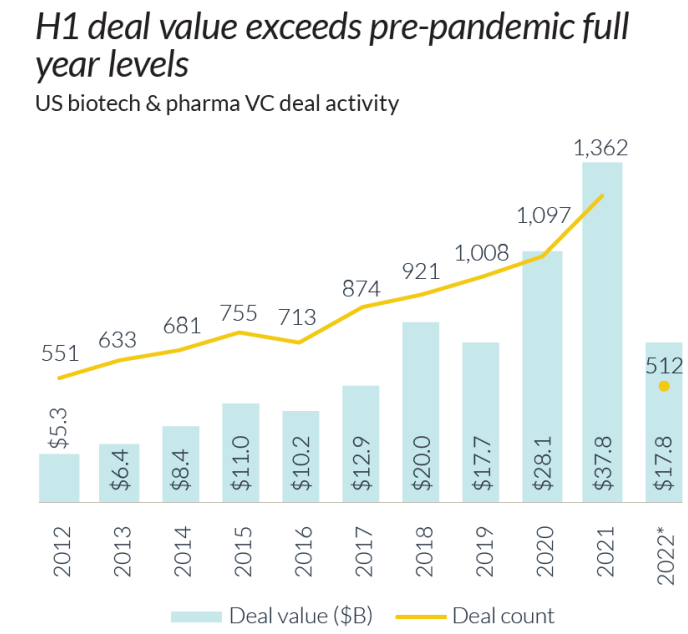


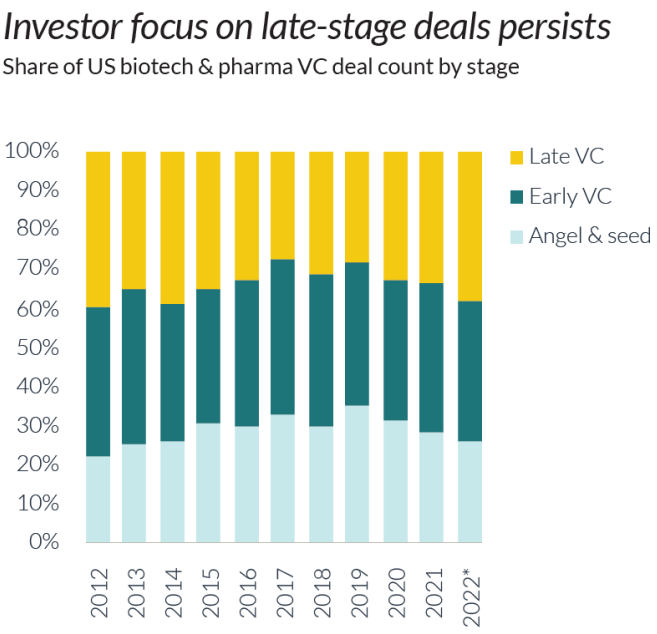
So, is it time for cautious optimism? Can biotech M&As take the place of private and public funding since those have slowed? Can M&As act as a lever to keep biotech growth and need for CRO/CDMO services growing?

We can see that the total value of VC deals for 1H of 2022 already exceeds the value for all of 2019, and there has been a growing focus on late-stage deals over that same period (Figure 4).

Additionally, the average U.S. biotech VC deal size has grown by over 25% from 2021 to 2022 (from $30 to $40.4 million), and average pre-money valuations are at an all-time high (from $114.6 to $169.4 million as of June 30, 2022) (Figure 5). This data suggest that new VC investment, for now, is skewed toward later phase and less risky assets.

Figure 4. Pitchbook-NVCA Venture Monitor. As of June 30, 2022.



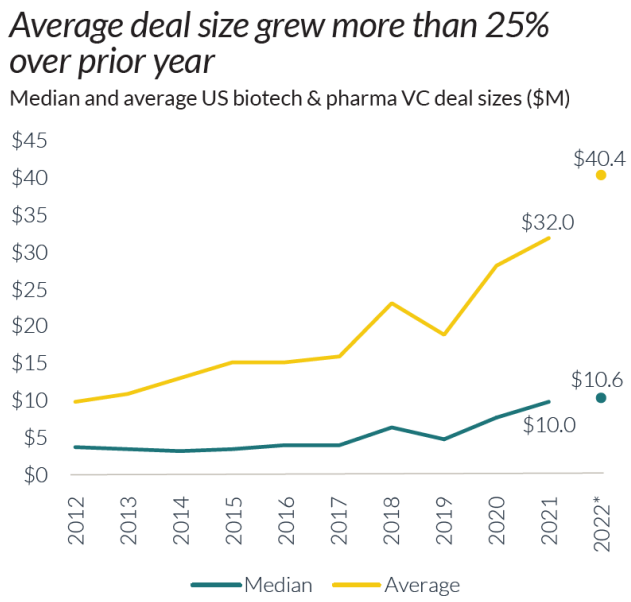


Strong VC & PE Funding = Strong CRO/CDMO Sector

Due to their virtual nature, biotechs and emerging pharma work almost exclusively with pharma services companies. Overall, VC cash flows through biotech companies and into CROs/CDMOs, which has bolstered demand for pharma services. The unprecedented level of biotech funding has spawned an unprecedented number of new therapeutics in development (Figure 6).

The thousands of new compounds in development are translating into new opportunities for pharma service providers. The pattern is very interesting in that the steepest growth is for compounds in early development. This is where most of the emerging pharma companies reside. These companies generally prefer to work with smaller CROs (Figure 7). The advantages of outsourcing to smaller, more "boutique" CROs that provide specialized expertise, speed, and high-touch relationships play well with the innovative nature of emerging companies.

Figure 5. Pitchbook-NVCA Venture Monitor. As of June 30, 2022.



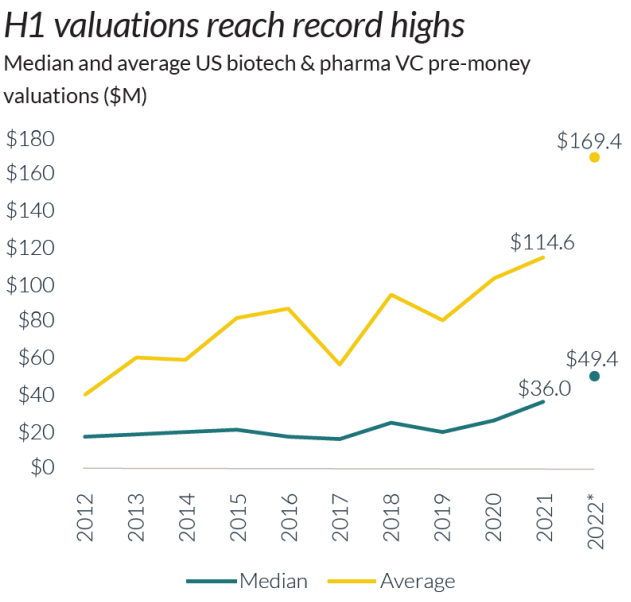


Figure 6. William Blair Equity Research. August 2022.

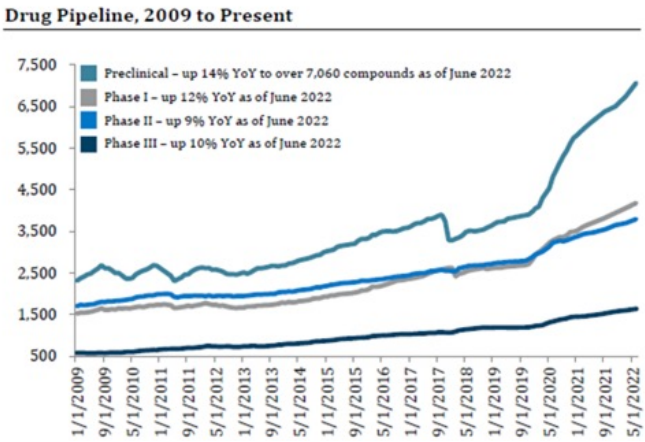


Figure 7. Credit Suisse Research.

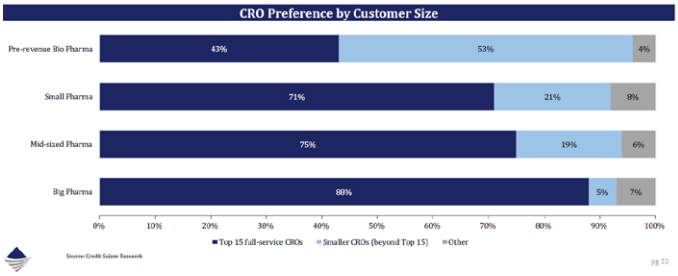
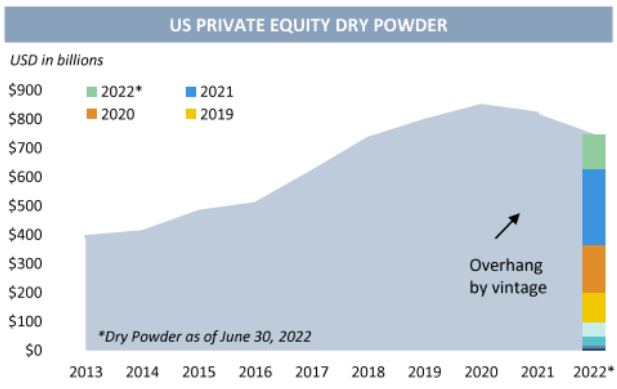


Figure 8. Bourne Partners. Pharma Services Snapshot (1H). As of June 30, 2022.



As compounds move further along in clinical phases and toward commercialization, emerging pharma companies grow into larger entities or are acquired by big pharma. At this point, the demand pattern shifts toward more integrated CRO's/ CDMOs as the outsourced provider preference.

The key takeaway is that pipelines are extremely full across all phases of development, and growth has only accelerated. Smaller pharma service companies tend to match up well with bigger players in early phases of development, whereas the larger integrated CROs/CDMOs dominate in mid and later stages. Regardless of how biotech funding modulates or ebbs and flows between earlier and later stage investments, the large number of compounds already in pipelines are effectively "queued" up for further development as funding levels resume.

In addition to funding levels into biotech, an especially strong indicator for the health of the pharma services sector is the amount of dry powder that remains to be utilized in private equity. In June of 2022, the U.S. private equity capital overhang was about $749 billion, and even though fund deployment has decreased the amount of dry powder compared to Q4 2021, private equity groups are on pace to raise record funding in 2022 (Figure 8).

The $749 billion total overhang in private equity, the need to deploy capital, and the limited supply of actionable CDMO/CRO M&A mean that PE-funded pharma services company valuations are likely to remain elevated relative to historical

values. It should be noted that based on numerous discussions we have had with investment banks and private business owners, private CRO/CDMO valuations seem to have modulated (maybe 3-4 turns of EBITDA) in the past 6-9 months, so that a "high teens" multiple might be more in the "mid-teens," though still at historically high levels. Public CRO/CDMO company valuations have seen a more pronounced decline (Figure 9).

Figure 9: William Blair Equity Research. August 2022.

Public company valuations have experienced volatility and decline from record levels.

Equity Performance

	Companies	Market Cap ($M)	YTD Price Performance	2022E Revenue	2022E EBITDA	21-22' Revenue Growth	2022E Gross Margin	2022E EBITDA Margin	EV / LTM EBITDA	EV / 2022E EBITDA
CDMOs	AVID BIOSERVICES	$1,215	(29.1%)	$134	$26	40.0%	32.0%	19.4%	NMF	44.4x
	Catalent	20,269	(9.2%)	5,040	1,334	12.4%	34.2%	26.5%	19.0x	17.1x
	Lonza	44,916	(23.1%)	6,185	1,967	14.3%	41.1%	31.8%	29.5x	20.7x
	SOCIETAL	51	(47.7%)	91	15	9.7%	24.9%	16.6%	7.8x	8.2x
	Siegfried	3,106	(20.2%)	1,228	254	11.4%	22.8%	20.7%	13.9x	12.8x
	Median	$3,106	(23.1%)	$1,228	$254	12.4%	32.0%	20.7%	16.4x	17.1x
	Mean	$13,911	(25.9%)	$2,536	$719	17.6%	31.0%	23.0%	17.5x	20.6x
CROs	charles river	$12,734	(30.8%)	$4,006	$1,030	11.8%	37.7%	25.7%	15.4x	14.7x
	ICON	19,668	(18.5%)	7,838	1,708	5.0%	27.9%	21.8%	16.2x	13.7x
	IQVIA	44,835	(12.2%)	14,539	3,357	4.8%	35.1%	23.1%	19.0x	16.1x
	labcorp	24,346	(12.1%)	15,316	3,029	(5.6%)	29.8%	19.8%	6.5x	9.5x
	MEDPACE	5,255	(20.9%)	1,395	263	22.1%	62.2%	18.9%	24.1x	21.5x
	Syneos	8,118	(20.4%)	5,661	845	8.6%	23.9%	14.9%	14.4x	13.1x
	Median	$16,201	(19.4%)	$6,750	$1,369	6.8%	32.5%	20.8%	15.8x	14.2x
	Mean	$19,159	(19.1%)	$8,126	$1,705	7.8%	36.1%	20.7%	16.0x	13.9x

EV / LTM EBITDA Multiples Over Time

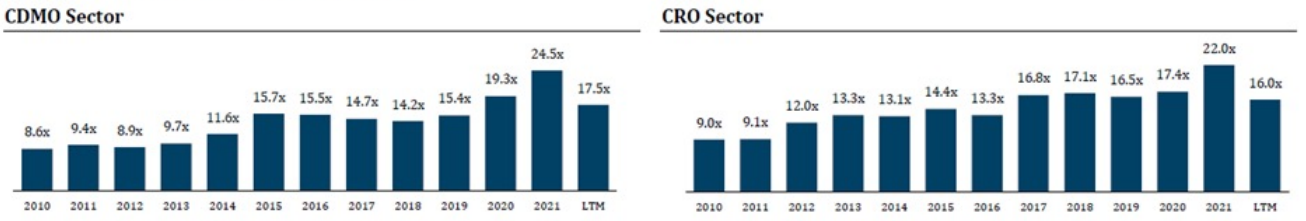


Figure 10. William Blair. Pharma Services Market Trends. August 2022.

Despite the public markets cooling off, and valuations modulating a bit, transaction volume is strong in the CRO/CDMO sector. Specifically, 1H of 2021 saw 29 transactions for CDMOs and 36 for CROs, while 1H of 2021 saw 25 and 35, respectively (Figure 10). The number of deals remains high, and even though total value has dropped, this is in part due to mega-sized deals that happened in 2021, skewing the numbers. Some examples:

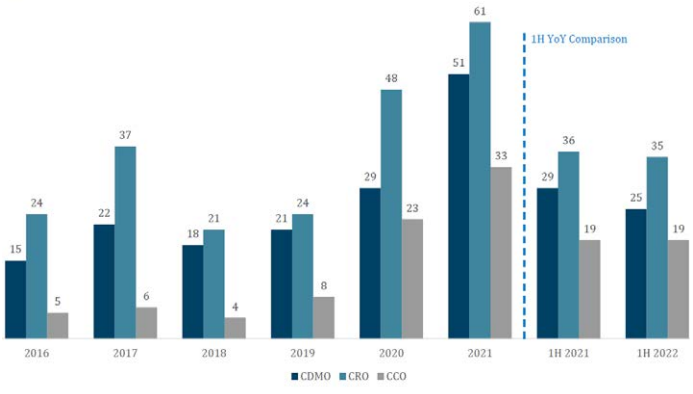
- **Icon acquisition of PRA Health** = $12 billion
- **Thermo Fisher acquisition of PPD** = $17.4 billion
- Total = ~$30 billion

In short, the number of M&A deals is on par with 2021 and activity looks very healthy through the first half of 2022. The appetite for CRO/CDMO M&As is strong, indicating that the sector outlook is still very strong.

Based on the positive macro trends, analysts continue to be bullish on the longer-term growth prospects in the pharma services sector.

Transaction Volume by Segment

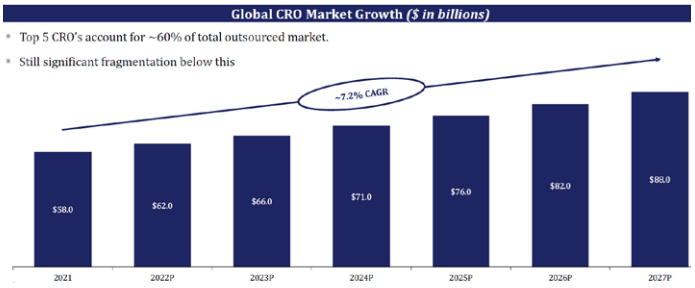
(Transaction Count)



The global CRO market is predicted to grow from $58B in 2021 to $76B in 2025 (~7.2% CAGR) due to increased R&D spending and outsourcing. Similarly, the CDMO market is predicted to expand from $177.2B to $246B (~8.5% CAGR) over the same period due to growth in drug development and outsourcing (Figure 11).

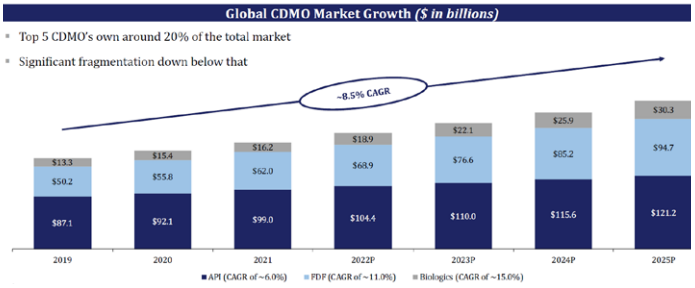
Figure 11. Top: Piper Sandler. Bottom: Edgemont Capital, Piper Sandler, William Blair.

The CRO market is expected to exhibit strong growth trends due to increasing R&D spend and outsourcing.



Source: Piper Sandler

CDMO market is expected to exhibit simular growth trends to the CRO market due to drug development growth and outsourcing dynamics.



Source: Edegmont Copital, William Blair, Piper Sandler

Will CROs/CDMOs See Any Slowdown in the Next 24 Months?

Many have asked, "when can we expect the economic slowdown to actually hit the CRO/CDMO space?" It is not clear that it will in any meaningful way, though a variety of issues must be considered.

Factors affecting the demand and valuation in the pharma services space:

VC and PE: We have explored at length the relationship between VC/PE and the CRO/CDMO sector in this article. All signs are generally positive for continued strength in demand for pharma services and continued healthy CRO/CDMO valuations due to the amount of PE dry powder and more limited inventory of pharma service assets. However there is some negative pressure on pharma service valuations due to a more difficult leverage environment.

Public Markets: The IPO environment is currently not great; market volatility is high and stock values are down. This has dampened VC exits in later-stage biotechs. We are starting to see signs that some VC-funded biotechs (particularly later stage) are beginning to stretch out CRO/CDMO programs where possible to slow the cash burn. This is putting negative pressure on the pharma services outlook.

Big Pharma M&A: With all the dry powder in big pharma coffers and a sub-optimal IPO environment, M&A activity should pick up in this area as they shop around for good strategic assets. This should be an overall positive for the pharma services sector, but the advantage will be skewed toward the larger integrated CDMOs because they have more strategic relationships with big pharma companies.

Supply Chain and Re-Shoring: The re-shoring phenomenon is real, and the momentum it gained during the pandemic is continuing due to ongoing global geopolitical concerns. The Russian/Ukraine conflict, EU energy concerns, and U.S.-China and Taiwan-China tensions are all causing uncertainty about materials moving around the globe. In addition, Kearney's 2021 Reshoring Index shows that an increasing number of U.S. companies are returning offshore sourcing, production, and assembly to the States. In the same report, Kearney also disclosed the following information from U.S. executives:

- 92% express positive sentiments toward re-shoring
- 79% of those with offshore manufacturing operations have either already moved a portion of operations back to the U.S., or they plan do so within 3 years
  - o An additional 15% are considering

Other anecdotal factors:

In addition to the macro items described above, it should be noted that several of the discussions we have had with CDMOs and investment banks have pointed to some interesting issues impacting on the overall health of the pharma services market going forward:

- *Turnover within the FDA*: The agency has lost numerous reviewers due to turnover, which could be contributing to the significantly lower number of approvals in 2022 YTD. This could impact commercial launch of many drugs awaiting approval over the near/midterm.

- *Book-to-bill ratios at public CROs*: While most have maintained greater than 1.0, there are a few CROs where this has dipped below 1.0. This may start to impact revenue growth in Q4 of this year (and beyond?).

- *Slowing cash burn at late stage biotechs*: This is impacting CDMO contracts. Our discussions with a number of CDMO BD staff have indicated biotech CFOs are getting more involved in the proposal process to keep a closer eye on cash burn. In addition, average proposal values are starting to drop, owning to some biotechs chopping programs into smaller pieces to slow down cash burn.

- *PE Investment Committee Pushback*: we are hearing more broadly about more pushback from PE investment committees on valuations and deal structures in the current environment, as compared to the past couple of years.

Summary of the Health of CRO/CDMO Sector

While it is true that private funding is down in the short term versus the past couple of years, and many factors are contributing to negativity and fear in public markets, there are also many reasons for optimism in the CRO/CDMO sector. Both PE (pharma services) and VC (emerging pharma) funding are historically high, demand for services is strong, dry powder is massive, and VC funds will — and must — be used. There is also movement among U.S.- and EU-based companies to re-shore manufacturing operations in the next few years, which should somewhat modulate the impact of uncontrollable global factors in these regions. For these reasons and others discussed above, the current and future health of the sector appear relatively strong, though not at the levels we have seen the past few years. Time will tell, but barring any major escalation in geopolitical events, there is more than sufficient cause for cautious optimism over the next 1-2 years.

CPHI Additional Q&A Insights

CPHI: Figure 6 on the make-up of CRO/CDMO preference by customer's size. Coupled with smaller companies mostly being earlier in development. Does this imply small and medium CROs/CDMOs will do very well in the next two years (out of the early-stage pipeline). With perhaps some using this pipeline to become medium CROs. But then in two years' time and onwards, this pipeline is going to secure massive revenues to large CROS.

BS: *"Some of the small CRO/CDMO's will begin to invest in more scale to enable "continuity of supply". One example here, is where a smaller chemistry house doing small scale custom synthesis of API's to support medchem through GLP tox lots invest in some small scale GMP capability to allow them to produce from preclinical through first-in-human GMP lots."*

CPHI: Or is the patten of late phase growth for large CDMOs already set. I.e. they are doing exceptionally well now from late phase projects (please put aside the benefits of Covid projects which we have to assume will gradually reduce) and will just continue to do well or better.

BS: *"I think the pattern for growth for the larger CDMO's is largely set. As the increasing number of compounds make their way into later phases of development (and commercialize in some cases), the larger, more integrated CDMO's will dominate. Not in all cases, but I'd say the majority of later phase programs. In order to "feed the beast", the larger, integrated CDMO's have traditionally bought the smaller players to enable more pipeline of programs."*

CPHI: What can we read into this statement for the next 2-5 years? 'the advantage will be skewed toward the larger integrated CDMOs because they have more strategic relationships with big pharma companies'?

BS: *"It's not really significant as a blanket statement. All I mean by that statement is that the advantage for later stages of development goes to the large CDMO's because these require more integrated resources and scale to support later phases of development and commercial launch. The advantage for the earlier phases of development, generally speaking, is with the smaller CRO/CDMO's who, by virtue of their size/ culture, match up well with the emerging pharma companies."*

CPHI: 'the dry powder overhang' as this has to be spent soon; do we think this has been accounted for in growth projections for CRO/CDMOs or could we see growth over and above the 7.2% and 8.5%? (figure 11).

BS: *"I don't believe the dry powder overhang has been accounted for in CRO/CDMO growth, but keep in mind the dry powder overhang for PE's is different than the overhang for VC's. The PE overhang will more drive both valuations (supply of cash against more limited CRO/CDMO targets) and capacity expansions to support market demand. The VC overhang/spending will support the demand side (i.e. funding more compounds in development)"*

CPHI: Does this mean for example that we might see lots of drugs funded to go much further into development and more approvals in the next 2-3 years? (granted I also noted that the FDA may be under resourced).

BS: *"VC funding overhang (supply of cash) may push funding into later phases of development. However, this should be tempered by the geo-political/inflation/public market headwinds."*

CPHI: do you have any view on whether the big CROs/CDMOs might become too big and over the next 2-5 years (seems they look set to get the best of the growth) and it might be counter production for biotechs in the future – or do you think we will see an emergence of a midsized class of CRO/CDMO to work with biotech's.

BS: *"I believe the market moves in cycles. The big become bigger by consolidating the available mid-sized players. This, in-turn creates a void between the big and small players (we see this today). Next, some percentage of the small players will themselves grow into mid-sized CRO/CDMO's, then the cycle of consolidations come back again. Finally, there is no shortage of supply of small CRO's/CDMO's. Some of these desire to grow into mid-sized, others remain small as "lifestyle" businesses for the owners."*

CPHI: looking at the table appears the bulk of future growth is in biologics and finished dose. Where would you invest CRO/CDMO resources with most certainly (mRNA, finished dosages, biologics, advanced therapies, HP etc etc)?

BS: *"Candidly, I'd invest in any pharma services company that is differentiated, has a proven track record of technical expertise and delivery, and can tackle challenges of today's advanced therapeutics. When I say "advanced therapeutics", I'm not only talking about large molecules. Could be large or small molecule."*

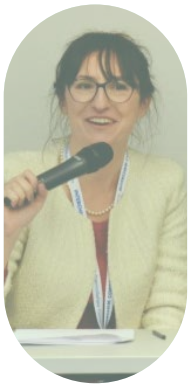
CPHI: The US has a tremendous biotech growth engine (with perhaps not enough local CDMOs), China a quickly growing one, Europe relatively steady. Do you have any thoughts on the prospects for CDMOs in the USA, Europe, India and China. Are they all winners? (are there bigger winners among them – or is simply size is the main driver of the big winners?)

BS: *"Each region has its advantages, and the industry is starting to get serious about a more balanced approach in terms of supply chain balance given both Covid and now the geopolitical challenges the world faces. I think the prospects are strong in the regions you mentioned because the world is not a static place. China and India have both build formidable pharma services infrastructures, and we have been seeing companies in both countries invest in global strategies to ensure a multi-continent approach; ensuring facilities are strategically located across the globe. Much like the US and EU companies did over the past 25 years in those regions. The US has a unique challenge because it is still the largest pharmaceutical marketplace in the world, and still the largest hub of pharmaceutical innovation. Yet, there are relatively fewer pharma services companies on the continent. This has set up the supply/demand imbalance we are seeing in North America right now."*

Part 3

Psychedelics and post covid effects on CDMOs

CPHI Frankfurt 2022



Fiona Barry
Editor at PharmSource, a GlobalData product

Psychedelics: The Next Trip for the Pharma Industry

Mind-altering psychedelic drugs such as LSD, "ecstasy", and "magic mushrooms" are moving into the pharmaceutical mainstream and creating substantial opportunities for CMOs with controlled substance handling qualifications. Regulators have recently approved clinical trials and even marketing authorizations for these chemicals, as doctors incorporate them into regimens for widely prevalent indications such as post-traumatic stress disorder (PTSD). Physicians hope their use will help reduce opioid prescriptions to combat the addiction epidemic. The potential market for psychedelics is huge: according to GlobalData's Epidemiology database, there were 29.2 million cases of PTSD alone in 2020 across the 16 major markets.

the FDA and EMA approved Johnson & Johnson's Spravato (esketamine) in 2019 for treatment-resistant depression, their first approval of a psychedelic treatment for a psychiatric disorder in both the US and EU.

Psychedelics (also known as serotonergic hallucinogens) are compounds with appreciable serotonin 2A receptor agonist properties that can alter consciousness in a marked and novel way. Naturally occurring psychedelics are DMT, mescaline, psilocybin, THC, and LSD. Synthetic psychedelics also exist. These substances tend to also be classed by their structure: tryptamines (structurally resembling serotonin), phenethylamines (structurally resembling epinephrine and norepinephrine), and ergolines (derived from ergot).

Amphetamines are on the market

Amphetamine-based psychedelics such as Adderall (amphetamine aspartate + amphetamine sulfate + dextroamphetamine saccharate + dextroamphetamine sulfate) have long been used as therapeutics, and now researchers are exploring other psychedelics, either repurposing illicit drugs or by altering the chemical structures of marketed pharmaceuticals to produce safer and more predictable results.

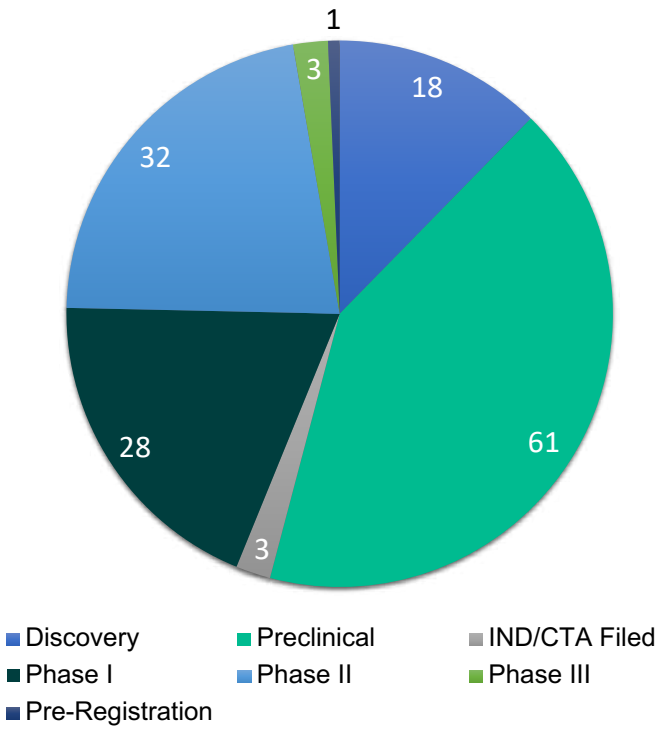
In the latter category, the FDA and EMA approved Johnson & Johnson's Spravato (esketamine) in 2019 for treatment-resistant depression, their first approval of a psychedelic treatment for a psychiatric disorder in both the US and EU. Esketamine is derived from the anesthetic ketamine. In August this year, the FDA approved Axsome Therapeutics' Auvelity, (bupropion hydrochloride + dextromethorphan) for major depressive disorder. Clinical trial results suggest Auvelity works faster than traditional antidepressants, which can take weeks to have an effect.

Related psychedelics are not far behind. Avanir Pharmaceuticals is developing a Phase III NMDA receptor antagonist, deudextromethorphan hydrobromide + quinidine sulfate, for schizophrenia and traumatic brain injuries. Similarly, the nontoxic and nonhallucinogenic chemical cousin of ibogaine, named DLX-7, has shown success in preclinical studies by Delix Therapeutics for anxiety, depression, and addiction.

LSD and mushrooms

Drugs such as MDMA (midomafetamine), psilocybin, and LSD have long been taken recreationally but are increasingly being used in medical research. GlobalData's Clinical Trials database shows at least 51 trials were initiated for psilocybin, 10 for MDMA, and six for LSD during 2019–2021. The closest to market is MDMA, in Phase III for PTSD and Phase II for social anxiety disorder, sponsored by the non-profit Multidisciplinary Association for Psychedelic Studies. AWAKN Life Sciences has an MDMA product in Phase II for alcohol addiction. MindMed's LSD product is in Phase II for major depressive disorder, attention deficit hyperactivity disorder (ADHD), cluster headache, and anxiety disorders.

Figure 1. Pipeline Psychedelic Drugs for Central Nervous System Indications



Source: GlobalData, Pharma Intelligence Center. © GlobalData

Notes: IND = Investigational New Drug; CTA = Clinical Trial Application.

Psilocybin is the active constituent in what are commonly known as 'magic mushrooms,' a naturally occurring chemical compound that is increasingly seen as highly safe and effective in treating many forms of mental illness and substance use disorder. It is currently in Phase II development for multiple psychiatric indications by Braxia Scientific, Tryp Therapeutics, Compass Pathways, Ceruvia Lifesciences, Revive Therapeutics, and a Copenhagen psychiatric hospital.

Even if these drugs are approved, their accessibility and the scalability of the regimen to all patients will be an obstacle that could reduce use among any potential treatment population. Studies so far suggest that for the greatest level of benefit, psychotherapy is needed alongside psychedelics. That creates an additional requirement that will limit scalability in the marketplace compared to traditional treatment models, which only require the patient to consume medicines.

Legal obstacles – but CMO opportunities

Imprisonment for psychedelic possession in the US increased after 1986, when President Reagan signed the Anti-Drug Abuse Act. This allotted $1.7 billion to the War on Drugs, and established mandatory minimum prison sentences for specific drug offenses. Many of the strict legal and social stances formed against psychedelic drugs in the 1980s have begun to relax. On January 11, 2022, the launch of the International Therapeutic Psilocybin Rescheduling Initiative (ITPRI) occurred, a global coalition working to promote and secure a rescheduling of psilocybin under the 1971 United Nations Convention on Psychotropic Substances.

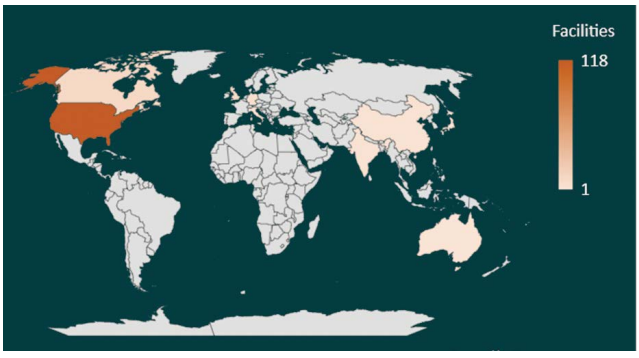
CMOs have already secured manufacturing agreements for marketed psychedelics such as Takeda Pharmaceuticals' Mydayis ER (amphetamine aspartate + amphetamine sulfate + dextroamphetamine saccharate + dextroamphetamine sulfate) for which Cambrex Corp is producing the API and Patheon (owned by Thermo Fisher Scientific) is manufacturing the finished dosage form.

Authorisations for manufacturers to produce controlled substances require very strict security for the production and storage of the active substance, and vetting of the personnel involved in the active substance manufacture. In the US the Drug Enforcement Administration (DEA) classifies

Controlled substance capabilities and facility requirements can be prohibitively expensive. Smaller pharma companies are not able to possess or purchase these kinds of sites, so CMOs have a good chance to generate business by owning controlled substance capabilities.

chemicals into five schedules depending upon the drug's acceptable medical use and the drug's abuse or dependency potential. The abuse rate is a determinate factor in the scheduling of the drug; for example, Schedule I drugs have a high potential for abuse and the potential to create severe psychological and/or physical dependence with no currently accepted medical use. Examples of Schedule I drugs include heroin, LSD, cannabis, MDMA, methaqualone, and peyote. If any of these substances were to become FDA-approved then their associated DEA schedule would have to be lowered. Perimeter fencing, steel vaults, and electronic monitoring are the kinds of requirements an API manufacturer of a Schedule II drug would need to provide.

Figure 2: DEA Schedule 1 Contract Manufacturing Facilities

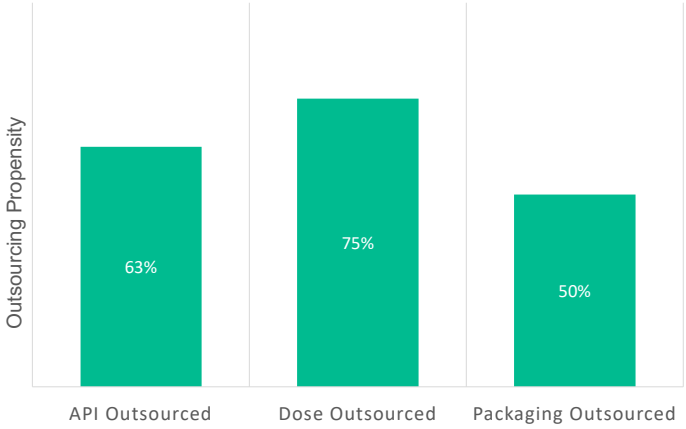


Source: GlobalData, Pharma Intelligence Center. © GlobalData

GlobalData's Contract Service Provider database shows there are 245 contract manufacturing organisations with 386 facilities worldwide permitted to handle DEA-scheduled products (excluding pharmaceutical companies that also offer contract services). Only 152 of these sites can carry out Schedule I manufacture, and 272 facilities able to carry out production of Schedule II or III substances.

Controlled substance capabilities and facility requirements can be prohibitively expensive. Smaller pharma companies are not able to possess or purchase these kinds of sites, so CMOs have a good chance to generate business by owning controlled substance capabilities. As observed in Figure 2, a significant proportion of innovator psychedelic drugs approved in the US, UK, and/or EU are outsourced, with dose manufacturing being outsourced for 75% of these drugs.

Figure 3: Approved psychedelic drugs – by outsourced manufacturing rate



Source: GlobalData, Pharma Intelligence Center. ©GlobalData

Note: Includes only innovator drugs approved in the US, UK (post-Brexit) and/or EU, specifically through the EMA's centralized authorization procedure.

Question and Answers with CPHI Frankfurt & Fiona Barry (FB)

CPHI: Are you able to put any predictive figures (or a range: e.g. xxx-xx`x million) on the potential size of the manufacturing opportunity with these drugs. Assuming that approvals do start to happen. (I.e. assuming we get say 1-3 drugs approved in the next 5 years?) Or looking at the pipeline of drugs coming through if we see a typical level of attrition/approval? (do you have any analysis for how many might make it)

FB: *"We estimate that the total number of major depressive disorder cases alone in the eight major markets (US, France, Germany, Italy, Spain, UK, Japan, and Canada) will rise to more than 55 million by 2029. That is an enormous market, even if psychedelics capture only a small portion of it. We predict sales of Axsome Therapeutics' Auvelity (dextromethorphan + bupropion) to reach $1.3 billion in those eight major markets by 2029."*

CPHI: do you think synthetic psychedelic drugs (e.g. synthetic psilocybin) will be the majority of research targets in a few year's time, as they provide better ability to gain patent protection.

FB: *"Interesting question but can't comment unfortunately. Will look into this for a future article!"*

CPHI: with the FDA leading on journey towards approvals, and the USA having the most schedule ii sites, is this an area where US based CMOs look well placed to pick up the majority opportunities in the next few years?

FB: *"Pharma companies are focusing their psychedelics development on the US market, with 100 products in the pipeline aimed at this country, dwarfing Canada at 22 and the EU at 18. So CMOs with FDA authorizations to produce these substances will be very well placed to win contracts over the next few years. Most of the contract manufacturing facilities with the necessary permissions to manufacture DEA Schedule II products are understandably based in the US, where there are more than 250 qualified CMO sites. This dwarfs the rest of the world, which has fewer than 50 DEA Schedule II-approved contract facilities."*

CPHI: one of remaining difficulties is that patients are likely to need top-ups with another round of therapy (does this therefore make for stronger business care or just adds extra regulatory complication?)

FB: *"That would need to be balanced against the advantages of psychedelics – for instance, there might be greater patient compliance on Auvelity than traditional antidepressants; trials showed Auvelity was not associated with weight gain, one of the undesirable side effects of antidepressants. If psychedelics become prescribed as part of a regimen that also includes psychotherapy, this would push the price higher. Auvelity's price has not yet been announced, but we expect it to cost over $1,000 per year, which is already expensive. We might see psychedelics' use restricted to second line therapy."*

CPHI: any comment on the CPHI Survey Findings? (400 executives) – pre-release data below?

"By when will the FDA approve its first psychedelic drug* for a therapeutic treatment? (e.g. MDMA for PTSD / Psilocybin for depression or alcohol addiction etc)?"

1-2 years: 27% **3 years: 44%**
4+ years: 22% **Never: 7%**

***Defined here as a drug than induces a hallucination**

"Looking ahead, how many new FDA approved psychedelic drugs will be on the market in 2032?"

0 drugs: 6.5% **1-2 drugs: 25.5%** **3-5 drugs: 39%**
5-10 drugs: 16% **10+ drugs: 13%**

FB: *"It can be difficult to predict approval rates for psychedelics, since we have no historic precedents for some of these molecules. Aside from those already approved (amphetamines, Johnson & Johnson's Spravato and Axsome Therapeutics' Auvelity), some of the closest to market are MDMA, in Phase III for PTSD and Phase II for social anxiety disorder, sponsored by the non-profit Multidisciplinary Association for Psychedelic Studies; and MindMed's LSD product in Phase II for major depressive disorder, attention deficit hyperactivity disorder (ADHD), cluster headache, and anxiety disorders."*

Adam Bradbury
Analayst, GlobalData

COVID-19 Variants and Advanced Biologics Drive Injectable Opportunities and Innovation

The imminent approval of Omicron-specific vaccines globally and the increasing presence of market approved advanced biologics will drive demand for injectables and will continue to provide lucrative contracts for CMOs beyond 2022.

On August 15, the UK became the first country to approve an Omicron-specific vaccine. The Medicines and Healthcare Products Regulatory Agency (MHRA) conditionally approved Moderna's bivalent vaccine for use in adults. Moderna's bivalent COVID-19 vaccine targets both the original version of SARS-CoV-2 and the Omicron BA.1 variant and will be rolled out alongside the original Moderna, Pfizer, and Novavax COVID-19 vaccines as part of the autumn booster program.

Packaging has created bottlenecks in producing injectable drugs, as the industry had lacked capacity to make and fill enough vials in the face of high volumes of COVID-19 vaccine production. But other packaging types are growing in popularity: injectable drug approvals are trending towards self-administrations via auto-injector syringes. Meanwhile, ampoule-packaging facilities are common globally but account for a very small percentage of FDA and EMA innovative approvals as they have largely been replaced in North America and Western Europe, but are still extensively used in emerging markets because of their low cost.

Pfizer's and Moderna's Omicron-specific vaccines are in late-stage development or conditionally approved across most of the seven major markets (7MM: the US, France, Germany, Italy, Spain, the UK, and Japan), have demonstrated good efficacy against the COVID-19 variant, and will likely be available to citizens in the developed markets in the autumn to provide an additional booster and increase demand for injectable manufacturing.

Despite the advanced stage of COVID-19 vaccination programs in richer countries, which would suggest an approaching drop-off in contract manufacturing demand, there is still considerable need for variant-specific boosters. Once new vaccines for the Omicron variant are approved, they will partly make up for the waning interest in older COVID boosters in developed markets. The Omicron variant spreads more easily than earlier variants of the virus that cause COVID-19, including the Delta variant, and also has the ability to sometimes evade immunity from vaccines, previous infection, or both. The first case of Omicron was announced on November 24, 2021 by South Africa, with the first positive sample dating back to November 9. Vaccines were developed from the original SARS-CoV-2 strain but the variants that exist today are very different.

On June 25, 2022, Pfizer and BioNTech reported pivotal Phase II/III data demonstrating the safety, tolerability, and immunogenicity of two Omicron-

adapted vaccine candidates. This data has been shared with regulators, including the FDA, and a request for US emergency use authorization (EUA) is planned. Pfizer completed a submission to the EMA for an Omicron-adapted bivalent COVID-19 vaccine candidate, based on the BA.1 sub-lineage on July 19, 2022.

On July 11, Moderna announced Phase II/III clinical data for its bivalent Omicron booster candidate, named mRNA 1273.214. It is an adapted version of Moderna's approved Spikevax vaccine. The booster dose elicited a significantly higher neutralizing antibody response against Omicron subvariants BA.4 and BA.5, compared to the currently authorized Moderna booster, regardless of prior infection status or age. On June 27, the EMA started a rolling review for this Omicron-adapted vaccine and the FDA plans to review the vaccine for EUA.

On August 4, the US Department of Health and Human Services declared monkeypox a public health emergency, a move required to grant EUAs. On the same day, the FDA granted an EUA to Bavarian Nordic's Jynneos vaccine. The drug was already approved for subcutaneous use in adults at risk of monkeypox or smallpox, but the EUA will allow more people to be treated with a smaller dose by giving it to adults intradermally, which requires only one fifth of the volume of a subcutaneous injection.

Advanced biologics are also driving injectables demand. Certain innovative products like cell and gene therapies have a limited pool of staff and expertise that can engage with their production; large CMOs have been acquiring these capabilities in recent years and, even large and mega cap sponsors will require these services. Larger sponsor companies can also choose to dual-source their manufacture (using both in-house and outsourced production) and can use contractors as an additional site in a multi-site supply strategy that increases supply chain security and offers backup capacity. This is especially the case in an age of supply chain disruption caused by the pandemic and the Russia-Ukraine war. Outsourcing may also be pursued if it is more favorable in terms of time and/or cost. Contract packaging of cell and gene therapies also requires specialist capabilities, and contractors manufacturing doses often also provide the packaging as part of an integrated approach.

Packaging has created bottlenecks in producing injectable drugs, as the industry had lacked capacity to make and fill enough vials in the face of high volumes of COVID-19 vaccine production.

Increasing Self-Administration for Injectables

The majority of biologics are delivered through intravenous infusion or by subcutaneous injections. Innovative FDA auto-injector products are primarily biologics, and tend towards self-administration and patient-centricity. Injectable CMOs and CPOs with capabilities to manufacture and/or package this class of products and in packaging that allows for self-administration will be at an advantage in the future.

Subcutaneous injectables are far more common in the pipeline than among marketed products. Subcutaneous injections are more readily self-administered compared to intravenous and other types of injectable routes of administration. The number of marketed auto-injector products is currently low, but about half of those have been approved since 2017, indicating the packaging type will gain more popularity in future. Increasing evidence has shown how patients tend to opt for auto-injectors over prefilled syringes or conventional syringes. In the last 10 years, patients' waiting times for an appointment have sometimes been excessive, and hospital-administered injectables add burden to typically overstretched clinicians. Injections that are self-administered and are as convenient as possible also encourage higher levels of patient compliance, thereby improving treatment outcomes.

Contract Packaging Leaders by FDA and EMA Contracts

In the "Contract Injectable Packaging Trends in the Bio/Pharma Industry" publication, GlobalData assessed packaging contracts for US and EU innovator and biosimilar injectables approved between 2012–21. The top contract packaging organizations for injectables are well-known dedicated CPOs like PCI and Sharp, along with large CMOs such as Patheon, Catalent, and Vetter, which are more renowned for their commercial dose manufacturing but also offer integrated packaging services. Apart from Pfizer CentreOne

(the contract manufacturing arm of Pfizer Inc), all the top contract packagers for injectables have a dedicated contract business model.

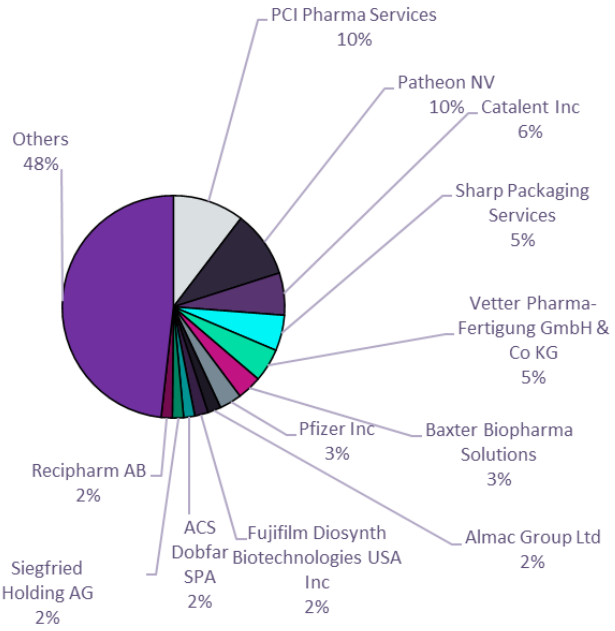
Since 2016, PCI Pharma Services has acquired manufacturing facilities in North American, EU, and Asia-Pacific markets, and has expanded its packaging business through acquisitions of Sherpa Clinical Packaging, Pharmaceutical Packaging Professionals, Millmount Healthcare, LSNE, and Bellwyck Pharma Services, and has boosted its capacity for packaging. PCI's 10 commercial packaging and 12 clinical packaging facilities are in the US, UK, Canada, Germany, Ireland, and Australia. These facilities serve the US, EU, and Asia-Pacific markets. A high number of clinical packaging and containment facilities add to the value of the company's service offering. Clinical packages are typically customized for specific clinical trials and only a small number of batches are produced to meet the need of the clinical trial. Clinical packaging requires specialized capabilities that commercial packagers do not typically possess.

Overall, Thermo Fisher Scientific (Patheon) has 17 sites offering some form of commercial packaging and 32 sites offering some form of clinical packaging. In January 2021, Thermo Fisher Scientific acquired Henogen SA, a provider of contract manufacturing services for vaccines and therapies to biotechnology companies, from Novasep Holding SAS. Henogen has two locations in Seneffe and Gosselies, Belgium. The transaction has allowed Thermo Fisher Scientific to expand global capacity and address growing demand for cell and gene therapy, including viral vectors.

In May 2022, Catalent started investing $350 million in biologics API and dose manufacturing at its facility in Bloomington, Indiana, US. Catalent will add 2,000L single-use bioreactors, QC laboratories, and fill-finish and packaging space for cartoning, auto-injectors, syringe filling, barrier isolation filling, and lyophilized vials. When completed in Q4 2024, the site will offer clinical and commercial fill-finish. Overall, Catalent has 24 sites offering some form of commercial packaging and 24 sites offering some form of clinical packaging.

The top sponsors for commercial injectable packaging contracts are some of the largest pharma companies worldwide, even though large or mega cap companies are less likely than smaller companies to outsource to contractors. Larger bio/pharma companies have the funds to invest in their own injectable packaging facilities. CPOs will have to find ways of enticing larger cap pharma companies, which often have the largest portfolio of products to outsource. There has been considerable supply chain disruption caused by the pandemic, and large cap sponsors use additional sites in multi-site supply strategies to increase supply chain security and offer backup capacity, which can be an advantage for CPOs looking to increase their business with larger customers.

Figure 1. Top contract packagers for injectables approvals packaging, 2012–21



Source: GlobalData, Pharma Intelligence Center Drug Database (Accessed April 7, 2022) © GlobalData Note: Figure excludes generics, and drugs present may have more than one form of packaging.

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COMIRNATY
Sterile concentrate
COVID-19 mRNA
6 doses after dilution
Discard dated
PAA174601
LOT/EXP
FG7387
11/2021

Part 4

Excipients

CPHI Frankfurt 2022

Iain Moore
Global Head of Quality Assurance, Croda

Building a more resilient supply chain for excipients

The COVID-19 pandemic had an unexpected and traumatic impact on business supply chains, but as many nations begin to learn to live with the virus, the aftermath seems to be as severe and painful as all the initial lockdowns. It is like the pandemic took a spring and compressed it to its maximum, then as the tremendous success of the COVID-19 vaccines allowed lockdowns to end, the spring has been explosively released, resulting in a tremendous surge in demand. Whereas all supply chains are susceptible to the bullwhip effect, where small changes in demand, usually at the consumer level, are then magnified across the supply chain until the primary suppliers see major swings in demand, this situation is like nothing we have experienced before.

The increased demand spurred manufacturing organisations to get back to work in order to stock depleted supply chains. This was the first aftershock and set everything in motion, and as this report is prepared, we are seeing the "return" of the initial expansion with a downturn in demand now coming as supply chains re-saturate. This natural deceleration has been exacerbated by the surge in energy costs and the associated negative economic impact on demand.

The increased demand spurred manufacturing organisations to get back to work in order to stock depleted supply chains

It is important to remember that much of that previous stability was because the systems had come to a balance point and as a result were quite resilient to outside influences. Before COVID, there was a low-risk supply chain, and inventory strategies like Just-in-Time (JIT) could be implemented successfully, keeping low stock inventories, relying on suppliers to deliver on their promise dates. Indeed, that stability allowed for supply chains to extend globally almost without any difference in risk to supply.

The procurement of excipients is not exempt from these supply-demand economic forces, although the impacts are different depending on whether the excipient is manufactured exclusively for the pharmaceutical market or is it predominantly sold for other applications. In the latter cases it can be that only a small proportion is sold to the pharmaceutical market.

Where the excipient is manufactured exclusively for pharmaceutical use, then there will be insulation from much of this turbulence at least on the demand side, as people will still require medicines and put a priority on their safe supply. But for non-dedicated excipients then it can be expected that they will be more vulnerable to the general economic demand fluctuations and so continuing manufacturing availability may also be a contributing factor to an uncertain supply.

Nevertheless, the logistics of obtaining excipients in a timely manner and then having them delivered to the drug product manufacturer is the current challenge, regardless of the type of excipient. In this respect for the immediate short term, we can expect further inaccuracies to abound in predicting when excipients will be delivered. The supply chain disruptions will continue, and it is looking like the current uncertainties will persist well into 2023.

To deal with the new now, successful organisations need to adapt to these circumstances and the immediate future. Continuing with purchasing and supply strategies that were fine pre-pandemic are not going to be successful in the mid-term while the current disruptions continue. Hoping that matters will settle down soon and return to "normal" does not look a viable option.

New strategies that generate greater resilience will be required to buffer current oscillations and any subsequent shocks. This change will have to apply along the supply chain and excipient suppliers will also have to revisit their own supply chains and identify where the risks have changed. Likewise, the pharmaceutical manufacturers.

New strategies that generate greater resilience will be required to buffer current oscillations and any subsequent shocks.

To begin with a careful analysis and a measured approach to the changed circumstances are required. Thus, revisiting supplier and excipient risk assessments is an excellent starting point. There have been many changes in the supply chain and so the risks will have altered. What may have been a low risk in the past is now a high one, and what may have been a good mitigation technique is now ineffective. A systematic and objective analysis will then allow for revised strategies and tactics to be identified and implemented. Any new control measures will also have to be evaluated to make sure that there are no adverse impacts elsewhere.

Combining the procurement risk assessments with the knowledge about the supplier in the one required for the determination of the GMP to be applied by the excipient manufacturer These risk assessments should already contain some information about the excipient manufacturer and their location, and for which some supply chain risks should have been identified even if they were not relevant to the determination of the required GMP.

What is certain is that more information about sources of raw materials for the excipient as well as the excipient distribution process will be needed, so that the vulnerabilities in those supply chains can be included in the assessment. Such a structured approach will then highlight specific strategies and tactics to secure the supply chain for each excipient.

What is certain is that more information about sources of raw materials for the excipient as well as the excipient distribution process will be needed,

There are a few obvious options to build more resilience directly, including building buffer stocks of the excipient. But as stock levels may already be low at this point of the pandemic, and demand

now so high, it will be difficult to rebuild them to the required or even greater levels in the short term. This tactic may not be applicable to all excipients, particularly those with short shelf lives.

Another more attractive option is to shorten the supply chains with more local sourcing even if these prove to be more costly to procure. The higher costs will be tolerable if there is more accuracy and certainty about the timeliness in receiving the excipients.

Good suppliers were always at a premium and provided value beyond a price charged for the excipient, so seeking new suppliers is another risk to manage as well. In this regard the International Pharmaceutical Excipients Council (IPEC) has published an increasing number of guides and position papers over the past ten years which have set achievable, pragmatic standards which have also received good regulatory acceptance. Several guides are focussed on effective communication between the excipient supplier and their customers, the excipient users. Where both parties agree to use the format of these communications, supplier qualification can be accelerated with no loss in the quality required. Key IPEC Guides here include the Excipient Information Packs (EIPs) and Quality Agreement templates.

Good suppliers were always at a premium and provided value beyond a price charged for the excipient

In terms of manufacturing then, the widespread acceptance of the IPEC-PQG GMP Guide and the EXCiPACT excipient GMP certification standard also allows for a speedier approval of new suppliers where they operate in compliance to these definitions of GMP.

In previous times that approval process may have been stepwise with the “paperwork” having to be approved first before any technical evaluation of the excipient itself is completed. And here is an opportunity to accelerate that process when a new supplier demonstrates compliance to IPEC-PQG or EXCiPACT GMPs, then the qualification of the supplier is likely to be much lower risk than one which is not demonstrably compliant. For these compliant suppliers, the two steps of supplier qualification and excipient approval can be completed in parallel with confidence, thus saving time.

Excipient suppliers may have to change their manufacturing processes too, with newly sourced raw materials for example. There may also be changes in the logistical arrangements of delivering excipients, and this is where another IPEC Guide, the Significant Change Guide can be used to help identify when to notify excipient users about changes, thereby allowing them to perform their own impact assessments In some cases, significant changes can require a lot of work for the pharmaceutical user including update of risk assessment and even regulatory filings.

In the mid-term, unexpected material availabilities look likely to recur, be it from the manufacturing or the logistical delivery of excipients and so a continuing trend will be for the rapid sharing of knowledge and information along the supply chain. Much more than is currently the case, particularly in the logistical phase of delivery. Here real time methods to track and trace shipments will help the customer to plan for the goods arrival with more confidence. This will draw transport and intermediate warehousing companies into the picture, so that they can contribute to the communication of the position of the excipients while in transit. For intermediate warehouses, the IPEC GDP (Good Distribution Practices Guide) and the corresponding EXCiPACT GDP and GWP (Good Warehousing Practices) standards will be very valuable for the qualification of these supply chain actors.

If this is the situation now and in the near term, then what does the future hold? We should remain hopeful that we can dampen the current supply chain oscillations. However other factors, some political, look likely to continue to drive a retraction from the global nature of prior supply chains. We can expect to see more local supply, and thus shorter transport routes. This has to be good in sustainability terms too with the concomitant reduction in scope 3 carbon dioxide emissions. Sustainability issues will also be increasingly important in the industry in the mid to long term, but that is another topic altogether.

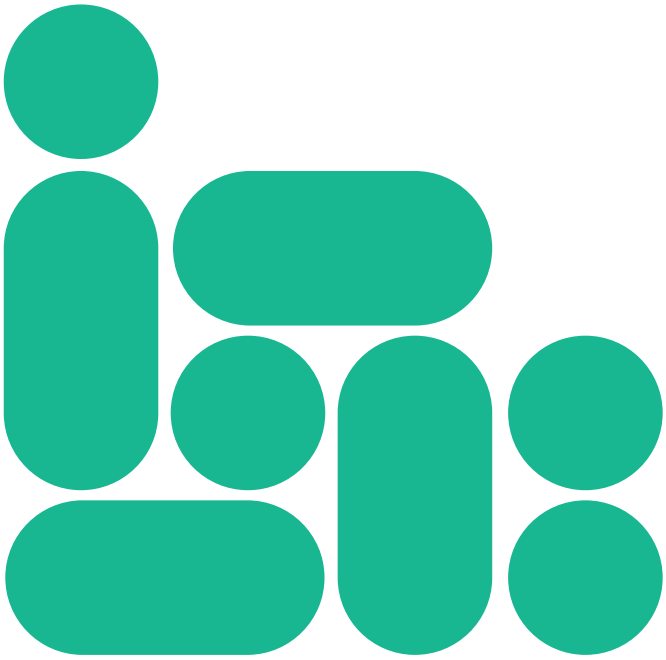
We should remain hopeful that we can dampen the current supply chain oscillations. However other factors, some political, look likely to continue to drive a retraction from the global nature of prior supply chains.

In the mid-term the need for local supply and demand solutions is going to increase as strategies to reduce our impact on global warming accelerate. The current pressures may mean we have lost the momentum towards globalisation. However, with sourcing more locally we will still require the use of well accepted standards and guides, so there will be no loss in terms of having greater harmonisation.

In conclusion there are four things to build resilience in the supply of excipients:

- Greater knowledge sharing between suppliers and users of excipients concerning the risks to the supply chain of raw materials, the excipients themselves as well as live information about the status and position of shipments, even to the extent of real-time data availability.
- Revised risk assessments to identify and mitigate supply chain threats, with likely shorter supply chains
- Review of buffer stock levels.
- Greater use of standard methods of exchanging information so that more rapid qualification and assessment processes can occur.

There is no doubt that the application of the IPEC guides and EXCiPACT standards will be of increasing importance in adding resilience to the supply chain and in assuring the safety and availability of excipients.



Nigel Langley
Global Technology Director at BASF Corporation Pharma Solutions

CPHI's questions on co-processed excipients

CPHI: Given your close and active involvement in the Novel Excipient's Pilot programme - where do you think we are in terms of having novel excipients available to drug developers (or having it listed in the inactive ingredients list) in the next 5 years.

NL: *"Certainly, the novel excipient pilot process should provide both an incentive to develop novel excipients and also to accelerate their adoption. It is unclear at this stage how many novel excipients will be in approved drug products during the next 5 years as the pilot program is only half way through the two-year evaluation period."*

CPHI: You mentioned that while waiting for the FDA's decision on the pilot programme findings, your organisation has been gaining support from other excipient manufacturers and petitioning (presenting the case) for removing co-expressed excipients from novel excipients category. Could you please elaborate on that and outline of this might develop over the next few years?

NL: *"Industry consortia are currently working on a concept to engage the FDA in accepting co-processed excipients that meet certain, defined criteria. It is unsure how this will develop over the next few years; however, we hope to convince the FDA to consider this approach and then assist in global acceptance."*

CPHI: What are the main issues and why might co-processed excipient changes be in reality an even bigger benefit than the current novel excipient pilot programme (e.g., the rise of continuous manufacturing)

NL: *"The consortia believe this could potentially impact a greater number of excipients than what would be evaluated under the novel excipient program. This would allow greater usage of co-processed excipients in both innovator and generic drug products, especially in the area of CM. It is expected that less safety data and review time would be needed for co-processed excipients utilizing excipients that have already been reviewed/approved for safety in approved drug products (i.e., listed in FDA IID). This could result in faster commercialization and use of drug products."*

CPHI: Is there some type of standardisation or testing we could apply that could show these excipients don't have any interactions – how might we as an industry simplify this for the FDA and or other regulators?

NL: *"The type of testing will be very dependent on the type of excipients that may be evaluated/ considered. Testing is specific however the approach for demonstrating that no covalent bonds are formed should be standardized."*

CPHI: What is the bigger picture for novel excipients and co-processed excipients from global regulators (how do we ensure we work toward a standardised global regulatory viewpoint)?

NL: *"This is very important as the users of excipients are developing medicinal products for global markets. Our approach is to get FDA acceptance of this concept and then their willingness to take this up on a more global platform via ICH, to ensure a consistent, harmonized, global position."*

CPHI: Do you have any perspective in future processed excipient manufacturing – e.g. we read about the potential of 3-D printing and 'Fused deposition modelling' recently?.

NL: *"Although there has been one FDA approved 3D printing drug product, the technology and its application for personalized medicine is still developing. Therefore, the specific excipient needs are somewhat undetermined at this time. As new manufacturing processes are developed, it is likely that excipients with new and/or different functional properties will be required."*

CPHI: There are obviously lots of potential excipients out there to combine – so if this goes ahead, are we now just at the start of new period of experimentation where we could make incremental advances that improve excipient performance year on year? (a kind 'gold rush of excipient innovation' if you will).

NL: *"If the perceived regulatory burden could be lifted, it should stimulate innovation and commercial success. This would likely lead to the potential for further innovation and potentially allow for customization of co-processed excipients to deliver the desired functional properties for a given application. This would be a good example of designing for purpose and could allow an excipient supplier to have a menu of options (different ratios of the same excipients) for these materials. This would however require both a regulatory and business model change."*

CPHI: How might this play out between excipient makers – could we see more collaborations in a world where co-processed excipients are not seen as novel?

NL: *"Collaboration between excipient suppliers and pharmaceutical manufactures would be critical in order to make customized co-processed excipients both financially viable and available in the future."*

CPHI: What might be the role of AI in the development of future formulations and/or novel excipients (I believe BASF has something called ZoomLabs – don't know any more beyond that though)

NL: *"Digital tools to enable drug formulation will be used more frequently in the future; however, it is too early to say that they would accelerate and/or improve conventional drug development processes and/or timelines."*

CPHI: Do you think wider pharma has yet realise the potential to make their drug development simpler, and/or the possibilities co-processing might offer in making previously unviable candidates viable? [e.g., can you see big pharma taking a more active interest now, do you think they should]

NL: *"Certainly, co-processed excipients have the ability to simplify and improve consistency and robustness of some drug manufacturing processes."*

CPHI: We have focussed mostly on novel drug creation – but longer -term lower manufacturing costs and continuous processing should deliver the biggest benefits to generic companies (what is your perspective here on co-processed excipients)

NL: *"Truly novel excipients based on new chemistry are limited to innovators. Co-processed excipients would be one area that could benefit both innovator and generic drug manufacturers in lowering manufacturing costs and implementing continuous processing."*


PASSAGE
WEISS
FRAUEN
Schindler
& Werb AG
TAXI

Part 5

Next generation manufacturing and near home care

CPHI Frankfurt 2022

Bikash Chatterjee
Chief Executive Officer, Pharmatech Associates

Continuous Manufacturing Will Alter the Drug Manufacturing Landscape a Decade from Now

As we emerge from the COVID pandemic to assume a new normal for business, the industry has changed in several positive ways. The speed with which the COVID vaccine was developed, tested, and approved, reminds us of what is possible if we harness our collective intelligence and expertise as an industry and focus on a problem that had to be solved. The pandemic however exposed the weaknesses of a global supply chain in the absence of a strong business continuity plan. Backed by strong government support, the merits of Pharmaceutical Continuous Manufacturing (PCM) as a cost-effective tool for reshoring essential APIs and medicines is now front and center in the U.S.' and many other countries' preparedness strategy. PCM is a topic that has been much maligned and debated over the last half century. PCM's detractors cite a myriad of hurdles to implementation that they believe are too large to overcome for a risk-averse industry, but it is a mistake to look at barriers to PCM adoption in isolation. The industry is pursuing innovation in many areas and the skills and infrastructure required to make each innovation area will work together to lower the risk of adoption of any one initiative, including PCM. Shifting to PCM will forever change the dynamics of the marketplace and allow the pharmaceutical industry to realize the next level of business performance and move toward on-demand manufacturing.

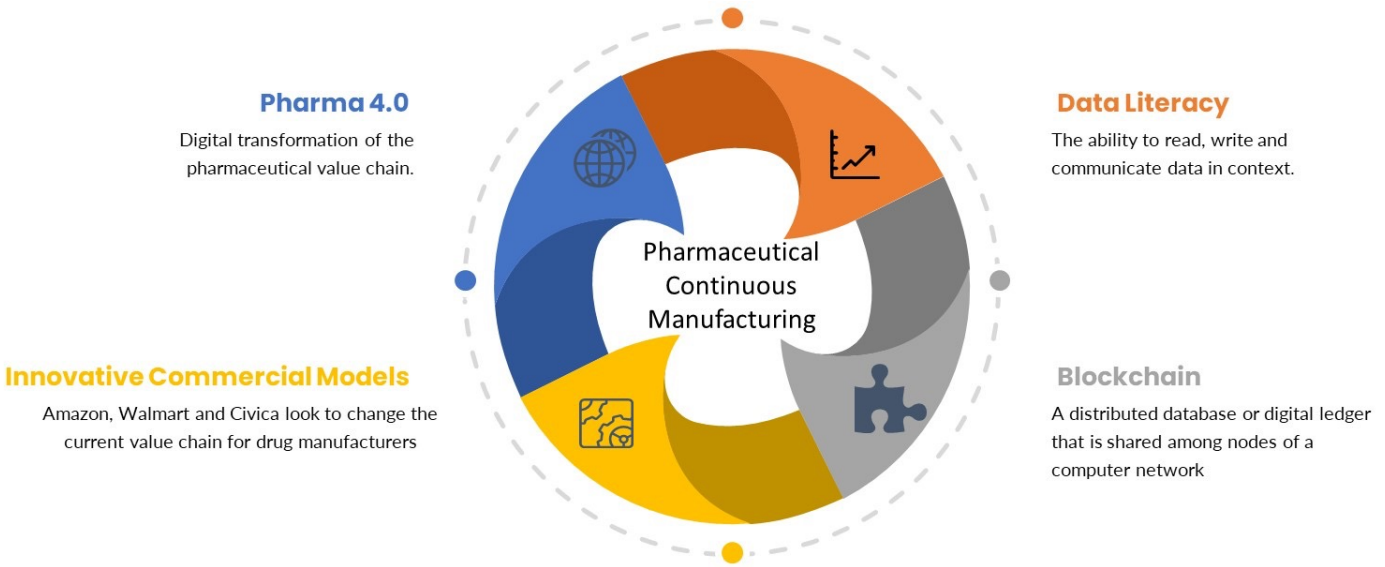


Figure 1. Innovation drives PCM adoption

Industry Innovation Initiatives

Coming out of the pandemic, digital initiatives such as Pharma 4.0, developing data literacy and implementing blockchain technology have been broadly supported by the industry as essential to being competitive. These strategic initiatives require drug manufacturers to acquire the expertise and capability to both implement and maintain them. Figure 1 captures four initiatives that either share predicate capability requirements or emphasize the strategic value PCM represents to the industry.

The Case for PCM

PCM differs from classical batch manufacturing in several ways. Unlike batch manufacturing, in PCM the material transfer rates between each process step are the same. Some have attempted to equate continuous manufacturing with temporal measurements, e.g., operating 24/7 for multiple days, but this is more of an application consideration than a predicate component of PCM. In fact, continuous process manufacturing cycle times are much shorter than batch process times to manufacture the same amount of finished product mainly because there is no intermediate product storage, sampling and testing required to release the product to the next processing step.

The advantages of PCM are many, when compared to conventional batch processes

The advantages of PCM are many, when compared to conventional batch processes. Batch processing requires scaling up the process and equipment as the drug therapy moves through its clinical phases. Beyond the large capital and facility space required to support the process development, the complexity of characterizing and controlling scale-independent and scale-dependent variables to develop a defensible control strategy must be confronted at each step in the development of a commercial process. PCM avoids this complexity since a commercial process does not require larger capacity equipment and can be achieved by simply running longer. This translates to shorter development times and lower regulatory CMC risk. PCM does require a higher level of characterization and the initial control strategy may rely on a more sophisticated analytical control strategy including off-line, at-line and in-line testing. But once that is done, fundamentally the drug sponsor has reduced any health authority's risk in terms of the clinical material used in each phase of the development program. This greater depth of characterization for PCM also simplifies any technology transfer to another site or CDMO if the drug sponsors pivotal clinical and commercial plan is to outsource manufacturing.

In the U.S. the FDA has cited lower process scale-up risk and heightened level of material and process understanding as a big reason for PCM's faster times to market and regulatory approval[1] vs. conventional batch submissions. This trend will continue as more filings are submitted to the agency.

PCM: Quality and Time-to-Market

Another big advantage PCM has over batch processes is the savings in terms of cost of quality. A Cost of Quality (COQ) methodology is useful to evaluate impacts to an organization from poor quality or to estimate savings from process improvements as they are implemented, to ensure high quality safe and effective drugs, one of the basic tenets of our industry. COQ considers the costs associated with ensuring good quality product and the costs associated with investigating and dispositioning non-conforming material. These expenses can cannibalize the profitability of a drug very quickly. The material and process understanding, and the monitoring strategy for PCM provide the opportunity to make corrections when process drift is detected during the process minimizing the amount of non-conforming product for every manufact uring run. The results are higher yields, greater process predictability and greater product uniformity. This enhanced process understanding also allows quality to make more informed decisions regarding the suitability of non-conforming product.

The material and process understanding, and the monitoring strategy for PCM provide the opportunity to make corrections when process drift is detected during the process

While many ethical drug manufacturers are making the jump to PCM, the benefits for generic drug manufacturers are equally compelling, particularly when it comes to quality. Even though the investment in skill set and equipment may

seem large at first the same benefits of shortened regulatory time, higher yields, and gross margin recovery in a downward pricing market more than offset the costs. One area of perennial challenge for all generic drug manufacturers looking for approval in the U.S. is satisfying the quality by review (QbR) component of a submission. This is often the core driver for the multiple back-and-forth conversations with FDA that extend a submission's approval.

As we near another patent cliff of blockbuster drugs this decade, the ability of generic drug manufacturers employing PCM to be first to file and be ready to rapidly expand to grab and hold market share is invaluable.

The QbR is a general framework for the chemistry, manufacturing, and controls (CMC) assessment of FDA's abbreviated new drug application (ANDA) which, incorporating the most important scientific and regulatory review questions, focuses on critical pharmaceutical attributes essential for ensuring generic drug product quality and comparability to the reference listed drug (RLD). The QbR serves two purposes for the CMC assessment of ANDAs. First, it provides a guide to the reviewer to evaluate whether a product is of high quality and determines the level of risk associated with the manufacturing process and the design of the product. Second, it provides transparency to sponsors about the logic that reviewers invoke in their CMC reviews. The byproduct of PCM process design addresses the primary elements of the QbR, thereby reducing regulatory risk and shortening the review and approval cycle. As we near another patent cliff of blockbuster drugs this decade, the ability of generic drug manufacturers employing PCM to be first to file and be ready to rapidly expand to grab and hold market share is invaluable.

Implementing PCM brings the industry one step closer to "on demand" manufacturing that provides tremendous flexibility to adapt to market opportunities and unprecedented supply chain flexibility. The bottom-line impact of exploiting market opportunities is just too compelling to keep the industry from jumping to PCM.

Lastly the environmental benefits of adopting PCM are becoming an ever-larger consideration for many organizations as evidenced by the rapid emergence of **environmental, social and governance** (ESG) programs. As an industry that generates a larger carbon footprint than the automotive industry[2] the impact of PCM to reduce the carbon emissions of a facility is a compelling benefit. From a business perspective, we recognize that for some markets ESG considerations are a key element for entering a market[3]. For example, Amgen's continuous biomanufacturing plant in Singapore generates 69 percent less carbon emissions than their conventional batch processing plant. Sanofi's plant in Massachusetts generates 80 percent less carbon emissions than its first-generation manufacturing facility [4].

PCM Adoption

So, when the benefits and advantages of PCM are so compelling why has it taken so long for the industry to make the move? The most prevalent reason given is regulatory uncertainty. While FDA and EMA have been pushing the industry to adopt PAT since 2004 there has been a lack of harmonization regarding what health authorities will require.

This is evolving. The FDA issued its guidance on the Quality Considerations of Continuous Manufacturing in 2019 that highlighted the key considerations in drug manufacturing impacted by PCM. Moving forward in 2021, the International Committee on Harmonization (ICH) issued its ICH Q13 draft guideline for public comment building upon the FDA's guidance and providing greater guidance regarding PCM process development and characterization. The United States Pharmacopeia (USP) has made PCM a core focus area by building a seasoned team of experts with experience successfully bringing PCM manufacturing-based drug therapies through FDA and providing frameworks for financial evaluation of the business opportunity on a product-by-product basis, and detailed support in terms of control strategy and CMC support. This is just the tip of the iceberg for PCM support to industry. Look for more structured guidance from other industry groups to demystify the development roadmap.

For early adopters, one challenge is the ability of equipment to meet all the operational requirements of PCM. Without universal standards for PAT implementations every integration of an

intelligent sensor is a development exercise to some extent. For some low-dose processes, the industry bumped up against the capability of feeders to maintain the accuracy and precision requirements to support the synchronized material transfer requirements. Simple operational realities such as cleaning validation and equipment changeover are still an issue but are being addressed by manufacturers and have improved at a rapid rate. There is tremendous industry focus on these issues from drug sponsors and equipment suppliers, and that is paradigm shifting.

For generic drug manufacturers the reluctance to pursue PCM has been due to a perception of high risk without substantial financial payback. Being able to reconcile the sunk cost in existing equipment and facilities against any new investment is a very real issue, as is a lack of access to the expertise to implement a PCM line. While at first blush these seem like daunting impediments the reality is the financial and business performance advantages of PCM are tangible enough to outweigh those early challenges. The financial ROI is justifiable when the model incorporates other business factors such as inventory carry cost (that often ties up 50 percent of available cash), increased yields, lower cost of poor quality (COPQ), and shortened approval times. The global PCM market is expected to grow to $3.06 billion by 2027 which might be incentive enough for generic and brand drug sponsors alike to look closely at the advantages of PCM[6].

PCM and Synergistic Benefits of Digitization

The pharma industry is no different from any other industrial sector, in that an organization's ability to effectively gather data and translate it into insight will fuel future business performance. The push to digitize the pharmaceutical supply chain and value chain, known as Pharma 4.0, means acquiring many of the same core capabilities that support PCM. Both are data centric and involve building a basic capability in data literacy at all levels of the organization. Data literacy[5] is the ability to read, write and communicate data in context, including an understanding of data sources and constructs, analytical methods and techniques applied, and the ability to describe the use case, application, and resulting value. It is an essential capability of any organization to avail of data that drives better business performance. Both Pharma 4.0 and PCM rely on managing large amounts of data that are organized, curated, extracted, transformed, and loaded into software solutions to analyze the information. These systems must be qualified and validated, just as any other GMP system. The same organizational components required to ensure the integrity of the data acquired and analyzed for Pharma 4.0 apply to PCM. Developing a comprehensive data management plan is a prerequisite for both. A data management plan addresses data management strategy, data governance, data quality, data operations, platform architecture, and required infrastructure and support systems required to ensure data integrity. These elements require significant investment in expertise and systems to effectively acquire, manage, and defend the validity of any GMP data used for quality decisions or regulatory submissions.

Another undeniable trend within the industry is the adoption of blockchain. The global healthcare blockchain market is estimated to grow to $7.3 billion by 2028[7]. Blockchain was first developed as the framework to support cryptocurrency but has evolved into a powerful vehicle to promote supply chain transparency. The initial attractiveness of blockchain was its ability to create a secure digital ledger that cannot be altered by either party in a transaction. This gives absolute transparency to both parties and ensures that each party fulfills their contractual obligations. Built for security not speed, blockchain solutions have evolved with the integration of machine learning and AI algorithms.

The core contributions of blockchain to the pharmaceutical industry include a universal upgrade in the data literacy requirements across most organizations,

As with PCM, implementing blockchain requires a high data literacy level, programming language capability, and database architecture understanding along with basic understanding of digitization of assets. Blockchain is being applied in a variety of ways beyond supply chain management to become a primary weapon against counterfeit drugs, addressing data privacy and governance requirements for clinical trials, and is being used to foster collaboration between R&D organizations in a secure manner. The core contributions of blockchain to the pharmaceutical industry include a universal upgrade in the data

literacy requirements across most organizations, making the relatively focused investment requirements for PCM a minor consideration to adoption, by contrast.

Innovative Commercial Channels

In the U.S., two major disruptors—Walmart and Amazon—have taken aim at the high cost of generic drug therapies and are looking to change the paradigm for drugs that make it on to the national formulary. The three largest pharmacy benefits managers (PBMs), namely CVS Caremark, Express Scripts and Optum Rx control more than 80 percent of all prescriptions processed in the U.S. These retailers believe they can provide a better customer experience and be more efficient than the current model. Downward pricing pressure has continued as the U.S. Congress looks closely at relationships between PBMs, pharmacies and health plans since the industry appears to be rife with the potential for self-dealing. Courts across the country are further questioning the terms of pharmacy "prescription benefit" card (or "cash card") agreements with PBMs and health plans, as critics charge that the walls between the business models turn out to be more like screens. Simplifying the value chain from manufacturer to patient will reward drug manufacturers that can manufacture as close to real time as possible, and produce high quality, safe and cost-effective drug therapies. The ability to rapidly acquire market share will change markedly as these new paradigms that remove the middleman gain traction. Even with the expected pushback from PBMs to undermine these new models, the overwhelming market movement toward patient centricity in all facets of drug development and healthcare makes these business initiatives very difficult to derail.

Exploiting Price Elasticity

Most healthcare services, including pharmaceuticals, are price inelastic, meaning the demand for healthcare services changes very little, regardless of whether prices rise or fall. Elastic prices, on the other hand, imply prices that have a big effect on demand, and there are many examples where drugs do show price elasticity. For example, in the U.S. market, a pharmaceutical company dropped the price of Adenosine 3 mg/ml from $42 to $39. This change brought about an increase in demand from 2,579 units to 4,833 unit[8]. Price elasticity allows a company to predict the effect a change in price will have on total demand, revenue, and margin, and charge different prices in different markets if elasticities differ across income groups. PCM provides drug manufacturers with a highly responsive manufacturing solution independent of inventory to exploit price elasticity strategies where they exist.

Conclusion

So, the next decade of the industry will see a very different marketplace than that of today, underpinned by the business performance horsepower of PCM. The impact of supply chain transparency via blockchain, the deployment of control towers, and the ability to effectively translate supply chain data into action that drives business performance will no longer be innovation initiatives, they will be the foundation of everyday business. The current PBM value chain will be radically altered with new more efficient frameworks putting patients in a position to enjoy high quality, cost effective and unadulterated drug therapies—with PCM anchoring the industry's ability to adapt to new business dynamics.

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Bikash Chatterjee (BC), Questions and Answers with CPHI Frankfurt

CPHI: CM is still very limited, how many CDMOs do you see being invested in CM in 3, 5 or 10 years?

BC: *"While today there are a handful, I see CDMOS growing slowly and steadily as the pharma industry adopts continuous manufacturing. The challenge for CDMOs with continuous manufacturing is that the processing is somewhat tailored to the formulation. Hence CDMOs can invest in equipment for platform processes such as direct compression but must understand there is no true one size fits all. The cost-saving and efficiency advantages of CM are attractive so I would look for most major CDMOs in the major markets in the U.S. and EU to invest in basic capabilities in the next decade with smaller markets lagging in their adoption. If I were to speculate on the number of CDMOs investing in CM, I would see <1% in the next three years, 3-5% in the next five years, and 5-10% in 10 year' time would have some continuous capability for the major markets."*

CPHI: By when do you think CDMOs would have to be invested in CM to not be left behind?

BC: Over the next five years, as the regulatory and operational benefits become more broadly known and realized in industry, CDMOs will have to build CM capability and expertise to remain competitive.

CPHI: What do you see as a next development of CM, next steps?

BC: *"The are several evolutionary stages ahead that will make CM more broadly adopted. Look for equipment designs to become more robust focusing on standardization of PAT technology and addressing the challenges with cleaning and change over. Look to PAT technology to become more robust and for comparability strategies become part of all vendors playbook. Look for more evolved data and control management software solutions to be available in the marketplace to address the basic compliance requirements as defined by ICH."*

CPHI: Do you think FDA/EMA will move to disincentivising batch manufacturing in the next 3-5 years, i.e., Slower approvals for batch? Or not?

BC: *"I think both health authorities have invested in shifting to a regulatory review process based upon science. CM lends itself to this philosophy. I do see CM submissions having the advantage of greater characterization and control leading to fewer questions and faster approvals."*

CPHI: Do you think CM will be used in API or Biologics or Finished products manufacturing? If so, can you put a timeline to that, for each?

BC: *"CM has a been used in API manufacturing for nearly 50 years. Still, there are some reactions that cannot be done safely with anything but a flow reactor. To date, there have been 11 finished drug products approved that were based on CM and I would look for that number to increase. Biologics are considering CM but as a hybrid solution in which upstream or downstream may be operated independently applying continuous principles. As PAT sensor technology continues to improve look for the industry to leverage CM to maximum benefit."*

CPHI: Can you give a geographical context to CM? Which region or countries do you think will invest in CM first?

BC: *"In the U.S., large Pharma and Biotech are leading the CM charge with concentrations on both coasts. Europe, especially Germany, has the most advanced equipment vendors driving innovation to address the needs of CM."*

CPHI: CPHI conducted a global survey among 400 pharma executives and over 93% think we will see an approval for either of these two drugs, with 70% predicting it inside the next 3-years. Looking 8-10 years out, the industry believes five therapies (average answer) will be approved. Do you have any thoughts on the data?

BC: "I do not think the FDA will approve a psychedelic in the next decade because most of these are classified as schedule 1 drugs, which are drugs that have no therapeutic benefit. DEA is notoriously conservative in changing their designations unless there is an overwhelming need to address. We have seen this with marijuana and CBD-based therapies today. Getting two federal agencies to collaborate and coordinate their programs is not quick and easy."

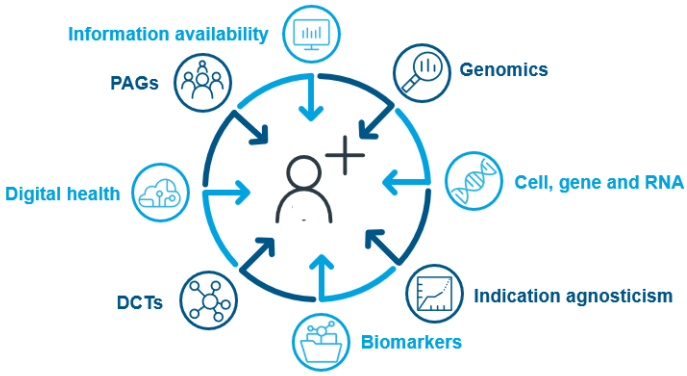
Aaron Wright
Analyst, EMEA Thought Leadership, IQVIA

"Your Order has been Dispatched": Opportunities in Moving Patient Care Closer to the Home

Introduction

Healthcare and pharmaceutical industries have increasingly moved towards treating patients at an individual level, both in terms of patient centricity and personalised medicine. As part of this phenomena there is a growing focus on providing patients greater flexibility with the location where they receive care.

Figure 1. Factors contributing to increased patient indivifuality



Source: IQVIA EMEA Thought Leadership

From the one to many: Treating patients as individuals

The trend towards "near-to-home" care is part of a broader movement within the healthcare and pharmaceutical industries that has been occurring over the last twenty years. Some of the elements in this movement are illustrated in Figure 1. From the advent of biologic products in the early 2000's through to the emergence of indication-agnostic therapies such as checkpoint inhibitors, and advanced therapies such as cell and gene therapies, medicines have become more personalised. New techniques have also contributed to the growth of personalised medicine, with genotyping and biomarkers playing an important role, especially for indication-agnostic therapies.

Alongside personalised medicine, patient-centric approaches to care are becoming more prominent. These range from increased information availability through ePortals to a greater usage of Electronic Health Records (EHRs). Patient centricity has also been a point of focus in clinical development. The inclusion of Patient Advocacy Groups (PAGs) in clinical trials is becoming more common, and decentralised clinical trials (DCTs) have been able to eliminate much of the burden associated with trial participation for patients[1].

The microscopic elephant in the room: The impact of COVID-19

The need, and the benefits, of moving care out of the hospital and nearer to the patient has been illuminated by the COVID-19 pandemic, as healthcare systems resorted to abnormal operating procedures to reduce the burden of dealing with a large influx of patients. Funding constraints have become an even greater issue, with COVID-19 vaccines alone forecast to cost a

total $251bn globally by 2026[2]. Wait times have also been impacted. At the same time, the pandemic has negatively impacted healthcare professionals (HCPs), with one in three clinicians considering leaving their job by 2024[3].

Despite these herculean challenges, the pandemic has also provided opportunities. As a result of attempts to limit in-person interaction, telehealth services increased exponentially[4]. For example, Germany implemented several changes including reimbursement for postal dispatch of prescriptions and special regulations for prescribing home nursing, and NHS England issued interim guidance to reduce the frequency of in-person interactions in order to free up capacity[5,6].

An interwoven tapestry: Elements of near-to-home care

Near-to-home care is comprised of a myriad of factors, and there is no one-size-fits-all approach to a system of near-to-home care, and as previously noted, the COVID-19 pandemic has accelerated the shift towards this form of care. The following section will explore three important areas, namely delivery methods, telehealth and formulations and devices.

Points of administration

One aspect is where and when care itself is administered, including but not limited to:

- Outpatient clinics, which can provide complex treatment but may require patients to travel some distance (although still shorter than traveling to a relatively fewer number of hospitals).

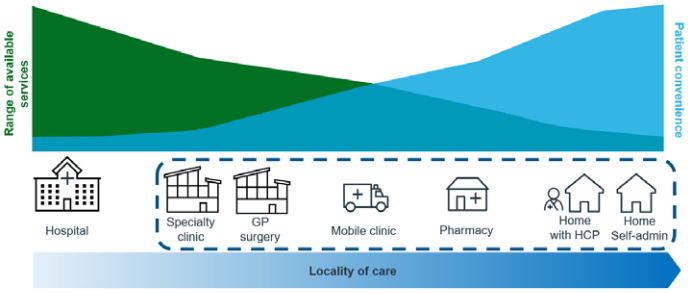
- Mobile clinics, which can travel to more remote/rural patients and still provide complex treatments like an outpatient centre, but at a smaller throughput due to their smaller physical size.

- Local pharmacies, which are more numerous and more local than outpatient clinics, but still require patients to travel and are unlikely to be able to administer treatments more complex than IV formulations.

- At-home treatment, with or without an assisting HCP. At-home treatment is the most convenient option for patients but requires significant investment in logistics and personnel.

These options, highlighted in Figure 2, are not mutually exclusive, and a near-to-home care system can comprise multiple care administration endpoints. Germany already has a near-to-home system in place with the *Ambulante Spezialfachärztliche Versorgung* (ASV) system which allows for treatment of complex conditions in clinics and practices without hospital admission. Additionally, in the UK some pharmacies have been transformed into "healthcare centres" which can administer medications as well as testing and screening[7].

Figure 2. Care delivery methods



Source: IQVIA EMEA Thought Leadership

Near-to-home care is suitable for both primary and secondary care and across high-value therapy areas. The top 3 therapy areas by value in 2021 in Europe (oncology, immunology and antithrombotics) were all compatible with a near-to-home care system. So too are orphan medicines for rare diseases: Onpattro, a medication for hATTR amyloidosis, is available for home administration in Italy through Alnylam Italia's AMYCARE programme[8].

Telehealth

The delivery of medicines to patients' homes, either using private couriers or national mail carriers grants greater convenience to patients who no longer need to travel to hospitals or pharmacies to pick up their medications.

Telehealth also comprises digital health solutions, including teleconsultations and telediagnosis, which reduce the number of in-person visits required for both patients and HCPs. There are many other components within digitised healthcare that are applicable to a near-to-home care system as well.

Mobile phones and Internet of Things (IoT) devices like smart watches also play a role. Due to their increased complexity and the inclusion of many kinds of sensors including cameras, gyroscopes and microphones, these devices can collect vast

amounts of health data for users in the form of digital biomarkers[9]. This data can in turn be used by HCPs to aid with monitoring of chronic health conditions, diagnosis and preventative care regimes. Digital therapeutics (DTx) are particularly suited to at-home care. In September 2020 at the height of the pandemic, Germany passed a law allowing for the reimbursement of DTx, a major step in driving their adoption in the country[10].

Formulations and devices

Globally between 2016 and 2021, Humira saw sales of autoinjector formulations grow by 14% CAGR whereas sales of subcutaneous vials shrank by -33 CAGR[11]. In the same period, European autoinjector sales grew at 19% CAGR . Manufacturers are racing to develop more patient-friendly formulations, such as in the checkpoint inhibitor market where companies are looking to develop subcutaneous formulations to differentiate their brands in a highly competitive market[12]. Phesgo is another example; combining two pre-existing IV treatments (pertuzumab and trastuzumab) into one subcutaneous product has reduced administration time from 2.5 hours to 5 minutes[13]. Shifting drug formulations to simpler formulations including subcutaneous and oral formulations can allow for a greater number of products to be administered either by patients themselves, or in basic facilities by nurses.

Changes in the drug delivery device (DDD) market are also occurring in line with changes to product formulations. In the major seven developed pharmaceutical markets (US, Japan, EU4 & UK) between 2016-2021 and looking at a subset of high-value therapy areas (immunology, oncology, respiratory, diabetes, human growth factor), the number of autoinjectors sold has grown at 36% CAGR, compared to pre-filled pens at only 2% CAGR. In total, parenterals with a hidden needle nearly quadrupled their market share from 5% to 19% in the same period[14].

Hurdles on the running track: Challenges to implementation

Despite elements of near-to-home care becoming more prevalent, both those implemented before COVID-19 and those introduced as a result, there are still challenges facing a greater adoption of near to home care. These challenges, illustrated in Figure 3, must be solved in order to unleash the potential of near-to-home care.

Figure 3. Obstacles to the implementation of near-to-home care

Source: IQVIA EMEA Thought Leadership

Regulatory

In Spain, the home sale of prescription medicines is outlawed at the national level, severely handicapping the delivery of at-home care[15]. France allows for home delivery of hospital medications, but it is heavily restricted, again impeding one major aspect of near-to-home care.

Regulatory vagueness also plays a role and can create uncertainty for care providers and pharma companies. Italy currently has no legal framework for the home delivery of drugs. Despite this, some schemes have been implemented by pharma companies, although these schemes have raised concerns surrounding fair access to medicines.

Financial

Sufficient financial frameworks and incentives will need to be in place to ensure near-to-home care can reach its full potential. Neither Italy nor Spain has the national-level frameworks available to support home care, though individual regions may choose to implement their own due to the highly regionalised nature of these countries healthcare systems.

Financial incentives to encourage healthcare systems to switch to a new modality, and pharma and wholesalers to develop solutions for the new landscape, are currently lacking. Developing new reimbursement pathways for the administration of hospital medicines in community pharmacies would entice pharmacists to provide new services as one example.

Behavioural

Healthcare systems are large, complex organisms, and as a result large-scale organisational changes face significant institutional momentum. This behavioural hesitancy differs from country to country; in the UK, recommendations to make greater use of homecare providers to dispense hospital medicines have been around since 2016[16]. Comparatively in Germany, the prevalence of ASV

centres may make implementation of additional near-to-home care solutions more difficult.

Behavioural challenges also occur at the individual level. Despite the increased usage of telehealth systems by HCPs, there are varying levels of confidence in how effective and easy to use they are for diagnosis, treatment and monitoring[17]. This is also true of patients; whilst many may prefer the increased convenience of telehealth solutions, others may prefer to see a doctor face-to-face, or may not be technologically literate enough to use the solutions themselves.

Logistical

A shift to near-to-home care brings with it substantially more endpoints involved in the care delivery process and will require reconfiguring storage and transport logistics. Effective storage of medications must be considered, especially for high-value immunology or oncology products. Specialty medications, particularly those that require extra-cold storage present challenges as well, as many homes or pharmacies may not have compliant facilities to store them. So too must the deliveries be protected to ensure they arrive securely. Technological solutions such as ePrescriptions and tracked deliveries may be the answer here.

Ensuring adequate personnel are available is also important. An expansion of near-to-home care would require many more HCPs, in particular nurses, to deal with the many more care endpoints.

A bountiful harvest: Opportunities available to stakeholders

There are a range of opportunities available to stakeholders who are willing to commit to the changing healthcare landscape, summarised in Figure 4.

Healthcare systems

Near-to-home care offers a new model of health system, one focused on individual patients rather than a traditional, hospital-first approach. This format will reduce the number of patients requiring admission by moving as much care as possible out of the hospital, reducing the burden on strained HCPs and reducing costs to healthcare systems.

To achieve these benefits, policy makers must work to actively promote near-to-home care elements. This will involve addressing issues surrounding limiting or unclear regulations, implementing financial frameworks, and working to shift institutional and individual behaviours. Policy makers should work with the pharmaceutical industry to encourage the development of formulations that can be self-administered or administered outside the hospital by HCPs, as well as technological and logistical systems to support near-to-home care.

Pharma companies

Drug manufacturers will be able to gain access to a greater patient population in the near-to-home care market, potentially increasing sales revenues and helping fulfil any Environmental, Social or Governance (ESG) commitments made surrounding increasing access to medicine. By developing more-easily administrable formulations and more convenient DDDs, pharma companies can mitigate competition from competitors, especially as patients will have more choice over their treatments than ever before.

Pharma should prioritise engaging with policy makers to ensure regulations promote near-to-home care products and systems and the implementation of clear financial frameworks and incentives. Reaching out to HCPs will also be required, to explain the benefits of telehealth systems and alleviate any concerns they may have surrounding the technologies.

Wholesalers

As near-to-home healthcare systems can use community pharmacies for distribution of hospital drugs instead of hospital ones, wholesalers can take advantage of this new financial disbursement channel. Furthermore, if health systems choose to use pharmacies as an administration point for medicines, wholesalers can look to be reimbursed for these appointments, adding an element of service provision to their business model.

Separately, the distribution of medicines to patient's homes will require gathering large amounts of patient-related health data. This type of data will prove highly lucrative as pharma companies and healthcare regulators are increasingly looking to use real-world evidence in their decision making.

Wholesalers should focus on working with policy makers to ensure there are no legal hindrances

to the delivery of hospital medicines to patient residences, or for service provision within pharmacies. Due to the increased logistical requirements of near-to-home care, wholesalers should also seek to invest in the greater logistical and human resources that will be required, such as methods of cold chain delivery and last-mile delivery solutions.

Figure 4. Opportunities available to stakeholders

Source: IQVIA EMEA Thought Leadership

Conclusion

A near-to-home care system involves moving healthcare closer to the patient, in line with patient preferences. This involves using multiple care endpoints, although there are still hurdles that must be overcome. Despite these challenges there remains a bounty of benefits for stakeholders, ranging from cost savings to new revenue streams. Most of all, the increased flexibility in patient care delivery brings benefits to patients in the form of greater convenience, preference and choice.

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Part 6

Major market perspectives: EU supply chain regulation & India

CPHI Frankfurt 2022

Adrian van den Hoven
Director General of Medicines for Europe

EU supply chain regulation: What will it mean for companies attending the CPHI?

Pharmaceuticals are among the most heavily regulated manufacturing sectors in the world with a wide range of regulations, audits and inspections applying to different aspects of the supply chain. Manufacturers are, for example, well acquainted with stringent GMP requirements. CPHI participants should expect even more supply chain scrutiny in the future as regulators expand oversight to issues such as antimicrobial resistance and environmental pollution. The European Union is currently reviewing different aspects of its pharmaceutical regulatory framework that will impact manufacturing supply chains.

ESG reporting is coming in a big way

Big pharmaceutical companies are, in a way, anticipating this regulation with ESG (environmental, social and governance) reporting becoming the norm in financial reporting as sustainable finance plays a bigger role in capital markets. ESG reporting requires a significant collection of supply chain data to demonstrate, for example, a company's commitment to a low-carbon transition. This can cover carbon pricing analyses, energy usage (efficiency), waste and water. The aim is to oversee the climate risk and to align with global standards for climate change reduction or mitigation. Companies are required to analyse their wider ecosystem (including manufacturing supply chains) in their analysis. This means collecting data from suppliers on these issues and this data will become increasingly standardised due to the Corporate Sustainability Reporting Directive (https://ec.europa.eu/info/business-economy-euro/company-reporting-and-auditing/company-reporting/corporate-sustainability-reporting_en) which will establish formal tools and standards for this type of reporting.

This Directive will also apply to all large publicly listed or privately-owned companies and to any publicly listed small and medium sized companies (SMEs). In practice, this will cover most of the EU pharmaceutical sector from 2024 or 2025. As these legal obligations come into force in the EU, this will impact business at the CPHI as future contracts will need to integrate these data reporting elements. We can foresee how suppliers might add new advertising elements to their CPHI stands such as "low carbon emissions manufacturing", "reduced water use manufacturing" or "low PNEC wastewater from production" (PNEC=predicted no effect concentration) to complement current advertising about GMP compliance. While these requirements will create additional work and complexity for the first few years of reporting, over time, the industry will learn to develop standardised and more digitalised reporting tools to facilitate data collection across the supply chain.

Stricter PiE (Pharmaceuticals in the Environment) rules can be expected

The EU is also announcing stricter pharmaceutical regulation for the environment. Traditionally, pharmaceutical regulation has focused on the

quality, safety and efficacy of medicines. The environmental impact will be a new aspect of medicines regulation to consider namely in relation to manufacturing and to human use or consumption. The EU applies strict environmental rules to all manufacturers to reduce environmental pollution of soil and water. This followed from industrial accidents and pollution concerns in Europe in the previous millennium. As some aspects of pharmaceutical production can be toxic for the environment, the sector has been a strong focus point for this type of regulation. Recently, the EU has grown concerned over pharmaceutical manufacturing pollution overseas – often related to concerns expressed by environmental NGOs over pollution from production overseas.

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Most of this concern has focused on antibiotic production due to concerns about the development of antimicrobial resistance (AMR) hotspots developing near large antibiotic production centres (https://www.reactgroup.org/toolbox/understand/how-did-we-end-up-here/antibiotics-in-the-environment/). The EU is expected to introduce legislation requiring stricter control over the environmental waste from pharmaceutical production with potentially very strict oversight of antibiotic production due to the AMR risk. The pharmaceutical industry has anticipated this development and participate in the establishment of the AMR Industry Alliance (https://www.amrindustryalliance.org/) which has developed an international standard for antibiotic production to reduce its impact on the environment and AMR. This is a welcome development that could facilitate compliance with future regulations. On the other hand, there are no clear standards to apply for the production of other types of pharmaceutical products. Therefore, EU regulation in this field may prove to be very challenging for the manufacturing supply chain in the future. This is because pharmaceutical production and therefore production waste and environmental impact are not static and they can vary due to multiple industrial and external (i.e. drought reducing river flows) factors. In addition, pharmaceutical regulatory agencies do not have environmental expertise and therefore will struggle to review any such data. This will be relevant for CPHI participants and production waste standards develop over time and new regulatory requirements come into force. Companies that invest in complying with these standards will be more successful than those that ignore them.

The EU may also restrict the conditions of use of pharmaceuticals for environmental reasons. Already today, the EU restrictions the use of antibiotics for example by requiring prescriptions by physicians and stricter national guidelines for those prescribers. The purpose is to reduce the risk of AMR – although indirectly and paradoxically, this policy may also undermine efforts to treat AMR patients. Indeed, with strict prescribing rules and commodity pricing rules applied nearly everywhere in Europe, the market for antibiotics is extremely challenging and, in many cases, economically unsustainable (https://eu-jamrai.eu/wp-content/uploads/2021/07/1.3.1_Policy_brief_Improving_access_to_essential_antibiotic.pdf).

This is leading to the rationalisation of antibiotics in different markets in the EU which reduces the scope of antibiotic molecules available to physicians to treat resistant patients. The EU may consider applying similar restrictions (for example prescription requirements or restrictions) to other molecules to reduce their impact on environment related to human use. Indeed, the EU's Zero Pollution Initiative targets pharmaceutical residues from both farm and human use (https://environment.ec.europa.eu/strategy/zero-pollution-action-plan_en).

It is difficult to fathom, however, how the EU will balance environmental objectives like this with the more fundamental right of EU citizens to health – including access to essential medicines – which is guaranteed by the EU Charter of Fundamental (Human) Rights (***Article 35 states: Health care:*** Everyone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices. A high level of human health protection shall be ensured in the definition and implementation of all the Union›s policies and activities.)

In some ways, the EU, with its large and diverse pharmaceutical manufacturing capabilities able to produce volumes of chemical solid and injectable medicines, biologic medicines, and vaccines, is among the most secure pharmaceutical supply chains in the world.

In calling for the mobilisation of industry for a clean and circular economy in the Green Deal, the Commission stressed the need to leverage the potential of the digital transformation as a key enabler for reaching the Green Deal objectives. Capturing those benefits will require a common strategy of digitalisation across the European Union to avoid two-speed Europe. It should also lead to an increasing use of digital solutions, notably as part of circular economy strategies.

For example, as the Commission called for electronic product information to be implemented for all EU medicines, the removal of the paper leaflet could eliminate the paper waste at the design stage itself.

EU pharmaceutical supply chain security: To be improved

Pharmaceutical supply chain security has become a high-level political issues in the EU due to the Covid-19 pandemic. In some ways, the EU, with its large and diverse pharmaceutical manufacturing capabilities able to produce volumes of chemical solid and injectable medicines, biologic medicines, and vaccines, is among the most secure pharmaceutical supply chains in the world. In fact, the EU was a leading global exporter of emergency medicines and vaccines during the pandemic. The EU institutions also played a positive role during the pandemic to keep pharmaceutical supply chains operating by declaring pharmaceutical production essential, by reopening EU (internal) borders for pharmaceuticals and other essential goods in early 2020, by providing regulatory flexibility to allow manufacturers to scale up the production of ICU hospital emergency medicines and Covid-19 vaccines and by preventing EU Member States from hoarding medicines at the expense of their neighbours and the global community. This also pushed the EU to panic and adopt Covid-19 vaccine export restrictions to the dismay of the EU pharmaceutical industry and which was in total contradiction with the EU's role as the leading global provider of vaccines and stated ambition of support for global public health solidarity. To be fair, the EU was not the only region to adopt these counterproductive restrictions as the US and India did as much restricting and far less exporting than the EU.

The EU also organised a "structured dialogue" (https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/structured-dialogue-security-medicines-supply_en) involving the healthcare community (the pharmaceutical and chemical industries, distribution, healthcare professionals, patient groups, regulators and ministries of health) to review the EU's pharmaceutical supply chain security for the future. The dialogue produced four in depth consensus documents on supply chain security, supply chain disruption risks, defining critical medicines and innovation to supply chain security. Unfortunately, there has been no real follow up to this initiative.

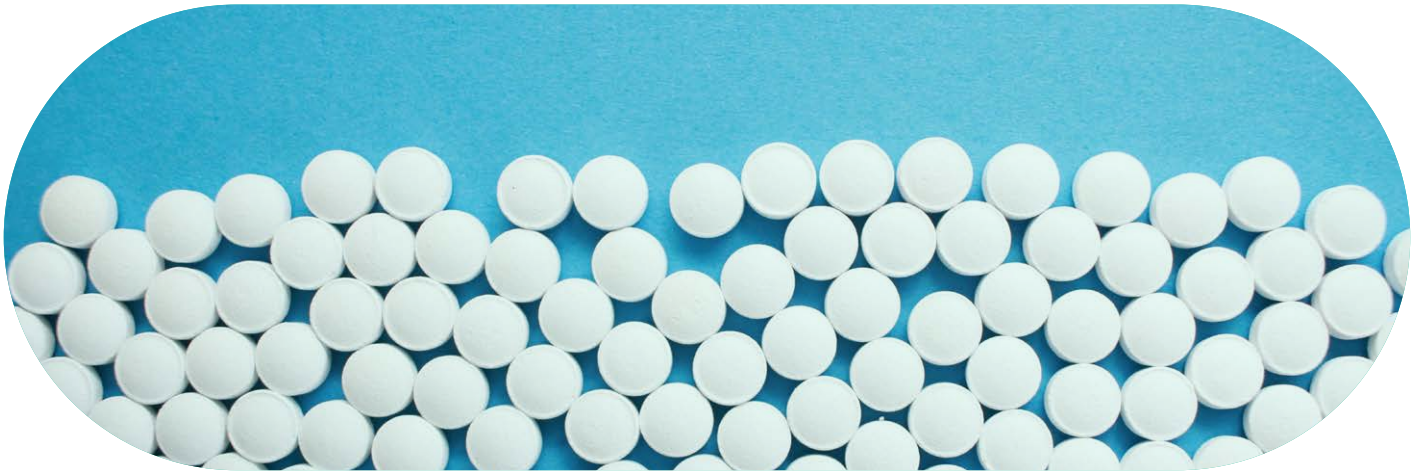
There was also a downside to supply chain security during Covid-19. Most notably, the EU had access to very little market demand and supply chain data or information during the pandemic. In the early stages of the pandemic, there were huge demand surges for medicines including hospital ICU medicines, common pain medication such as paracetamol or ibuprofen and many chronic disease medicines as patients stocked up. Later, there would be demand surges for flu and covid-19 vaccines. The EU struggled throughout the pandemic to predict these demand surges which created panic in many EU countries and in distribution as hoarding became the only tool to plan for surges. Much of this was caused by the EU's failure to standardise data collection in the pharmaceutical sector. For example, the European Medicines Agency collected shortage reporting data from pharmaceutical companies and from Member States but as the data was not standardised, it was effectively unreadable or unusable. Similarly, more European hospitals do not have digital management of pharmaceutical stocks so they cannot predict demand flows. And even though the EU is well advanced with anti-counterfeiting serialisation with an EU-wide data system that collects data on the dispense of all prescription medicines to patients, there was not technical capability to use this data to assess

demand surges or local shortages. Similarly, EU data on manufacturing supply chains, which is entirely in the hands of medicines agencies (as this data is supplied as part of marketing approval dossiers and in relation to GMP), was not accessible because of the absence of standardised and digitalised systems. Therefore, although this data was available to regulators, in practice, they could not read or use it for the purpose of a major health crisis.

On the positive side, the EU provided special competition law guidance for industry to collect this important data and to address demand surges and supply chain bottlenecks https://ec.europa.eu/commission/presscorner/detail/en/IP_20_618) under strict surveillance by the Competition and Health authorities. In addition, future EU pharmaceutical legislation will improve the digitalisation and useability of supply chain data. For example, the new EMA mandate on shortages requires the establishment of a common digital platform for the collection of shortage reporting data (https://www.ema.europa.eu/en/news/stronger-role-ema). The future EU pharmaceutical legislation is also likely to introduce new digitalisation requirements on the pharmaceutical industry and its 28 medicine agencies. The EU will also explore the use of serialisation data for similar supply chain security purposes. These requirements will vastly improve the data available for a health crisis and, likely, improve things such as large-scale drug shortage mitigation.

On the downside, the EU may also introduce more supply chain requirements on manufacturers and marketing authorisation holders to reduce medicine shortages. The EU has experienced a dramatic increase in shortage notifications over the last 10 years, however, the Commission's own data shows that 9/10 reported shortages are localised in a single EU country (https://op.europa.eu/en/publication-detail/-/publication/e964d173-5320-11ec-91ac-01aa75ed71a1). Industrial shortages (for example caused by API or raw material supply disruptions) would normally affect more than one EU market. This implies that the shortages are driven by local market conditions where payers and procurers seek to obtain low prices for medicines (http://graphics.eiu.com/upload/topic-pages/medicine-shortages/Addressing-medicine-shortages-in-Europe-EIU.pdf). As the EU has limited authority and even less political will to correct local market failures causing shortages, it is probable that the EU will increase shortage reporting requirements and other regulatory measures on manufacturers and marketing authorisation holders in the future. This will only deliver vast amounts of unhelpful data as earlier shortage reporting leads to the reporting of more risks than actual shortages and mitigation plans only make sense for certain critical drugs. On the other hand, the EU will also introduce measures to facilitate product allocation across the EU. As a region with 27 countries and 22 languages, packaging is not easy for the EU market. The EU has promised to simplify these requirements and enable the use of digital leaflets in the future (as it allowed for Covid-19 vaccines very successfully). This should make life much less complicated for manufacturers supplying the EU market in the future.

To conclude, CPHI companies can expect EU regulation to have a big impact on their business in the future. Whether it is related to reporting, to the environment or AMR or to supply chain security, more reporting and, hopefully more standardised and digitalised tools to enable that reporting, will be required. If you want to learn more, check out our website at www.medicinesforeurope.com



CPHI post review riposte: Questions and answers on the future

CPHI: Can you look ahead 5-years and predict how ESG reporting may have changed the market? (e.g. will standardisation in Europe mean that manufacturers here take a larger market share of the EU market or will international companies also adopt these standards). How might ESG reporting be policed?

AVH: *"I think European and international companies will apply these standards because ESG reporting is done for the most important markets (US, EU). Suppliers from Asia will also participate in this. ESG will likely be policed by private sector audits to confirm that the data is correct. I don't think that public authorities have the resources or technical abilities to do this."*

CPHI: the supply chain for pharmaceutical manufacturing remains extremely complex – where will the burden of proof fall (on the ingredients makers, the CDMOs or the license holders)?

AVH: *"I think the burden of proof will fall more on the license holders but they will need data from API providers and CDMOs to fulfil these voluntary and, soon, legal requirements."*

CPHI: could these changes put some ingredients providers at a disadvantage – e.g. if Asian or other manufacturers can makes the same ingredient at lower cost due to a lower regulatory burden (how will the EU or industry guard against this)?

AVH: *"This will definitely impact starting material, intermediate and API producers because of the environmental impact of upstream production. Finished dosage form production also has an impact (solvents, energy use) but it is less impactful than upstream manufacturing."*

CPHI: looking 5-years ahead what might drug manufacturers based in Europe need to see from their own supply chain partners to meet regulations (whether from API supplies or other ingredients) – i.e. these partners are often in Asia?

AVH: *"They will need data showing compliance with environmental requirements. Over time, there will be stricter standards on things like energy efficiency or wastewater from production. Data will be required to show this."*

CPHI: will digital leaflets (as opposed to box printing) potentially open-up the market for more international manufactures (potentially offsetting some of the ESG challenges above)?

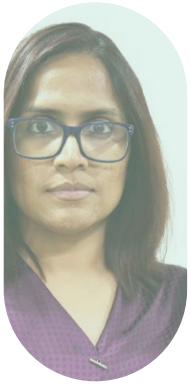
AVH: *"This will be important for the marketing authorisation holders (companies marketing the medicines in Europe). It will be a huge efficiency gain for packaging and will dramatically reduce the need for paper."*

CPHI: Do we think early adopters of ESG reporting/ manufacturing in the CDMO space will potentially see the biggest growth rates in the next few years. (i.e. many CDMOs use legacy factories and it might be easier for newer facilities to switch and upgrade manufacturing).

AVH: *"therefore, are investment decision this year critical for CDMO business outlook in a just few year's time. This could play a role but everyone will need to upgrade to a certain extent. Also, this will require companies along the supply chain to hire more experts able to collect this data."*

CPHI: Similarly, will having lower carbon manufacturing and full reporting become as critical has having capacity for CDMOs – I.e. will it be automatic rejection from a list of potential partners.

AVH: *"Not immediately but over time yes. Failure to meet this criteria will be a basis for switching to another supplier."*



Pushpa Vijayaraghavan
Director and Practice Lead – Health & Lifesciences,
Sathguru Management Consultants Private Limited

Aggressively pushing forward: Momentum across segments in India's CDMO and CRO landscape

India's brand recall is still strongest in the global pharma and biotech landscape as "pharmacy of the world". The country's export success in generics is well established. With close to $25 billion of exports in 2022 and more than 55% of exports being directed to highly regulated markets, the industry continues to consolidate its positioning as a high quality manufacturing destination that is also cost competitive. While the industry rests on this foundation of sustainable scale in generics, it continues to spread its wings across other prioritized avenues for growth – biosimilars, vaccines, and contract services. The resurgence of the API segment continues as a key priority as well for all stakeholders – industry, investors and policy makers. Of the various growth avenues gaining momentum, contract services continues to be the least discussed but is increasingly emerging as the dark horse. As a strategic advisor to several leading companies and private equity funds, I have experienced first hand the level of industry and investor investment appetitive across segments of contract services. This is supported by both macro forces driven tail winds as well sustained capacity enhancement by the growth oriented domestic industry.

The macro tail-winds – Evolving FDI direction and outsourcing preference

The macro forces are doubly powered. The World Bank's Global Pulse Survey covering a large pool of multinational enterprises clearly pointed to share of FDI earlier directed to China now being diverted to a mix of other countries in the post COVID world. Within that, India is pitted to substantially gain on FDI in the pharmaceutical manufacturing and services space. Beyond FDI being redirected, conversations with stakeholders in global pharma and the CRO industry point to increasing focus on reducing level of outsourcing to China. This is likely to impact all segments of opportunity – early discovery, medicinal chemistry, small volume synthesis, in-vivo and early biology activities and large volume manufacturing of APIs.

Riding the tide – Shoring up capability to capitalize on expanding opportunity

Combined with this preference for near shoring and ally shoring of pharmaceutical outsourcing activities is the continuing trend of Indian industry investing in capabilities and growth. Over the past few years, Indian CROs, both standalone and service arms of pharma companies, have made organic and inorganic investments to enhance breadth and depth of offering and value proposition.

Focus on biology and biologics: Indian CROs have long standing engagement in medicinal chemistry and the country enjoys perception of being a reliable and experienced hub for chemistry services. This continues across the continuum of molecule synthesis to small batch and large batch manufacturing. However, while doing so relatively

late compared to regions such as South Korea or even Europe, several Indian CROs and CDMOs are now embracing the opportunity in biology and biologics. The biology opportunity has been within the spectrum of discovery and early development services and has been largely the driver for several strategic investments in the last few years. The most active focus has been on integration of GLP in-vivo capability within the overall discovery or development services offered. It is notable that most stand alone GLP in-vivo providers in India have greater business concentration in toxicology as compared to discovery focused PK services. This has been primarily due to constraint of market reach to innovative ventures globally, a barrier that can be broken by larger strategic investors with presence in high value discovery markets. We anticipate that the transaction and expansion momentum in in-vivo services will continue over the next few years. This is likely to provide a strong growth lever backed by the opportunity to offer more integrated services to global customers. While sufficient large animal capability still remains a constraint for ADME and DMPK work in discovery, the strategic focus on a more integrated and wider offering to customers is likely to reap benefits in the short term as well as medium term.

Strategic Investments with focus on Biology:
Aragen – Intox: December 2021 transaction with leading Indian CRO with focus on discovery services acquiring in-vivo capability

Veeda Clinical Research – Bioneeds: July 2021 transaction - Clinical services focused CRO expanding scope of services with acquisition of preclinical capability

Strategic Investments with focus on biologics:
Laurus Labs – Richcore Lifesciences: January 2021 investment that has now powered Laurus' presence in recombinant proteins (products and CDMO services) across food, industry, and pharma

Piramal – Yapan: December 2021 transaction with strategic investment by one of India's largest CDMO service providers in a biologics platform

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Beyond integrating biology service offerings, standalone CDMOs in India as well as CDMO divisions of larger Indian pharma companies have both also been focused on strategically expanding capacity in biotechnology. While Kemwell was a pioneer in biotechnology CDMO services from India, the overall momentum until now has been more geared towards proprietary product portfolio as compared to CDMO services. However, now we note expanding momentum in CDMO services across the range of peptides, biosimilars, novel biologicals, vaccines and even next generation cell and gene therapies. Laurus' investment in Richcore and Piramal's investment in Yapan Bio emphasize this expanding trend. Global emphasis on scale-up partnerships during COVID, also led to more companies exploring contract manufacturing opportunity for vaccines (across both drug substance manufacturing as well as fill-finish). Several of these are now continuing to pursue the focus on contact services for peptide and protein production. Samsung Bioepis is a global benchmark is tactically combining proprietary portfolio with contract manufacturing services in biologics. The model is now gaining favor with several Indian pharma companies; and we expect the base of CDMO service providers in India for biologicals to further expand over the next three years. In addition to biopharmaceuticals, several CDMOs are also strategically focused on cell culture meat and industrial biotechnology, both large volume market opportunities with potential for geometric growth.

The funding fuel – enhanced Private Equity appetite

Indian capital markets have rewarded CDMO services with a valuation premium compared to generic manufacturers and access to capital has not been a constraint for CDMO providers in India. The overall investment momentum has also been spurred by significant appetite of private equity funds to invest in the segment. Multiple transactions in the segment reinforce the buoyant growth outlook for Indian service

providers. Notable transactions include TPG Capital's investment in Sai Lifesciences in July 2018, CX Partners' investment in Veeda Clinical Research in December 2018 (and subsequent bolt-on acquisition of Bioneeds by Veeda in July 2021), True North's investment in Anthem Biosciences in March 2021 and Goldman Sachs' investment in Aragen Life Sciences (earlier GVK Bio) in May 2021. With capital markets cooling off for IPO linked exits but industry's fundamental growth potential remaining robust, we anticipate private equity investment momentum to continue over the next few years. This will further provide fuel for consolidation, inorganic expansion and creation of higher value service platforms from India.

Getting closer to the customer: Focus on geographic expansion

Finally, in addition to the expansion in capabilities and capacity in India, several leading Indian CDMOs have acknowledged the value of being proximate to customers, especially the long tail of discovery ventures. In the context of COVID led disruptions to global supply chain and consequent impact on business operations, proximity is valued by both the customer itself and policy makers focused on re-shoring or near-shoring the pharma value chain. Several Indian CDMOs have been actively exploring acquisition opportunities across geographic borders. We expect this appetite for geographic expansion to continue given the macro propellants at play. In the next five years, larger Indian CDMOs are likely to nurture stronger onshore presence in US and Europe. This quest for onshore capability is most intense in discovery CROs but is also true of large scale API and formulation manufacturers.

The final word: The roaring lion and 'service in India' imperative

Opportunity in the pharma and biotech industry is rapidly evolving with biologics and next generation therapies gaining more ground. The global value chains are recovering from COVID caused disruption and evolving into a world where localization and supply chain resilience have gained greater prominence. As the dust settles in the post COVID world, Indian CROs and CDMOs are poised for growth with expanded capability, wider and more integrated service offering and a strong focus on offering greater value to customers. The industry bandwidth is increasing with standalone CROs bolstering balance sheets and aggressively pursuing global growth and leading Indian pharma companies more actively embracing the contract services opportunity. The next five years will be pivotal for these investments to reap rewards; and for Indian CROs and CDMOs to gain their space in the global landscape.

Opportunity in the pharma and biotech industry is rapidly evolving with biologics and next generation therapies gaining more ground. The global value chains are recovering from COVID caused disruption and evolving into a world where localization and supply chain resilience have gained greater prominence.


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