Annual Report

AI Transforming Manufacturing, the Rise of India, and the Return of Capital and the Contract Services Boom!

What's ahead for global pharma in 2024 and beyond... bright times ahead and sooner than most expect

CPHI Barcelona 2023

CPHI Barcelona

Overview: CPHI Annual Industry Report and Survey

The seventh **CPHI Annual Survey** will explore the perspectives of over 250 pharma executives, evaluating the likely trends in 2024 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 11th edition – features the detailed analysis of global experts exploring all facets of the industry today and a look ahead to predict the major trends of tomorrow.

Also look out for the bonus edition of the CPHI Annual Report to be published after **CPHI Barcelona 2023**

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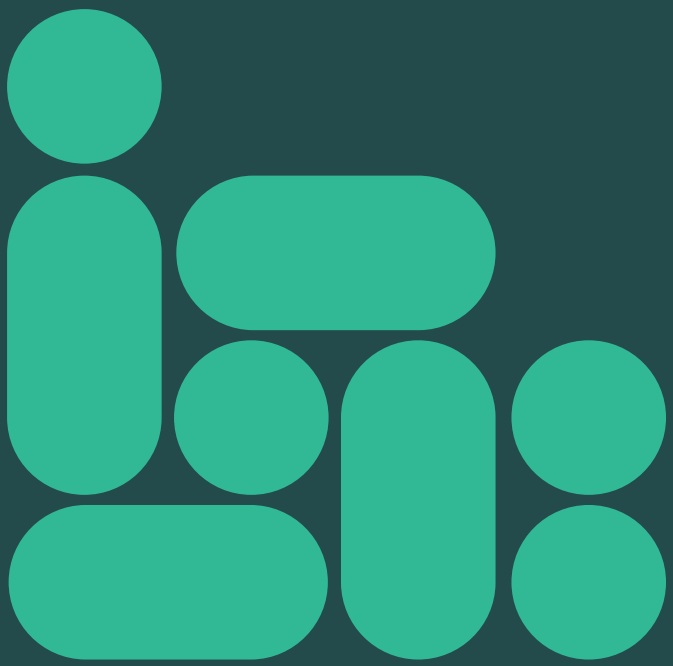

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The CPHI Annual Report 2023: Pharma Survey and Industry Rankings

Introduction

The ability of the global economy to adapt and recover has been in full evidence in the last year as the war in Europe continues, and the industry has adapted to ongoing supply chain and energy shocks. Yet despite this uncertainly, overall, pharma has used the last few years to build in more resilience and, with clinical development continuing in force again, the remaining primary drag factor on future prospects is the relative weakness in early-stage funding and valuations. Inflation, the other nagging macro-economic threat, also appears to have reached the crescent of its accent. The majority of economists predict global figures will fall back in 2024, creating a more stable fiscal environment from which to invest and grow. In fact, the IMF's medium-term analysis is that western interest rates will return to pre-pandemic lows once inflation subsides[1].

To reflect the trends of the wider industry, this year's survey has also pivoted away from last year's psychedelic influenced focus to look more prescriptively at the role AI might play in the industry through the next 5 years – from manufacturing process innovations to marketing dossiers and, of course, in the development of more druggable targets. The other notable shift has been the gradual and, in some cases, sudden reduction in the value of COVID-19 related contracts for CDMOs and CMOs. Yet, remove the market distortion caused by this once in a century event, the underlying growth for the industry looks very healthy and robust with many new targets and classes proliferating. So, even accounting for the medium term run through of potentially reduced outsourcing contracts as a result of the presently cooled funding environment, prospects on the whole look strong.

Technology has however, advanced unrelentingly with microbiome therapies, cell and gene therapies and both RNA and oligo targets continuing to generate much excitement – not least among CDMOs who have invested in increasing capacities to develop these newer product classes. To take one specific example, LNPs (lipid nanoparticles) have already been proven effective in delivery to the liver and research into their use in other tissues for advanced therapy products could deliver a breakthrough in the next 12-24 months. LNPs also

Methodology

This is the seventh **CPHI Annual Survey** and explore the insights of **over 250 industry executives** from every region of the globe. The rankings evaluate all 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 will this year provide first ever reading on the biotech industry in Europe - with the launch of the European Biotech Rankings – as well as categories across biologics 'quality of bioprocessing', 'growth' and 'innovation'.

This report is published annually and released at **CPHI Barcelona 2023** (October 24-26)

1. https://www.imf.org/en/Blogs/Articles/2023/04/10/interest-rates-likely-to-return-towards-pre-pandemic-levels-when-inflation-is-tamed

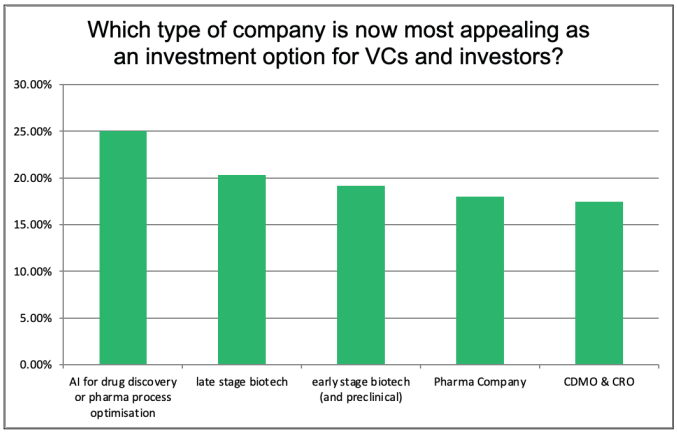
come with lower manufacturing challenges and reduced toxicity – compared to adeno-associated virus (AAV) vectors – so this could be a potentially step change improvement that advances targets while bringing down costs.

Looking at the spread and make up of global pharma markets we have seen significant market ambivalence in both information and rhetoric around macro and geopolitical factors. For example, in manufacturing and chemistry services pharma news and governmental interest has often focussed on the importance of secondary supply chains, resilience and local manufacturing – yet companies in China and India (widely believed to be 'the losers' of the drive for near-sourced manufacturing) have on the whole performed very strongly. For example, profits at CDMOs WuXi Apptech[2], Pharmaron[3], Syngene[4] and Asymchem[5] have continued to reach record levels in the last 18-months. While this might partly be attributed to strength in their domestic markets and/or growth in newer regions outside of the West – it perhaps suggests that undoing 20-years of outsourcing is perhaps easier said than done. In fact, when digging through their respective Annual Reports it quickly becomes clear that their growth in Western Markets is no less impressive.

Another shift we have seen is in the location of global R&D centres. Biotech hubs are proliferating, and we have seen this accelerate throughout the pandemic years. While the handful of larger metro hubs in the USA are known (i.e. the Bay area, San Diego, Boston, Philadelphia, Raleigh/Durham et al[6]), as are the fast growth centres in China (notably Beijing, Shanghai and Pearl River Delta areas[7]), European hubs in contrast have diversified quickly and have not yet received the international credit they perhaps deserve. In response, this year CPHI will introduce the *European Biotech Ranking* in which we will monitor the rise and fall of major research hubs across the continent. In particular for 2023, with our eponymous event being held in the city, Barcelona's emerging biotech and manufacturing region will to be explored in much greater depth. The survey will focus on what the wider region needs to do to continue its rise and potentially become more of a globally significant driver of new therapies, technologies and life science breakthroughs.

Finally, looking much further into the future, we asked the market for their perspectives on: 'when and how a cancer vaccine could potentially come to market'; 'are microbiome therapies at a watershed with Rebyota's approval'; 'what technologies will be in routine use in 2026'; and, of course, 'where might the perpetual advance of AI take us' and is the hype justified. For example, in what year will the industry record the first fully 'AI discovered, developed and commercialised drug therapy' approved by the FDA and what percentage of drugs will be developed using AI by 2033.

Artificial Intelligence



In line with the buzz across other industries, executives in pharma forecast that artificial intelligence (AI) development and use in pharma will continue to increase extremely quickly. Companies developing AI technologies for drug discovery (24.85%) were identified as the most appealing investment options for the first time. Historically, in all other years of the survey's history 'innovation led biotechs' were selected as the most promising investment option. This emphasises a huge shift in business strategies, indicating that while historically biotech has been the chief money generating sector of the industry, AI is now becoming a serious contender and can be used far wider than previously envisaged.

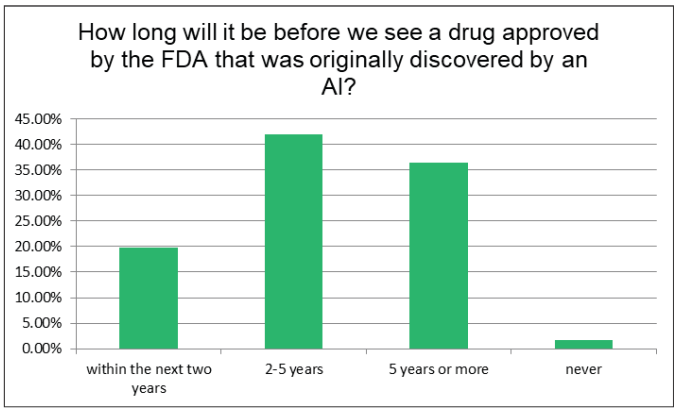
Majority of executives now think AI will be a major force evolving the pharma landscape during the next 5-years.

Significantly, AI drug discovery was identified by some 60% of executives as a technology that will be 'used routinely in 2026', with 42% forecasting that the first 'FDA-approved drug discovered by

2. https://www.wuxiapptec.com/news/wuxi-news/5248
3. https://ir.pharmaron.com/media/1152/e22ar.pdf
4. https://annualreport.syngeneintl.com/
5. https://asymchem.com/february-newsletter-2/#:~:text=January%2030%2D%20Asymchem%20released%20its,company%20is%20approximately%20%24485M.
6 https://www.fiercebiotech.com/special-reports/top-biotech-hubs
7 https://www.cambridgenetwork.co.uk/news/overview-chinas-biopharma-clusters#:~:text=Biopharma%20Clusters%20in%20China&text=For%20instance%2C%20Shanghai%20is%20the,to%20Tianjin%2C%20Dalian%20and%20Qingdao.

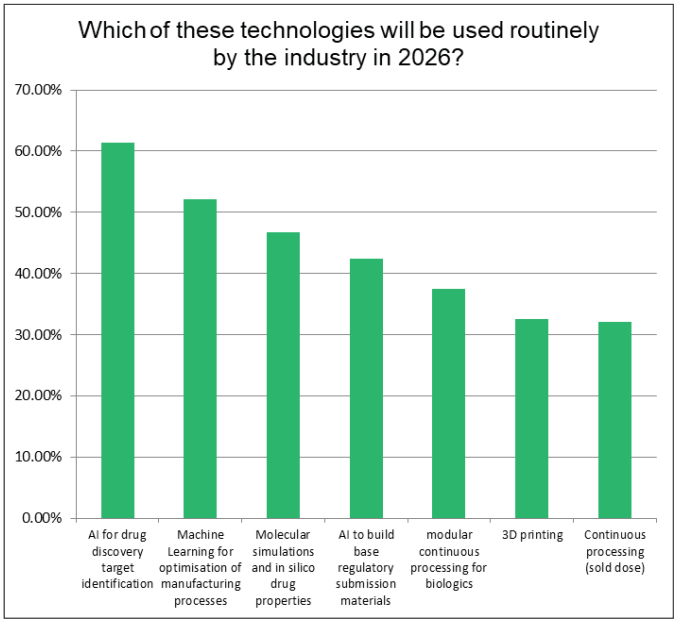
AI' will be seen in the next 2-5 years, but this may well happen even sooner. Pharma companies seem to agree, and we have seen a who's who of big pharma partnership with tech companies from Sanofi, Merck, Pfizer and GSK to Bayer, BMS, Lilly, AZ Jansen and Novartis[8]. While Moderna has described itself as 'laser focused on AI' and Morgan Stanley is predicting industry spending on AI will top $50bn per year within the decade[9].

Bikash Chatterjee – President and Chief Science Officer, Pharmatech Associates, a USP Company – added *"The tools we have today to evaluate genetic material and protein structures are tremendous. As we gather data, the models we use for evaluation within AI will improve and our criteria and insight will become more refined, allowing us to design and direct evaluation models more efficiently. I would agree that we are very near to seeing AI discovered molecules getting approved today—within the next two to five years. In the next decade it is likely most drug therapies will be identified by some element of AI."*



Similarly, while machine learning may not be considered true AI, it is still a significant technology that rarely requires direct human input and will help accelerate many processing activities – particularly those that require ongoing monitoring. Additionally, executives also suggest that AI has the potential to help build base regulatory submission materials and this will be a frequently used approach as the technology matures.

If we take a step back, we also see that AI is heavily involved in all four of the top technologies predicted to be used routinely in 2026, illustrating that the majority of executives now think AI will a major force evolving the pharma landscape during the next 5-years.



Already we have seen several promising programmes and the much-promised rapid development. For example, it was reported earlier this year that an experimental psoriasis drug delivered a compound that was discovered by AI in just six months and has already progressed to the final stages of clinical trials[10]. Ordinarily, the process would have many taken years to advance to this stage. If it succeeds, this would be one of the first therapies discovered by AI.

AI is not only beneficial for areas in pharma like drug discovery and development, but can also support the global economy. Bikash Chatterjee, added, *"A recent study estimated that global GDP could be up 14% higher in 2030 as a result of AI – the equivalent of an additional $15.7 trillion – making it the biggest commercial opportunity in today's economy."* Additionally, AI attracts nearly $3 billion in venture capital investments. Despite the promise AI holds, it still faces challenges, specifically related to scale, growth, diversity, and uncertainty of data AI uses. Later in this report, Bikash Chatterjee will cover how AI will impact drug development and pharmaceutical manufacturing more in depth.

Sheila Mikhail, co-founder and former CEO of AskBio – a company currently using AI to design capsids and screen targets/options more efficiently – envisions AI being used to streamline gene therapy processes and clinical trials. She states, *"I think AI is even going to be used for clinical trials to help us accelerate the process in terms of patient selection and possibly even simulations. I think we'll be able to have much more predictive capability. AI is therefore an essential component for the future of gene therapy."*

8. https://www.pharmaceuticalprocessingworld.com/ai-pharma-drug-development-billion-opportunity/#:~:text=Merck%20partnered%20with%20BenchSci%2C%20Atomwise,drug%20design%2C%20and%20lead%20generation.
9. https://www.economist.com/business/2023/07/13/big-pharma-is-warming-to-the-potential-of-ai
10. https://news.bloomberglaw.com/health-law-and-business/ai-drug-discovery-is-a-50-billion-opportunity-for-big-pharma

Global executives agree with Mikhail, predicting boldly that in as little as 10-years' time, 'over 50% of new drugs will have used AI in some part of its discovery, development or manufacturing'.

Related automation is also accelerating and a report from VisionGain highlights that 75% of pharmaceutical organizations aim to implement automated solutions, particularly for injectable drug delivery, to address challenges like customized dosages and prefilled syringes[11].

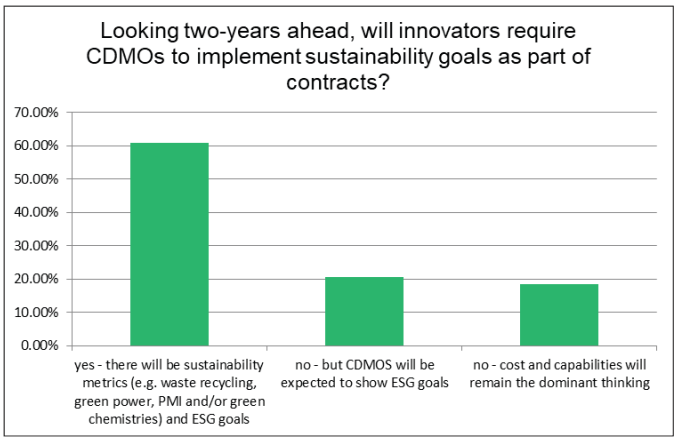
Sustainability

Alongside AI, sustainability remains a pan-industry critical issue, with 90% of executives citing 'visibility on supply chain partner's sustainability record' as extremely important or important. This indicates that pharma executives will take into account the sustainability of supply partners and, already, this is now affecting when and how industry partners are selected.

In addition, 60% of executives forecast that innovators will require CDMOs to implement sustainability goals as a part of contracts in the upcoming years, which is consistent with last year's findings. In fact, we have seen a continued raft of sustainability steps and announcements from CDMOs in the last 24 months[12], and yet, CMC analysts still state "it's the most daunting challenge."[13] This points to the ongoing duality we see in the manufacturing sector – particularly in API production where PMIs (process mass intensity) remain so high – in how they do they go about delivering the required product quality and speed to market while attempting to begin the formidable challenge of lowering the amount of waste produced. However, attempts are being made and increasingly we see chief sustainability officers (CSO) looking at how organisations can break this down into incremental improvements that collectively can deliver the step change improvements requires.

90% of executives believe that visibility on a supply chain partner's sustainability record is important.

Ultimately, it has been the economic not moral imperative that has been the chief catalyst of change, as a 'process improvement mindset' is showing real world financial benefits. So what we now have as the growing narrative is, can in the longer term a CDMO or manufacturer afford not to be investing in newer production methods that are reducing waste and lowering the cost per Kg of production. The added allure of potential market differentiation and brand enhancement further amplifies the economic rationale, and we now seem to be approaching a crescendo of adoption in the CDMO sector. What will be interesting is to see how quickly this mindset switches across to generics production, particularly in low margin areas – where decisions around the cost of initial investment and ultimate benefit is most acute.



Bioprocessing

Once again, the United States has been identified as the unquestioned leader in bioprocessing. The country ranked first in 'biological processing', 'manufacturing', and 'biologics growth potential', as well as remaining the top ranked nation for 'bio innovation'.

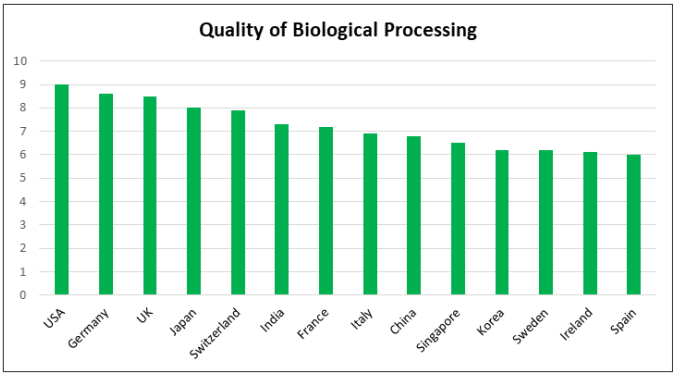
For biologics processing quality, year-on-year scores are very consistent across most nations. The United States has once again reclaimed its places as the world pre-eminent bioprocessing nation, supplanting Germany, with virtually the same score as in the 2022 survey – Germany however has fallen

11. https://www.globenewswire.com/en/news-release/2023/03/21/2631524/0/en/Automation-in-Biopharma-Industry-Market-is-Projected-to-Grow-at-a-CAGR-of-5-7-by-2033-Visiongain-Reports-Ltd.html
12. https://www.contractpharma.com/issues/2023-07-03/view_features/net-zero-pledge-cdmos-go-greener/
13 https://www.bioprocessonline.com/doc/survey-results-show-what-could-finally-make-sustainability-stick-0001

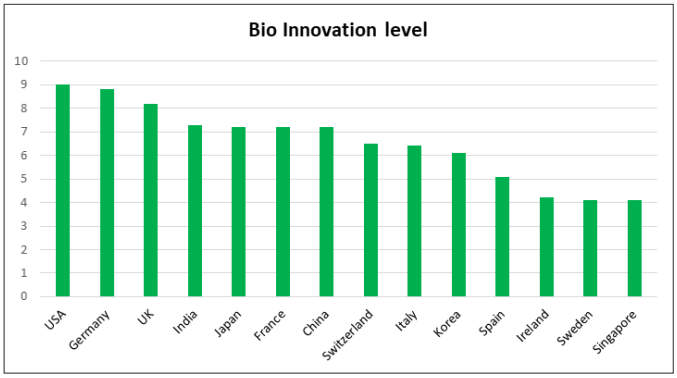
back slightly from the record quality scores of the preceding year.

The most notable change sees Japan once again fall a little further back on the top three – having previously maintained an equal score with the USA and Germany for the first 5 years of the survey [the survey is now in its seventh year]. India also maintained its position ahead of France and we now believe the 2022 results perhaps mark a watershed moment in India's rise in reputation of biologics production – notably, Covid vaccines, the Serum Institute, Bharat biotech, Biocon and, on the CDMO side, Syngene helping transform the country's reputation. A further notable aspect, the one area of Spain's improving reputation that still has some way to go, is in Biologics production, and our analysts believe this will be an area of heightened development in the next few years to help support growth in more advanced formulations.

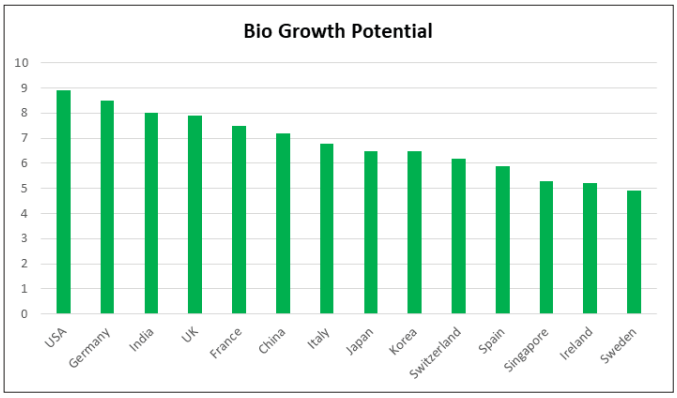
Raul Martin, Partner at Ysios Capital adds the context of new modality activity in Spain: "*The historical strength of the country is around small molecules. However, a number of companies have been created around more 'sophisticated' modalities including antibodies, cell therapy for regenerative medicine and oncology, gene therapy, RNA therapeutics, oncolytic virus. However, there are also now some initiatives to foster advanced therapies, but they are still too incipient to know if they will consolidate and become a driving force for the sector.*"



In terms of innovation, Spain has again risen quickly up the table, with very little change in the top five – for score and places – with United States and Germany continuing to lead and India having again cemented its recent reputation as a member of the top 4. Spain has risen, albeit from a lowly base, by 25% year-and-year and this perhaps hints at some of the changes in molecules researched in the country and an increased focus on advanced therapies.



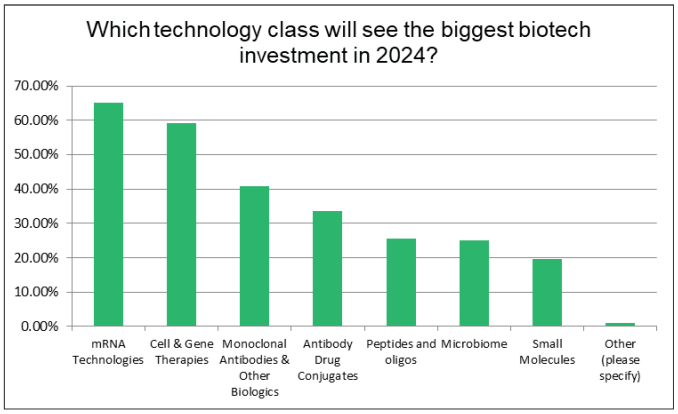
The United States has continued its seven-year dominance at the head of the bio growth table, with Germany maintaining second place ahead of India and the UK. The one surprising change was that France has seen an 8% growth in 2023 and has risen above China for the first time. However, Spain was once again the biggest year-on-year winner and shifted from bottom place to close to Switzerland - improving by a massive 30%. So, although its biologics industry is still somewhat early in its story, all the indicators in this report point to significant growth potential over the next 3-years**.** Typically, rapid improvements in any category's scores are significant leading indicators of above market growth ahead.



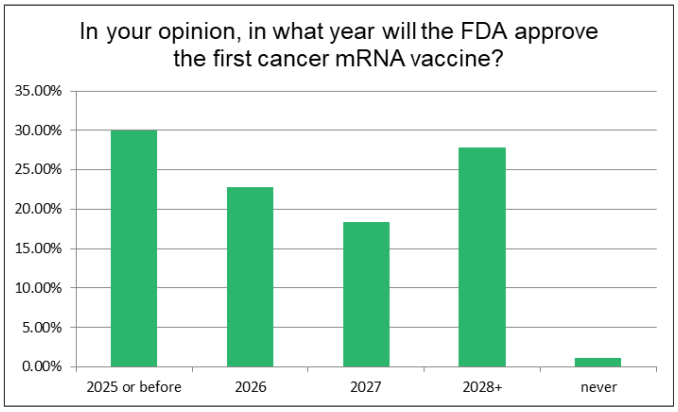
In terms of therapy class potential, mRNA technologies are expected to see the biggest biotech investments in 2024, followed closely by cell and gene therapies. Further conforming to the industry's prediction, roughly 31% of executives think the FDA will approve the first cancer mRNA vaccine in 2025 or before. In fact, on September 28th this year the *phase 2* clinical trials for the first mRNA vaccine against pancreatic cancer was initiated by the NIH at Memorial Sloan Kettering Institute and 80 other sites all around the world[14]. This just another example of promising clinical results bringing us one step close a first approval for mRNA cancer vaccine.

14. https://www.mskcc.org/news/can-mrna-vaccines-fight-pancreatic-cancer-msk-clinical-researchers-are-trying-find-out

Around 27% of the industry is, however, more reticent on the speed of development, predicting any cancer mRNA vaccine approval will come after 2028. The conclusion drawn, is that while all of the market does now predict future approvals for cancer vaccines, as with any new technology (Covid aside), the timelines for the first one to market remain shrouded in both developmental and regulatory uncertainty. For contrast, executives in the 2022 survey gave broadly similar results, however, the number forecasting a protracted approval process has now increased slightly.



Another trend that has been observed in other reports is the larger role that smaller biotechs are now playing in R&D pipeline – over larger biopharma companies – particularly for orphan diseases. A recent Deloitte analysis estimated that 55% of orphan drug pipelines are run by smaller and emerging biotechs[15].

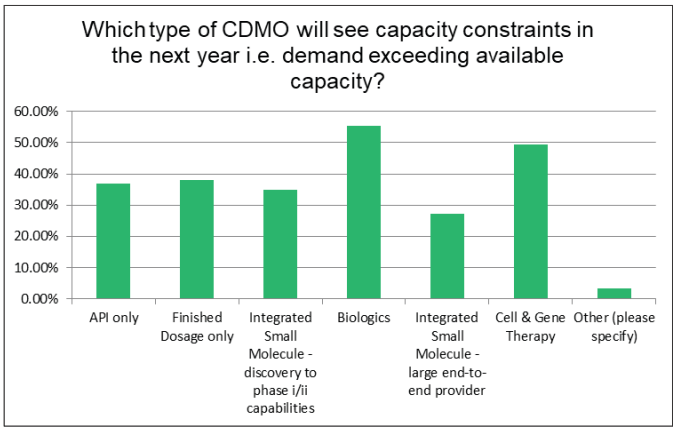


Using AI for early diagnosis: While cell and gene therapies are in general becoming increasingly more tailored, there is now tentative hopes to target large scale diseases, such as Parkinson's or Alzheimer's. What we are increasingly seeing is advanced therapy development is being run alongside other new technologies with biotechs for example, using AI to help target a cure, or at least predict the onset of Parkinson's. Recently, researchers created a test that can potentially predict early signs of Parkinson's in someone's bloodstream up to 15 years before symptom onset[16]. They used an AI platform, called CRANK-MS, to analyse combinations of metabolites in the bloodstream and identified 96% of people who develop Parkinson's within 15 years from these combinations alone. Of course, over the next few years we will undoubtedly see a proliferation of such AI generated learnings, but how these can transfer through to large scale clinical applications remains unclear. Not to mention that while AI can see pattens within these data-sets it has thus far not contributed anything to the elucidate the underlying metabolic pathways causing disease.

Cell & gene therapies and LNPs

Executives ranked cell and gene therapies the 2nd technology class to see the biggest biotech investment in 2023, which is indicative of the industry's continuing optimism and desire from CDMOs to build greater development and manufacturing sites.

In fact, 50% of executives anticipate cell and gene therapies will see significant capacity constraints in the upcoming year, with biotechs with early-stage clinical targets expected to have the greatest challenge in securing suitable resources. These challenges are compounded by well publicised slowdown in capital markets, as well as of course the viral vector demand that was previously sucked up by Covid. When these factors are compounded together it is understandable that many experts envisage that approvals maybe slower in the next 12-18 months. At least until the supply side challenges are worked through and some early-stage funding returns. So, what the market may in fact experience, is rather than an immediate slowing, that perhaps in mid 2024 we may see a moderate slowdown in contract numbers.



15 https://www2.deloitte.com/us/en/insights/industry/life-sciences/expanding-into-european-biotech-industry.html

16 https://www.medicalnewstoday.com/articles/ai-tool-detects-parkinsons-up-to-15-years-early-with-96-accuracy

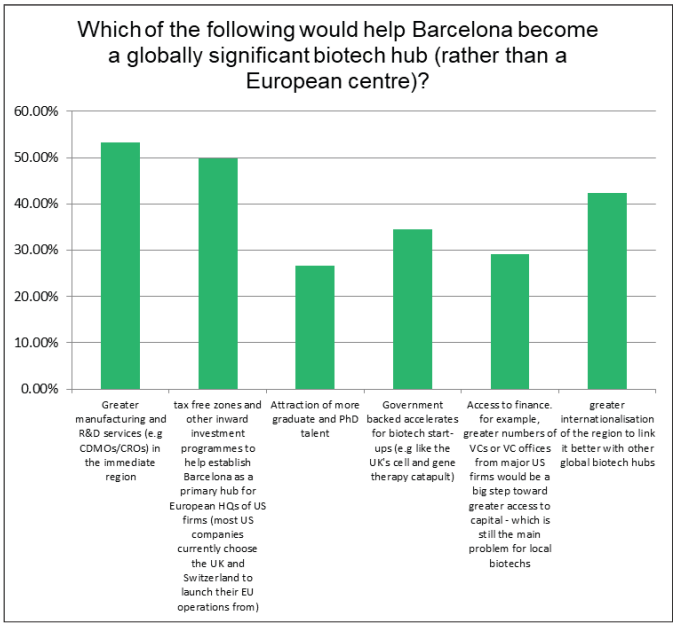
Despite this, many executives are excited about the potential applications of these therapies, namely how they can be used to aid, or even cure, large-scale diseases such as Parkinson's. Sheila Mikhail comments, "*Now that gene therapy is not only a possible solution for rare genetic diseases, but also a viable one, I'm excited to see how we can apply it to pathway diseases. We're beginning to have multiple tools to treat genetic diseases, and we are moving away from the 'one size fits all' approach. In the future, I would like to explore base and prime editing, the use of lipid nanoparticles in tissues other than the liver and repeat dosing.*" AI is expected to play an important role in gene therapies, particularly in target identification and altering protein sequences of genes. For example, AI is being used to predict the activity of RNA targeted CRISPER tools used in gene editing[17]

Lipid nanoparticles (LNPs) are another exciting area of cell and gene therapy and have numerous benefits. They are the most advanced non-viral vector alternative, and while they are currently being used to deliver to the liver, Mikhail forecasts them to be able to deliver to various other tissues. They are beneficial because "*LNPs don't have a lot of the toxicity associated with the adenovirus, and are less complex to manufacture,*" Mikhail comments. "*They also do not have the immune response and pre-existing neutralizing antibody issues.*" LNPs protect mRNA against degradation work as effective drug delivery vessels and can enhance the patient's safety.

Barcelona/Spain

Executives in the pharmaceutical industry are largely positive about Spain's prospects, particularly the Barcelona region. It was ranked as the second most productive environment for biotech/life science start-ups and made a significant jump in the 'overall competitiveness ranking' compared to last year – specifically, it moved from 14th place to 9th place. Spain's quality of pharmaceutical API manufacturing also saw a major increase, with Spain jumping from 11th place to 5th place, behind pharma giants such as the USA, Germany, and Japan. Spain also saw an improvement in their growth potential score for the biologics manufacturing industry. The trends seen in this year's survey compared to last year is overwhelmingly positive, with Spain advancing in the rankings in almost every area.

Spain was the biggest year-on-year winner improving by a massive 30% in bio growth potential.

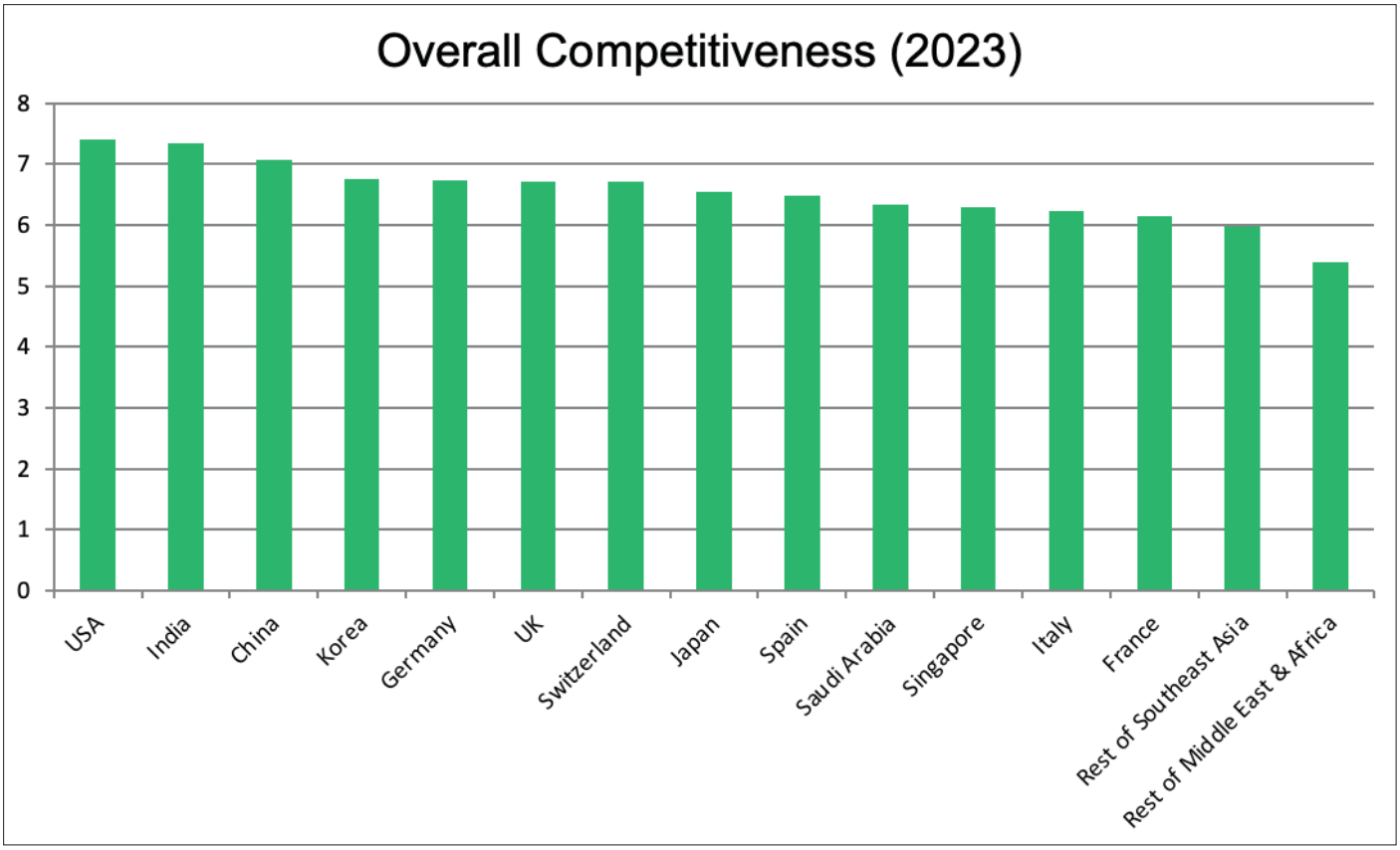


mRNA technologies are expected to see the biggest biotech investments in 2024, followed closely by cell and gene therapies.

While it made vast improvements, executives believe that there are still ways to boost the pharma industry in the Barcelona region. Most executives agree that for Barcelona to become a globally significant pharma hub, there needs to be greater manufacturing and R&D services in the Barcelona region, in addition to tax-free zones and other inward investment programs. The other interesting finding is that for the wider Catalonia region to continue its rise, executives would like to see the research community supported by greater numbers of services providers – in particularly non-clinical CROs and CDMOs to help advanced targets to market faster. With the CDMO market globally expected to add more than $100bn in revenues by 2030[18], Spain in general and Barcelona specifically, is extremely well placed to capitalise on this opportunity. It will therefore be likely to see both inward investment in terms of private equity backing to existing contract services players in the country and FDI from global CDMOs looking to expand in Spain – especially from Asian or US firms looking to gain a bigger manufacturing presence in Europe.

17. https://www.genengnews.com/topics/genome-editing/ai-predicts-activity-of-rna-targeting-crispr-tools/

18. https://www.genengnews.com/a-lists/top-10-contract-development-and-manufacturing-organizations/



Overall Competitiveness

Continuing the strength, we have seen in many other categories – and despite a year-on-year fall – India has further closed the gap on the USA as the most competitive market. Significantly, China has also quietly climbed back up the rankings, after the relative lows of the Covid years and is now once again ahead of all major European markets. The other big movers are Spain and Saudi Arabia, which both jumped 5 places in the rankings. The latter – which is making a well-publicised noise in Sports – has also been significantly investing and improving the country's pharma manufacturing infrastructure and there is an expectation that it is firmly on tract to become the only globally significant hub for production in Middle East and Central Asia. In fact, Saudi Arabia's Public Investment Fund (PID) has even provided the capital to launch a state-owned biopharmaceutical CDMO – Lifera whose goal is to 'help the bio industry grow and strengthen the country's manufacturing resilience'[19]. Over the next few years the Saudi government expects to vastly increase its local manufacturing of drugs – with analyst expectations that the number of factories (39) will increase quickly as will the percentage of domestically made drugs from 30% to past 50% within just a few years[20,21]. Perhaps the greater significance here is the desire to invest in advanced manufacturing immediately such as biologics – rather than the more trodden path of establishing small molecules production first – with the country having invested $3.9bn in R&D since 2021 alone. With the academic infrastructure in Saudi Arabia now already transitioned toward scientific research, regulatory reforms underway and investment guaranteed many – including PWC – expect the country to become a 'competitive biotech hub with the next 10-years,[22].

Saudi Arabia is firmly on track to become the only globally significant hub for production in the Middle East and Central Asia.

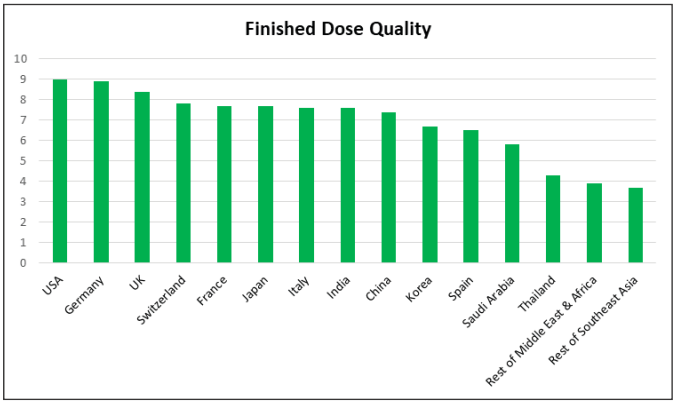
However, as any company in the world in biologics will attest, the most significant challenge it will face is bringing in international talent to support advanced manufacturing. It is perhaps within the confines of these ambitions that the country's recent cultural efforts to increase its 'soft power' and reach do indeed make a great deal of sense - promotion of the country as a good option for high tech industries and careers.

19. https://www.biopharma-reporter.com/Article/2023/06/20/saudi-arabia-s-pif-launches-lifera-to-elevate-pharma-manufacturing-in-kingdom
20. https://www.arabnews.com/node/2354486/business-economy
21. https://www.globalbusinessoutlook.com/saudi-vision-will-pharmaceutical-industry-get-much-needed-boost/
22. https://www.labiotech.eu/in-depth/saudi-arabia-biotech-hub/

So while still a smaller overall base relative to the larger industries in Europe, Asia and the USA, it is predicted that a talent acquisition of high-profile individuals to the Kingdom or joint partnerships to attract in expertise will cause ripples in the global industry and likely be the next stage of this multi-year approach.

In contrast, a country that is seemingly fading in influence [at least within the CPHI surveys] is France, which has once again been the biggest year-on-year loser and is surprisingly now ranked only a little higher than the nescient industries in Southeast Asia.

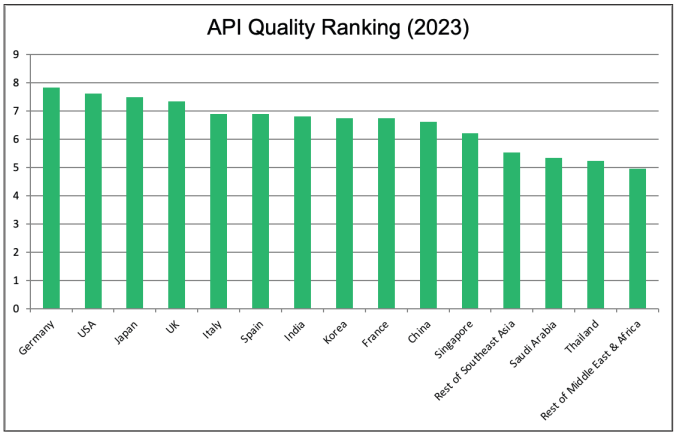
Finished Dosage Ranking



The top three countries for 'finished dosage' remained very stable with the USA, Germany and the UK ranking the same as the preceding year and with near identical scores to boot. The USA has continued to demonstrate its absolute strength to top score with 9, which remains then the category's all-time highest value. The UK did see a very slight decrease, dipping from 8.58 to 8.39, but the country is still notably higher than Switzerland (7.8), Japan (7.7) and France (7.7). Switzerland remained in fourth place despite another narrow fall, while France, Italy (7.6) and India (7.6) all improved their scores from 2024. In fact, taken as a whole, what we can see is that the entire industry is improving together with the majority of nations now making up a tightly packed group behind the top three nations. The biggest winner in this year's survey was again China, which has reached its peak score (7.4) after witnessing a surging improvement of 30% since 2021 [8% up this year]. At the foot of the table however, we have seen the bottom three (rest of MEA, Thailand and Southeast Asia) drop away, with Saudi Arabia reaming in a category of its own having failed to make any further ground on the middle tier of countries. As per the remainder of this report it will be interesting to see if the Saudi Arabia's ongoing investments in pharma translate into rapidly rising scores in the years ahead – our analysts think this is more probable than not in the years ahead.

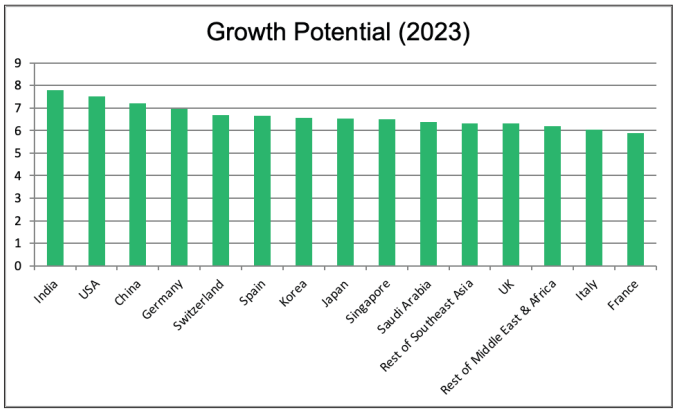
China, with an improvement of 30% since 2021, is now reaching parity or above with India, Italy and Spain in finished dose ranking.

API Manufacturing Quality



Similar to the 'finished dosage' ranking, Germany and the USA still hold the top two places, with Germany in first place. This is hardly surprising, as Germany and the USA performed strongly in the vast majority of categories this year. Japan and the UK stay in the top five, but the UK dropped from third to fourth place, and Japan rose from fifth to third place. India was replaced in the top five by Switzerland, which came in fourth, while India dropped to seventh place (previously at fourth place). Spain is again showing considerable promise and has increased their ranking from eleventh place to sixth place – it is now very closely ranked behind Italy, which is currently a much larger API production centre. The prediction we can infer from this; judging on past sudden moves in the annual rankings, is that Spain will see well above market growth over the next 24 months, particularly when compared to similar European markets.

Growth Potential



Significantly, most countries' growth potential scores dropped this year, which is in stark contract

with last year when they rose almost universally across the board. The UK's score decreased the largest amount, with a massive decrease of 19.23%. This reflects the worst inflation in Europe, with high energy costs potentially embedded within the medium-term future of the economy. In a more positive outlook for the UK – in news announced after the CPHI survey was conducted – the Bank of England now expects UK inflation to fallback in years ahead[23].

India, the USA, Germany, and China remained in the top five this year, which is unsurprising as all four have historically been see as high growth centres. What is notable and perhaps most significant is that while the other three have seen double digit percentage drops, India has not only cemented its place at the top of the rankings – overtaking China last year and the USA this year – but has also only seen a moderate fall in score. The outlook for India into 2024 continues to look very strong and overall, the best of any market in the survey – we can certainly say the country has been the biggest post pandemic winner of macro and regional manufacturing supply shakeups.

India is the biggest post pandemic winner of macro and regional manufacturing supply shakeups.

France has slid further back in the rankings, plummeting from seventh place in 2022 to last place in 2023, with a decrease of 14.49% and a whole one-point score decrease.

The only three countries to see an increase in value was Spain, Singapore, and Saudi Arabia. Notably, the three countries' scores increased by a dramatic amount, all increasing by around 15%. Out of the three, Spain saw the biggest increase in growth potential, skyrocketing from twelfth place to sixth place, and increasing by 17.85%. This demonstrates the industry's confidence in Spain to become a leading region in the pharma industry.

Country	2023 change in % score	2023 score (1-10)	Annual ranking change
India	-4.88%	7.8	+1
USA	-11.76%	7.5	-1
China	-11.11%	7.2	+1
Germany	-13.58%	7.0	-1
Switzerland	-1.47%	6.7	+4
Spain	17.85%	6.6	+7
Japan	-5.80%	6.5	+1
Korea	-1.51%	6.5	+2
Singapore	14.28%	6.4	+5
UK	-19.23%	6.3	-5
Rest of Southeast Asia	-3.08%	6.3	0
Saudi Arabia	16.67%	6.3	+3
Rest of Middle East and Africa	-3.17%	6.1	-1
Italy	-14.28%	6.0	-8
France	-14.49%	5.9	-8

CPHI European Biotech Index

A new addition to the annual report this year is the CPHI European Biotech Index, which evaluates the region/cities in Europe that have the most conducive conditions for start-ups and biotech investment. The clear of winner which was the golden triangle – the name coined for the combined life science areas of London, Cambridge and Oxford – which is home to a who's who of both British pharma players (including GSK and AstraZeneca) and international companies. What has been noticeable in the last few years is that this region has started to rival the USA for early-stage R&D innovation, with genomic, AI, biologics and advanced therapies advancement particularly notable. In response we are seeing increasing investment and in the last six months alone – to take just a few examples – we have seen Moderna confirm construction on Oxfordshire Innovation and Technology Centre (MITC)[24], with the Reef Group announcing in September they had secure approval for construction on a £900 million life sciences hub[25] in Stevenage. The latter development has been specifically designed to foster innovation from smaller companies by providing easy access to essential manufacturing and lab facilities. In fact, London has seen a 300% increase in the number of venture capital-backed biotech firms progressing beyond seed funding

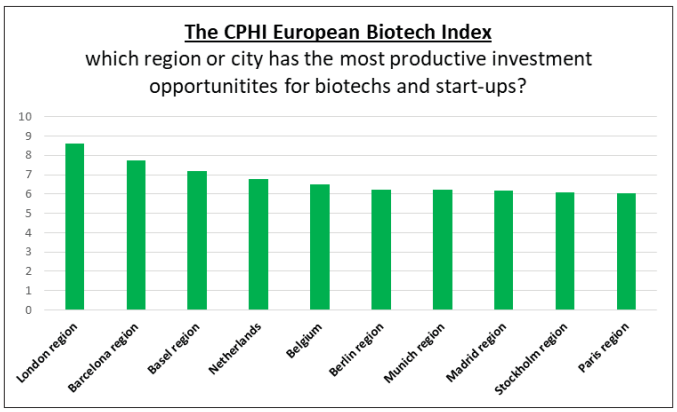
23. https://www.reuters.com/world/uk/uk-public-inflation-expectations-stabilise-bank-england-survey-2023-09-15/

24. https://www.fiercepharma.com/manufacturing/moderna-finds-home-british-research-and-manufacturing-plant-waiting

25. https://endpts.com/new-1b-uk-life-science-campus-gets-the-go-ahead-to-start-construction/

over the past five years, with a further £10billion in live capital reportable chasing investment here[26].

With these conditions as the report's backdrop, it is therefore perhaps unsurprising that the London region topped the CPHI biotech rankings with a score of 8.6. However, in clear second place was the Barcelona region (7.75), which finished well ahead of major European pharma centres Basel (7.2), the Netherlands (6.8), Belgium (6.5), Munich (6.25), Berlin (6.25), Paris (6). The 2024 report will compare these European biotech hub findings against the majors US biotech centres.



Raul Martin, of Ysios Capita, commenting on the Spanish results and Barcelona: *"Spain has surged up the European biotech map in the last years, with Barcelona clearly leading the game. I am positively surprised with Barcelona ranking second behind London, because I thought that other cities like Amsterdam, Zurich, Basel or Copenhagen were more attractive. My perspectives for the region's mid-term are positive based on the rate of creation of new companies, the increasing entrepreneurial spirit among the scientists and international exposure of the companies. I tend to agree with your outperformance expectations of Spain compared to the close peers in general, but I don't think it will be the case for biotech start-ups in the short-term."*

"In terms of the conditions needed to make this happen, well we still need incentives to foster innovation and a clear political leadership through to secure regulations, as well as measures to support science and innovation. Together this will provide Spain with an R&D system in line with its economic potential."

Inflation reduction act impact on biotechnology innovation globally

In August 2022, the Inflation Reduction Act (IRA) was passed in the USA. Among other things, the act requires the US government to negotiate prices for the top-spending Medicare drugs. In August 2023, the first 10 drugs up for price negotiation were announced, and notably, the number of drugs eligible for government price negotiations will increase to 60 drugs by 2029 – with the drug price ceiling at between 25% and 60% of its list price. Moreover, the negotiations are to begin after nine years post approval for small molecule drugs, and 13 years for biologicals. The net result of which according to lobby group PhRMA will be a reduced ability by innovators to reinvest profits into their R&D pipelines[27]. While reduced profitability may indeed lead to reduced R&D spend – particularly as it is estimated to reduce industry revenues by 100bn over 10 years [28] – it will certainly create marginal pressures and this will likely have a profound macroeconomic effect on both ingredients, outsourcing strategies and CDMOs over the next few years. It all points to marginal pressures, not re-shoring being the dominant narrative in the next boom of drug development and outsourcing strategies.

The investment banking community does expect deal volume to pick up later in 2023 into 2024. This will coincide with continuing improvement in biotech funding/valuation climate, and a stabilization/improvement in inflation and interest rates. However, as outlined later in this report, Brian Scanlan predicts softer demand, particularly from 'emerging pharma and in earlier phases of development, will extend for a period of 12-18 months'.

The Rise & Rise of India

It is well known that India is already supplying much of world generics demand: including 50% of drugs in Africa, 40% in the USA and around 25% in the UK[29], but what we are now seeing is a gradual shift in India toward high value drugs. First through value added generics and now the country's CDMOs look set to sizable growth in innovative medicine demand – driven in part by the fact that there simply aren't enough facilities in the west to support its innovation engine and desires to build these have cooled in an inflationary, low capital environment.

So while not unique to this industry, the stars have aligned for India in pharma in the last few years with a perfect combination of: a tremendously strong domestic manufacturing base with rising levels of innovation and returning scientists; the spectre of inflation and marginal pressures in western markets

26. https://www.egi.co.uk/news/harnessing-the-high-growth-potential-of-londons-life-sciences-sector/

27. https://phrma.org/en/Inflation-Reduction-Act

28. https://www.fiercepharma.com/pharma/us-drug-pricing-reform-here-effects-wont-be-felt-some-time-analystsb

29. https://www.investindia.gov.in/sector/pharmaceuticals

that is forcing a quick re-evaluation of partners; and the continued desire for diversified supply chains with a **China plus one strategy now the accepted paradigm for a majority of drug makers**. In fact, such has been the shift in a short space of time that India, even in a year of weekending growth sentiments, has seen an only marginal fall or rise in most CPHI survey categories and it has proved the most resilient market. For example, while the US leads in most categories, it has seen overall, larger falls in score.

Our analysts foresee that the landscape for chemistry services, APIs and intermediates of novel compounds is likely to adopt an "India plus one" approach in the next five years.

Putting all of this together, our analysts predict that, while there is certainly enough growth in the medium term for all markets/countries, the landscape for chemistry services and API and intermediates of novel compounds is more likely to be viewed as an ***India pus one*** approach looking **5-years ahead**. The only nadir of uncertainty in this regard is if either the USA or China can make step-change breakthroughs in AI use to reduce the number of physical compounds made during early stages of discover. Again, the analyst view is that this is unlikely to cut the need for physical chemistry services and research. It is more likely – if AI achieves its full potential – to bolster the industry's development capabilities and efficiencies. So looking five years ahead we will see record (FDA and European) approvals from Indian sites for APIs, a huge global development pipeline backed by subcontinent R&D [certainly surpassing 30,000 total drugs in development and perhaps rising to as many as 35,000 – up from 21,292 in 2023[30]], finished dose sites in the west backed by geo-sourcing for alternative sites, and India supplementing China as the primary driver of chemistry services and early phase products in development.

Yet, a further possibility has recently also come to bare, and while the AI technologies are largely driven by US and China based companies, India is well known to have highly capable IT workforce and we may in fact see a convergence of interest between India's two largest export industries (pharma and IT). In such a scenario India's pharma R&D centres may seek to get ahead of the trend – and remembering India has by far the world largest 'naive patient' base for clinical trials[31] – and start combining its human capital of scientists and technology companies to become a hub of secondary data analysis using AI[32]. This coupled with the country's prestigious pharmaceutical manufacturing could indeed be an incredibly attractive combination for many of the world's largest innovators.

The shift to biologics is also well underway in the country, not least led by the billions of doses of Covid vaccines produced, its role in biosimilars and the recent approval of Ogivri (Trastuzumab generic) in multiple countries. The other significant advantage that will likely help India to continue to invest in newer biologics technologies is that CDMOs here are typically operating EBITA margins as high as 35% verses just 20% in the west. For example, to name but a few, Serum Institute[33], Laurus Labs, Gland Pharma, Syngene International Limited, Divi's Laboratories, and Advent Pharma, are making significant investments to expand their biologics capabilities, and Piramal is a well-known major player in ADCs (antibody drug conjugates)[34].

The story is similar in biosimilars with a sixth fold increase in revenues expected in the next 6 years[35], with some 200 biosimilars under development India. Significantly, the majority of analysts state that on average biosimilar development takes just 3-5 years in India verses 7 in the West and costs on average 10X less – with prices as low as £10million in some cases[36]. Our prediction is that – just like we saw in generics where this capability quickly transferred through into the significant growth of CRO and CDMO services in India – the country is now on the cups of turning this biologics engine toward developing the next generation of innovative medicines. Syngene, for example, is currently launching large scale commercial capacity in the country and Aragen is also expanding its biologics capabilities. In fact, there are even now moves by manufacturing players and biotechs into advanced therapies with Immuneel – the Kiran Mazumdar Shah backed biotech focussed on CAR-T cell therapy for oncology – winning one

30. https://pages.pharmaintelligence.informa.com/RDREVIEW2023_INFO-THY
31. https://www.biospectrumasia.com/opinion/49/22674/why-india-is-most-preferred-clinical-trials-destination.html#:~:text=Although%20the%20overall%20participation%20rate,cervical%20cancer%2C%20etc
32. https://www.livemint.com/market/stock-market-news/how-ai-will-impact-the-indian-pharmaceutical-industry-11695969594987.html
33. https://www.fiercepharma.com/manufacturing/serum-institute-doubles-its-stake-biocon-biologics-300m
34. https://www.psmarketresearch.com/blogs/india-cdmo-industry-growth
35. https://www.insights10.com/report/india-biosimilars-market-analysis/#:~:text=The%20India%20Biosimilars%20market%20size,reach%20%242108%20Mn%20in%202030
36. https://www.pharmafocusasia.com/manufacturing/biologics-new-revenue-streams-indian-pharma

of this years' *Endpoints* prizes for the biopharma 'most promising start-up'[37].

Therefore, of all the biologics markets in the world, our prediction is that India will now see the fastest rates of overall growth in biologicals in the next 5-years, but also a quickly emerging bio CDMO space as we have seen in China and Korea.

Conclusion

The global pharmaceutical sector stands at an intriguing crossroads. As we peer into the next five years, there's a mosaic of technological advancements, strategic shifts, and regional metamorphoses that paints a largely positive future for drug discovery, manufacturing, and distribution.

One cannot underscore the looming prominence of Artificial Intelligence (AI) in reshaping this landscape. Within the forthcoming decade, AI's function in the pharma arena will be influence everything from drug discovery and manufacturing processes, through to clinical trials and post-market surveillance.

We also are witnessing an evolving narrative for Contract Development and Manufacturing Organizations (CDMOs), especially those from the Asia-Pacific realm, with the spotlight resting this year on India. The country is transitioning from being mainly a generics powerhouse to a hub for high-value drugs. This shift is further amplified by the west's inflationary climate and marginal pressures, alongside dwindling enthusiasm for building new facilities. **A China plus one strategy is the phrase de jour, but analysts envision a landscape where, five years down the line, the emphasis might shift from a China-centric to an "India plus one" approach**.

AI's ascendancy also brings forth another captivating prospect. While AI technologies largely emanate from the US and China, India's stellar IT prowess positions it as a potential leader in AI-driven pharma innovations. With the world's most extensive 'naive patient' base for clinical trials, the confluence of India's pharmaceutical and IT sectors could make it a global epicentre for secondary data analysis using AI.

Looking further into a three-year horizon, the landscape is rife with promise and potential challenges. Biotech investments will noticeably pivot towards mRNA technologies. The pharmaceutical industry's anticipation of an FDA-approved cancer mRNA vaccine by 2025 exemplifies the hopes pinned on this technology. In tandem with this, the "golden triangle" — London, Cambridge, and Oxford — is poised to further carve out its position as a dominant hub for biotech investments. Perhaps in a European duopoly alongside Barcelona where growth has been tremendous in recent years.

However, not all is smooth sailing. The US Inflation Reduction Act (IRA) of 2022 casts a long shadow on the global pharmaceutical canvas. By enforcing price negotiations for top-spending Medicare drugs, the IRA has the potential to restrict the revenue streams for innovators, potentially stifling R&D reinvestments. Such legislative shifts could engender seismic changes in CDMO strategies and outsourcing dynamics worldwide.

As we stretch our gaze to 5 years or more, the narrative becomes richer with regional dynamics playing a critical role. Spain, with Barcelona leading the charge, also projects an enticing image. Climbing the CPHI pharma rankings and showing potential to tap into the anticipated growth of the global CDMO market, Spain could become a focal point for biotech and pharmaceutical innovations. The nation's evolution in the pharmaceutical domain underscores the need for a holistic ecosystem, one that thrives on political leadership, regulatory clarity, and environment that can help nurture scientific advancement.

Yet, it would be remiss not to mention the emerging narratives from other regions. Saudi Arabia, with its clear ambitions in advanced manufacturing, is gearing up for a transformative phase. The Kingdom's strategy, accentuated by talent acquisition drives and collaboration initiatives, indicates its vision to establish a stronghold in pharma manufacturing in the Middle East and Central Asia.

And, while it has had its coattails metaphorically clipped in the last two years, China is very much here to stay as a global power horse and we anticipate that its resurgence will gather pace again in 2024. Once any one of these factors eases the dragon's fire could be lit again: global growth rates return, domestic debts pressures ease [not least those held it's property sector which are impacting wider finances] or the reshoring political narratives fade replaced by the continued speed and cost benefits of a globalised supply chain.

Essentially, what we have seen in the last year, is simply a return to the pre-pandemic underlying growth drivers for the industry – just with India, at

37. https://endpts.com/where-are-they-now-tracking-the-progress-of-past-endpoints-11-honorees/

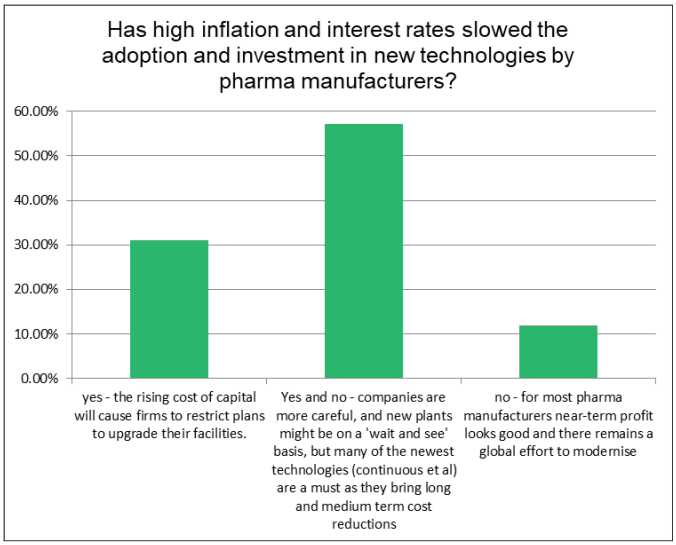
least in the short term, representing a higher growth arena than China. AI, mRNA, the Middle East and microbiome breakthroughs are the new additions to the story of rapidly growing pipeline as well as the gradual rise of outsourcing as a key driver.

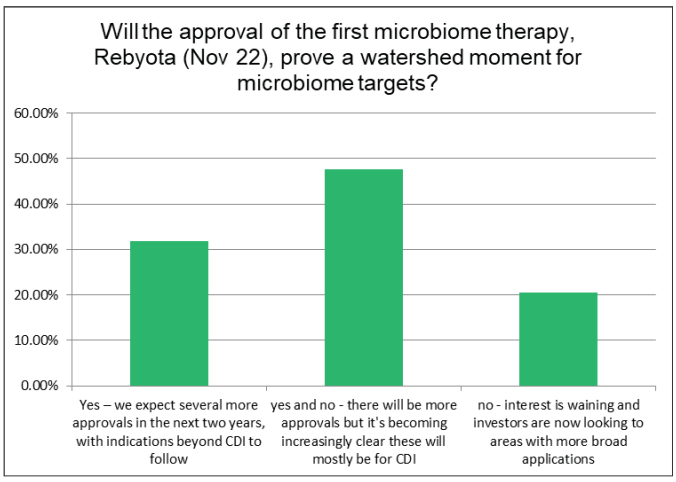
Finally, while sentiments industry-wide are down on the record scores of 2022, all data points now suggest the market has bottomed-out and we expect growth to gather pace very quickly in the first half of 2024. In fact, our experts predict 2024 will be a surprisingly strong year for both growth and innovation.

CPHI Pharma Index 2023

The CPHI Pharma Index is a composite average score of the (five) main small molecules categories across the leading 12 countries. This year-on-year score is an effective measure of overall confidence in the industry. The 2022 index reached its highest level (7.36) in the survey's 7-year history (with an 8.2% rise) and despite so much macroeconomic market turbulence, the 2023 metric has remained remarkably robust (7.16). **The Index is just 2.5% down from last year's record score, or over 5.5% up on 2021**. This equates to a record score in every other year bar 2022. The conclusion of which, is that confidence is only moderately down on the bubbling excitement of 2022 - driven by record revenues - but the overall industry remains on an upward trajectory and its underlying fundamentals remain extremely strong.

Additional survey questions





Part 1

Artificial Intelligence, Machine Learning and the Future of PAT

CPHI Barcelona 2023

How Will Artificial Intelligence Impact Drug Development and Pharmaceutical Manufacturing?

Bikash Chatterjee
President and Chief Science Officer, Pharmatech Associates- a USP Company

Ahead of CPHI Barcelona (scheduled for October 24-26, 2023), the CPHI Annual Report explores future trends, challenges, and opportunities. Featuring a panel of more than 12 industry analysts and insights from 400 pharmaceutical executives, the report provides a window into both near-term and medium-term opportunities in the Pharma sector. In this exclusive article for Pharmaceutical Technology, Bikash Chatterjee of Pharmatech Associates, delves into the implications of Artificial Intelligence (AI) on drug development and pharmaceutical manufacturing.

Advances in Artificial Intelligence are affecting many aspects of society and business today, and pharmaceutical and biotech sectors are no exception. A recent study[1] estimated that global GDP could be up to 14 percent higher in 2030 as a result of AI – the equivalent of an additional $15.7 trillion – making it the biggest commercial opportunity in today's economy.

AI includes multiple applications comprising Deep Learning, Generative Adversarial Networks (GANs), Reinforcement Learning (RL), Transfer Learning and Natural Language Processing (NLP), underscoring the maturity of the field as the tools and approaches are tailored for discrete processing frameworks. One recent entry to the AI solution set that has captured the interest of society, industry, and investors alike is generative AI. Generative AI is based on the GPT (Generative Pre-Trained Transformer) architecture, a model that uses unsupervised learning to generate human-like text based on the context and input it receives. This development is significant as it is the first architecture that can accept unstructured input. The ability to handle unstructured data inputs is revolutionary in the field of natural language processing (NLP). This means textual data, images, audio, and other forms of data that do not conform to a predefined data model or schema can be used for analysis, requiring no special preprocessing or expertise to use the system. Since much of the data on the internet is unstructured, this means industry can use real world data for analysis, basically opening the door for all industries—Pharma included—to benefit from its analytical capabilities.

While global funding from venture investors has

plunged compared to 2022, dropping nearly 50 percent to about $21 billion in 2023,[2] AI remains one of the bright spots for venture capital firms, attracting nearly $3 billion in investments.

Models like the open-source text-generating GPT and text-to-image have made it possible for ventures large and small to jump on the generative AI train, while open efforts have made available models that previously would have been sequestered by large commercial labs. For Pharma this will translate to faster ramp up times to gain competency.

FDA is Embracing AI

The FDA has been advocating for industry to pursue advanced manufacturing solutions for decades. The establishment of the Emerging Technology Team[3] in 2014 provided a vehicle for industry to discuss technical and regulatory issues relating to different stages of drug development with the objective of defining a path forward. Under the umbrella of advanced manufacturing, CDER established the **Framework for Regulatory Advanced Manufacturing Evaluation (FRAME**)[4] initiative to support the adoption of advanced manufacturing technologies that could bring benefits to patients. The technology priorities identified include End-to-End Continuous Manufacturing, Distributed Manufacturing (DM), Point-of-Care Manufacturing and Artificial Intelligence. In May 2023 the FDA issued two white papers to spur the conversation around AI and the subset of AI Machine Learning[5]. The agency highlighted that focused adoption of AI is happening with more than 100 drug and biologic applications in 2021 containing components of AI as part of their submission. However, to spur greater adoption the papers bring to light the risks including model biases used to train ML algorithms, emphasizing the need to address inaccuracies and completeness of the underlying model data. In addition, the paper outlines the role of monitoring the performance of models to ensure they remain reliable, relevant, and consistent over time.

Potential Applications for AI in Drug Development

CDER identified the following four areas in their white paper [5,6] to industry where AI could have an immediate impact:

- Process Design and Scale-up: AI models such as machine learning—generated using process development data—could be leveraged to more quickly identify optimal processing parameters or scale-up processes, reducing development time and waste.

- Advanced Process Control (APC): APC allows dynamic control of the manufacturing process to achieve a desired output. AI methods can also be used to develop process controls that can predict the progression of a process by using AI in combination with real-time sensor data.

- Process Monitoring and Fault Detection: AI methods can be used to monitor equipment and detect changes from normal performance that trigger maintenance activities, reducing process downtime.

Trend Monitoring: AI can be used to examine consumer complaints and deviation reports containing large volumes of text to identify cluster problem areas and prioritize areas for continual improvement. This offers the advantage of identifying trends in manufacturing-related deviations to support a more comprehensive root cause identification.

For most pharma and biologic innovators and manufacturers, the benefits of applying AI are still elusive.

AI in Pharma and Biotech

While our industry has historically been cautious in adopting technology, we are seeing targeted integration of AI. Figure 1 captures primary areas where the pharmaceutical industry is exploring how AI can drive business performance:

Figure 1. AI Applications in Pharma and Biotech

Drug Discovery and Development

Few enhancements have had as profound impact on the cost of drug development as improving the clinical success rate of molecules in development. Today nine out of 10 molecules never make it to market with nearly 58 percent failing after a successful Phase 2 clinical study, representing the majority of the cost associated with bringing a drug to market. There are multiple areas where we have seen AI provide value in reducing program risk, reducing drug development cost and time to market.

Drug Screening

Finding a novel molecule with the right balance of on-target affinity and desired physicochemical properties considering key factors such as toxicity

and bioactivity is the primary challenge during drug screening. AI allows a drug sponsor to increase the number of rationally designed compounds assessed, improving the chances for identifying a promising molecule. The field of digital chemistry utilizes machine learning (ML) and in-silico modeling to screen billions of molecular structures and fragments considering the pharmacokinetic criteria relating to Adsorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) criteria typically derived from Phase 1 studies.

Despite its advantages, AI faces significant data challenges relating to the scale, growth, diversity, and uncertainty of the data. The data sets available for drug development in pharmaceutical companies can involve millions of compounds, and traditional ML tools might not be able to easily deal with these types of data. Quantitative structure-activity relationship (QSAR)-based computational models can quickly predict large numbers of compounds or simple physicochemical parameters but have not matured to the point where they can accurately predict efficacy and adverse effects of compounds. QSAR has been integrated with Deep Learning modeling to address its limitations and have successfully screened compounds addressing efficacy and toxicity considerations, with very promising results. Artificial neural networks (ANN) coupled with QSAR have been found to be very effective in pushing the capabilities of in-silico predictive power and accuracy. The effectiveness of drug screening using AI will improve as we build and refine the training data set for evaluation.

Drug Design

One of the primary challenges in developing a drug molecule, it is identifying the correct target for treatment. Numerous proteins are involved in the development of a disease and, in some cases, they are overexpressed. To selectively target a disease, one must predict the structure of the target protein to design the drug molecule for. AI can assist in structure-based drug discovery by predicting the 3D protein structure. Understanding the 3D structure allows drug sponsors to not only predict the effect of a compound on the target but also will help identify safety considerations before their synthesis or production. AI can assist in predicting drug-protein interactions as part of determining efficacy and effectiveness. This can lower program risk for drug sponsors looking to repurpose existing drugs and reduce the likelihood of a drug molecule interacting with multiple protein receptors producing off-target adverse effects. AI provides two distinct advantages to drug sponsors from a drug design perspective by eliminating drug designs that have a higher risk of safety or efficacy issues early in the development program and isolating designs that have a higher probability of success. Getting to a "no-go" decision quickly is just as valuable as putting the time and money into a drug with a high probability of success.

A computational *de novo* drug design approach can leverage AI. The traditional method of *de novo* drug design is being replaced by evolving Deep Learning (DL) methods. With computer-aided synthesis it is possible to suggest millions of structures that can be synthesized as well as predict different synthesis routes for them.

Multiple AI platforms have demonstrated a superior effect when compared to the trial-and-error approach traditionally applied to drug design, reducing both time required and probability of an unexpected adverse response.

AI in Product Development

AI is being used to address product formulation issues and requirements including stability issues, dissolution, porosity and so on, with the help of Quantitative Structure–Property Relationship (QSPR) analysis. QSPR is an approach intended to find correlations between material properties and predefined structural descriptors, through regression or machine-learning approaches. Coupled with decision support tools, the development exercise is able to select the type, nature, and quantity of the excipients depending on the physicochemical attributes of the drug. Combining AI with established characterization techniques such as computational flow dynamics, discrete element analysis and finite element analysis has the potential to rapidly characterize and optimize the formulation and product development exercise.

This analysis can be framed to optimize patient centricity as well. Considerations such as the route of administration, dosage form, and even the primary container design can be added as constraints within the analysis framework to optimize the physicochemical, therapeutic and compliance considerations.

Advanced surrogates to human testing, such as Physiologically Based Pharmacokinetic (PBPK) modeling require the collection of species-specific physiological, and chemical-specific absorption, distribution, metabolism, and excretion (ADME) parameters, which can be a time-consuming and expensive process. AI can be used to create computational models capable of predicting input parameter values for PBPK models, especially for new compounds.

The FDA has stated that they no longer will require animal testing for establishing toxicological safety. The motivation behind this is the poor correlation between animal models and human models. Replacing animal testing requires models which can demonstrate first that they are as at least as

good as animal testing especially for predicting the ADME behavior in the body. This may seem like a simple undertaking given the poor correlation between animal and human models but drug sponsors will have to address the perceived value that animal testing provided rather than the actual correlation between models which is a much more difficult paradigm shift. For example a sacrificed animal post-testing may have an accumulation of a drug or impurity in the liver and historically that knowledge was perceived to be value prior to human testing, even though the actual correlation was not strong between models. Satisfying this thinking will make a surrogate model more difficult to validate. The FDA[7] proposed an alternative to animal testing utilizing toxicogenomics (TGx) that incorporates emerging genomic technologies into the conventional animal models. This offers an unprecedented opportunity to move away from animal testing by inferring toxicity mechanisms based on individual gene activities and developing safety biomarkers based on gene expression profiles. The TGx model utilizes a generative adversarial network (GAN) architecture to generate both gene activities and expression profiles in TGx involving multiple doses and treatment durations.

AI in Process Development

There are myriad applications of AI in large and small molecule manufacturing. Discrete Element Analysis (DEM) has been used successfully to determine the design space for high shear granulation processes. The DEM model is used to predict agglomeration as a function of impeller speed and liquid addition rate in a high shear wet granulator. The model tracks dynamic formation and breakage of liquid bridges between particles as liquid binder in the system is added and corrects for the change in material properties as a function of the binder content. DEM has also been successfully applied to understand the segregation of powders in a binary mixture as well as the effects of varying blade speed and shape in the granulation process. DEM has also been applied to downstream processes predicting the possible path of the tablets in the coating process, along with analysis of time spent by tablets under the spray zone.

Continuous processing generates significant data as part of the characterization of material properties and their behavior within each unit operation. For PAT applications, utilizing AI can greatly accelerate the intensive statistical analyses typically applied as part of this process development exercise. For example, combining artificial neural network (ANN) AI with Partial Least Square Modeling (PLS) as part of a chemometric analysis strategy has shown to provide better results than either model by themselves.

AI in Quality

AI is revolutionizing pharmaceutical Quality Control by enhancing the speed and accuracy of inspections. AI algorithms and machine learning models can analyze data to identify defects, reducing errors and costs while speeding up inspections. AI algorithms can analyze large volumes of data, such as images and sensor data, to identify subtle defects that may be difficult to detect with the human eye.

In Quality Assurance some drug sponsors are applying AI to critical quality systems such as their Deviation program. Using historical data AI can quickly compare an event observation with historical deviation to identify the appropriate response. This not only reinforces a more consistent application of the organization's QMS it ensures, but past solutions are being applied to avoid failed CAPA implementation and recurring CAPAs, all of which impact both productivity and product quality.

AI is being applied to the Continued Process Verification (CPV) program to trend and compare process behavior against predefined criteria and historical behavior, automating control chart generation and making recommendations from a process and quality perspective that is built on, not only the underlying Stage 1 development data but subsequent manufacturing data. Together these continuously feed the model design and data set.

AI In Clinical Studies

Clinical trials make up a significant portion of the overall drug development timeline with patient selection and recruitment being the primary challenge. In addition to the time invested, ensuring the proper cohorts are identified can make or break a clinical study. AI technology can help sift through large amounts of medical health records and generate data to help find eligible populations for a clinical trial. The technology can also simplify complex entry criteria and make it more presentable to potential candidates.

Once a population is selected, AI can help with recruitment. Traditionally, eligible patients are found though hospitals or clinics, but often, when recruiting large numbers of people, only a few will be suitable for a trial. When provided with eligibility criteria, an automated system can generate a list of potential participants by examining a database. This list can be used by clinicians to inform their patients about their eligibility, or the patients themselves can be contacted directly by the system. Natural language Programming (NLP) can help to stratify patients and, during trials can quickly identify patient safety events. It is easy to conclude that AI will have a deep and lasting impact on

both efficiency and effectiveness of clinical trial recruitment, reducing a significant portion of the overall drug development timeline.

Countries Commit to AI Strategy

Globally there is broad interest in the development and advancement of AI. A map of countries with published AI Strategies as well as strategies in development [8] is shown below in Figure 2.

Several countries are driving the growth and application of AI technologies:

The United States is the clear leader in AI development, with tech giants like Google, Facebook, and Microsoft at the forefront of AI-driven research.

China has made substantial investments in AI and is poised to challenge the U.S. as the AI superpower. The Chinese government has prioritized AI development through its "New Generation Artificial Intelligence Development Plan." China's AI ecosystem includes major tech companies like Baidu, Alibaba, and Tencent. The Chinese government has allocated billions of dollars towards developing the next generation of AI technology, from autonomous vehicles to facial recognition systems.

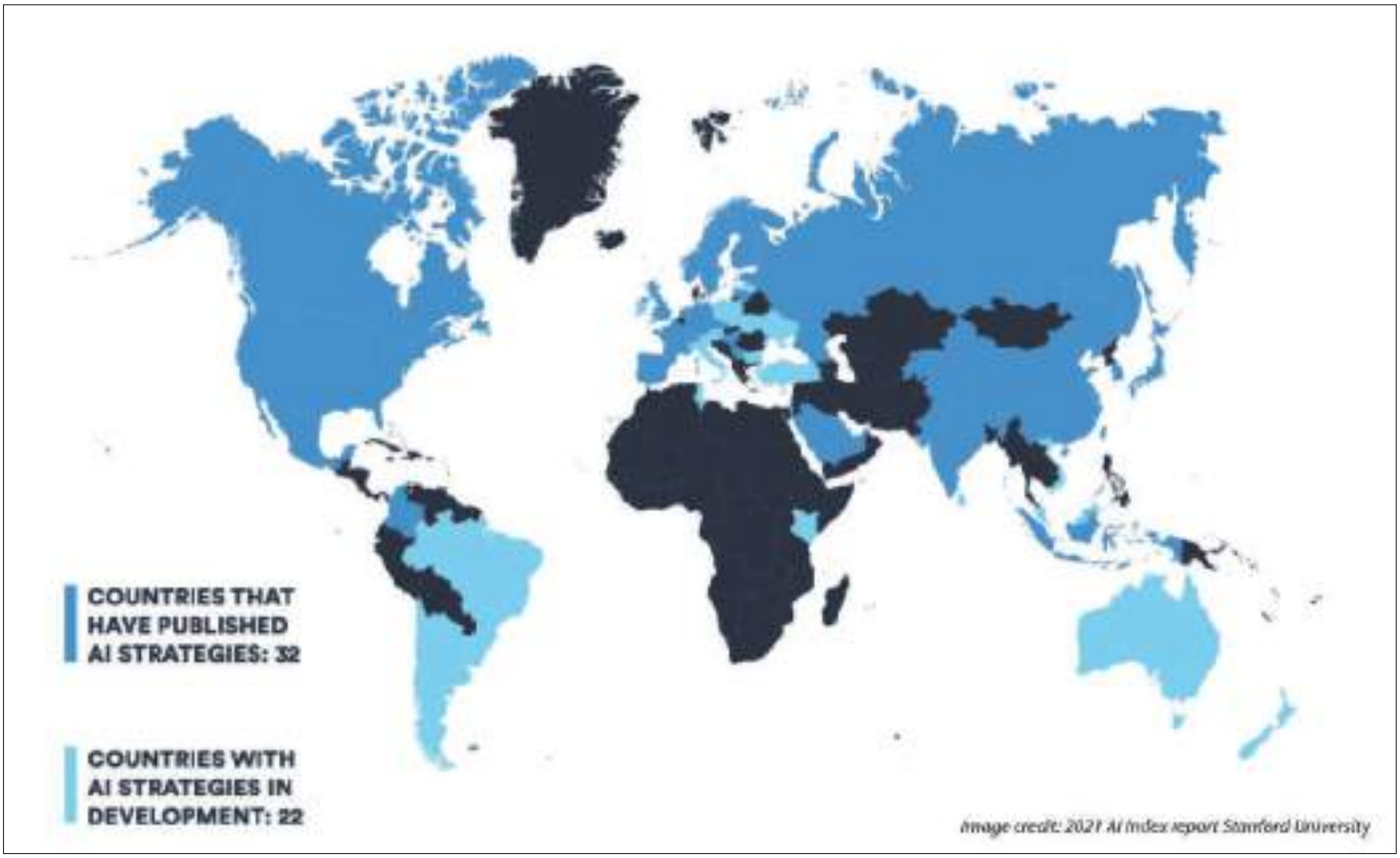


Figure 2. Countries with Published or Developing National AI Strategies

Other countries[9] such as Canada, Japan, and South Korea have made progress with their own initiatives in AI technology. Canada has invested $125 million to promote research and develop strong talent advances. Japan has made the adoption and incorporation of technology across all sectors of society the center of its future with its "Society 5.0" plan looking to make sure the next generation of students are equipped to harness the capabilities of big data, Internet of Things (IoT), artificial intelligence (AI), and robots fuse across all social segments. The plan directs that Japan should hone its strengths and establish leadership in AI applications in the field of sustainability. South Korea has made a huge commitment to AI by allocation 14 trillion won to the development of AI capabilities. These investments reveal that although China and the U.S. may be dominating headlines when it comes to the AI arms race, there are plenty more competitors looking to take control of this prominent field.

Europe may be lagging behind these other countries in terms of AI investment and development, but things are heating up there as well. The European Union (EU) has taken steps to build AI capabilities across the entire continent, launching the "AI for Europe" initiative in 2019 to provide an AI development platform for collaboration and cooperation across member states.

France and Germany are not standing idly by either. In 2022 they announced a program to jointly invest

€17.9 million to support five projects to develop new solutions in the field of artificial intelligence (AI) focusing on the areas of sustainability and to make the industry more resilient to supply chain disruptions. France has pledged to invest € 500 million to create new AI champions.

The UK government was ranked third in the 2021 global AI Readiness Index, and first in Europe. Since 2014, the government has allocated over £2.3 billion to the development of AI. Their Prime Minister, Rishi Sunak, recently publicly stated[10] that he wants to make the U.K. not just the intellectual home, but the geographical home of global AI safety regulation. The UK government has invested over £100 million in a Foundation Model Taskforce created to lead on AI safety domestically.[10] Since then the UK has pledged to invest £1 billion to supercomputing and AI research, as part of its quest to become a "science and technology superpower."

Conclusion

AI has made notable contributions to healthcare, including medical image analysis, disease diagnosis, drug discovery, and personalized medicine. Deep learning algorithms show impressive results in accurately detecting diseases from medical images, assisting radiologists in their diagnoses. AI-powered systems have also accelerated the discovery of potential drug candidates and facilitated the identification of personalized treatment options based on patient-specific data. Progress in AI research and development continues to unlock exciting possibilities and the potential to shape numerous industries in the years to come. AI is transforming the way scientists and researchers approach the discovery, development, and production of pharmaceuticals, offering new opportunities to accelerate the entire process, accurately and sustainably. In drug development, AI algorithms are being deployed to analyze vast amounts of data, including genetic information, patient records, and scientific literature. By leveraging machine learning and data mining techniques, AI can identify patterns, predict outcomes, and generate valuable insights that can guide researchers in designing more effective, targeted drugs. Not only speeding up the drug discovery process, AI stands to increase the success rate of clinical trials by identifying suitable patient populations and reducing potential risks. Although still nascent in its innovation journey, the development and application curve has been steep, with AI solutions evolving on almost a daily basis. As a significant component of our industry in the next five years, AI will be applied across the value chain, from drug discovery to logistics and finance, to become the basis for continued business performance and a catalyst that reduces the cost and time of bringing effective drug therapies to the patients who need them.

Additional Questions and Answers

How will AI impact drug development?

"AI has had a significant impact on drug development and its footprint is going to get larger. AI has the potential to select and design molecular structures, to support surrogates to animal testing, to optimize drug formulation and manufacturing, and thereby drive business performance across the pharma value chain. As AI models become more robust their accuracy and overall effectiveness will improve. Practitioners will also learn how to address the Model credibility requirements that will be essential to address regulatory concerns and will provide a more uniform understanding of what is required to have confidence in the model and its outputs."

How is AI currently being used in drug development?

"AI is being used across the drug development lifecycle today. A number of companies have built their business models using AI to design and select drug APIs/DS. We see AI actively used in many applications that require either the handling of large amounts of data or in the analysis and execution of specific data. AI is being applied to organ-on-a-chip (OoC) microfluidic surrogates to animal models. As a drug moves to First-In-Human (FIH) studies we are seeing AI being paired with digital models to build more accurate Physiological Based Pharmacokinetic (PBPK) models for absorption, distribution, metabolism and excretion (ADME). In manufacturing, AI is being applied to targeted unit operations such as chromatography operations to optimize separation effectiveness, and in finance and quality to execute tasks more efficiently and achieve a greater level of consistency in decision making. Across the manufacturing supply chain we see AI applied in the management and analysis of operational data from large data lakes and data warehouses that aggregate operational data. Clinical operations also rely upon AI to identify qualified candidates for clinical studies to make patient engagement easier to minimize dropout rates."

Will AI be used to further develop precision medicines?

"Absolutely. Look to AI to drive clinician and physician insight in terms of treatment regimens for approaches such as dynamic dosing especially in the field of oncology where the impact of drug therapies can have both a positive and negative effect on patients' well-being."

How specific can AI make drug development for precision medicine?

"Precision medicine is no different than other biologic drug development undertakings. We are still learning how to navigate the challenges of diagnosis and treatment of specific patient situations. Stratifying patients into discrete clusters for diagnosis and treatment is a key non-trivial phase and one of the long-standing challenges of precision medicine. AI can assist to do this more effectively or at least more efficiently as we establish criteria for evaluating each patient for treatment."

Will AI be more beneficial in cell or gene therapies, and what are the reasons for this?

"AI has the capacity to impact both in myriad ways. There is a huge potential for gene therapy because AI's ability to predict protein structures has been shown to enhance the DNA scissor technology like CRISPR, by making more cuts in a patient's DNA more precise."

Do you predict a future where all drugs will be developed using AI for precision medicine?

"I do believe we are only scratching the surface of AI's ability to analyze and provide insights. The models we have today are biased but will improve as we gather more data. We have seen the impact companion diagnostics has had on treating specific disease states effectively. The ability to reduce uncertainty by evaluating a patients potential response to drug therapy will continue to improve. It is not unreasonable to expect AI to become a part of the overall toolkit for all drug development including precision medicine. However, in the near future it is not likely that AI will be the only tool in the industry's toolkit that feeds the drug development pipeline."

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CPHI Barcelona expert calls for more collaboration to help expedite PAT Adoption in pharmaceutical manufacturing:

Sean Daughtry
Director of Technical Operations at Vertex Pharmaceuticals

Sean Daughtry discusses Process Analytical Technology (PAT) and its adoption in the pharmaceutical industry, along with the insights innovators should have when selecting manufacturing partners. He advocates that as an industry we need to proactively engage more to speed adoption - that means increasing the partnering between regulatory bodies, academia, innovators and manufacturers.

CPHI: What do you believe will be the most significant PAT implementation trend in the pharmaceutical industry in the next few years?

SD: *"In the coming years, we can expect a noticeable shift towards the adoption of multivariate process models, which could either complement or even replace PAT. While I firmly support PAT for its rich data and real-time process insights, its implementation can sometimes be challenging, and this is where multivariate processes can come into play. These models can deliver similar insights. But what sets PAT apart, especially in its spectroscopic applications, is its ability to perform chemical testing and scrutinize the precise chemical composition of materials, whether it's a powder, tablet, or any other product."*

For me, looking ahead, machine learning emerges as a potential game-changer. Whether through neural networks, support vector machines, or similar approaches, machine learning holds promise. However, it is new, and its successful integration will hinge on education, collaborative efforts with regulatory agencies to foster understanding and acceptance, and the establishment of robust safeguards and diagnostics to ensure its intended functionality.

Machine learning also holds promise to revolutionize model development, especially when dealing with complex and nonlinear data. Traditional methods like PLS or MLR are good, but machine learning can provide equally or even more accurate models."

CPHI: What developments do you foresee in the market concerning regulatory aspects of PAT adoption in the future?

SD: *"The FDA has been actively advocating for continuous manufacturing and PAT. Notably, we've seen significant developments such as ICH Q13, EMA's NIR guidance, and FDA's NIR guidance, all emphasizing the adoption of PAT. It's worth highlighting that PAT offers a data-rich environment and provides a high level of product quality assurance, especially in the context of continuous manufacturing.*

Several companies, including Vertex, Janssen, and Lilly, have successfully filed PAT within continuous manufacturing. Additionally, many CDMOs are incorporating PAT into their existing processes, whether continuous or batch-based. As a result, regulatory agencies seem to have grown more comfortable in reviewing, inspecting, and approving PAT applications. This will hopefully spur even wider adoption if companies chose to invest in PAT.

To further facilitate collaboration with regulatory agencies and ensure broader acceptance of PAT, companies investing in this technology should engage proactively. This engagement can take various forms, such as meetings with scientific advisory boards, discussions with the ETT, or the preparation of briefing books. These initiatives allow companies to align with regulatory expectations, gain a clearer understanding of agency perspectives, and approach the process with greater confidence."

CPHI: Is there any regulatory alignment between different regulatory agencies?

SD: *"Generally, there is a significant alignment in the regulatory landscape. Some agencies take a more hands-off approach, where once you're filed, they may not extensively delve into the PAT method, including updates and changes. Conversely, other agencies opt for a comprehensive review of these alterations and how they are handled. The overall process be more efficiently managed when a post approval change management protocol is in included in the filing. The PACMP clearly defines what requires approval or notification or what can be handled in your quality system.*

With recent guidance from both the FDA and EMA, we see a concerted effort to establish consistent governance and lifecycle management for PAT implementation. I also know that there is increased alignment and encouragement found in the approaches of Health Canada, Australia, and Swiss Medic regarding the adoption of PAT and continuous manufacturing. So it's all moving in the right direction."

CPHI: Could you provide a prediction on a specific technology shaping the future of PAT and CM within the pharmaceutical sector?

SD: *"In PAT, I'm seeing some noteworthy technological advancements. As you may know, Near-Infrared (NIR) and Raman spectroscopy are the two widely utilized techniques and one notable improvement is Spatially Resolved NIR (SPS), known for its swift acquisition capability. SPS enables tasks like detecting agglomeration and even facilitating near-100% tablet inspection due to its remarkable speed. Additionally, in the realm of NIR, High-Energy Transmission Spectroscopy is gaining attention. This approach boasts energy levels high enough to perform transmission scans through tablets. This is particularly beneficial because it allows for holistic tablet analysis, eliminating the potential biases associated with localized concentration variations within the tablet.*

Within the domain of Raman spectroscopy, Time-Gated Raman is a development worth mentioning. Traditional Raman spectroscopy faces challenges with fluorescence interference, where certain ompounds fluoresce, rendering Raman less effective. However, Time-Gated Raman employs ultra-fast acquisition methods, leveraging picosecond lasers and single-photon avalanche diode detectors. This enables spectral data collection to occur before fluorescence occurs, effectively mitigating the fluorescence issue.

These technological advances hold great promise, but the key question lies in how to seamlessly integrate them into automation, whether through online or offline applications. This integration becomes a pivotal consideration in the design of your control strategy.

In terms of continuous manufacturing, various approaches have emerged, such as wet granulation, dry granulation, and direct compression, typically used in series in some fashion The future trend leans toward a more modular design, allowing manufacturers to tailor elements of processes to their products for enhanced flexibility."

CPHI: From your perspective, what lessons can CDMOs learn from the current PAT landscape?

SD: *"Well, the ideal scenario is when a business partner expresses a strong interest in embracing continuous manufacturing and is willing to collaborate on its development and implementation. In such cases, simplicity should be a guiding principle whenever feasible. As I previously mentioned, adopting a more modular design approach can be highly effective. For instance, having a direct compression unit or a*

dry granulation unit that can be either combined or kept separate based on specific product requirements and control strategies offers flexibility.

However, it's essential to recognize that significant investments are required. You'll need to invest in building expertise, particularly in individuals well-versed in instrumentation, automation, and chemometrics if you're using spectroscopic PAT. This investment extends to lifecycle maintenance as well. Additionally, there are non-spectroscopic PAT options to consider, such as laser diffraction, physical testing, or soft sensors, which generally entail a lower burden in terms of lifecycle management.

It's worth noting that some CMOs and CDMOs have already made substantial investments in continuous manufacturing capabilities. Their proactive approach and ability to attract clients are promising signs for the industry, as they play a pivotal role in driving wider adoption and awareness of the benefits associated with continuous manufacturing."

CPHI: If you have a medium-sized CDMO, maybe just invested in PAT and we've got a smaller biotech with less knowledge in the space, any advice to that sort of partnership?

SD: *"Absolutely, if you're venturing into this territory for the first time, it's a smart move to bring in a consultant or an expert who knows the ins and outs. They can guide you through the regulatory requirements and the physical setup, especially when it comes to testing expectations.*

As I was mentioning earlier, simplicity can be a game-changer. Take, for example, a direct compression process with NIR integrated into the feed frame. This approach tends to be more manageable, especially when tailored to a specific product. But when you're dealing with a complex control strategy involving multiple steps, figuring out where and how to integrate PAT can be a development challenge.

For a medium-sized Contract Manufacturing Organizations I wholeheartedly encourage making the investment. However, having a strategic partner who's already well-versed in this arena can be your best bet. They bring valuable experience to the table and can help streamline the adoption process."

CPHI: How does PAT influence scalability and adaptability of processes in the context of the growing emphasis on continuous manufacturing?

SD: *"What PAT does is that it fully enables continuous manufacturing, and CM provides for faster to market development and validation. Reflecting on Vertex's experience with TRIKAFTA, a continuously manufactured product, it's worth noting that it became the second-fastest non-oncological medicine to transition from discovery to commercialization.*

Continuous manufacturing in the development phase allows us to work at scale without concerns about blender or bin sizes. This results in reduced API usage, efficient design of experiments, and quicker time to market. Moreover, incorporating PAT introduces a data-rich environment that ensures product quality, thanks to real-time monitoring. It provides rapid feedback on process changes, allowing for flexible implementation at various stages, whether post-blending, post-granulation, or within the feed frame of tablets. This adaptability makes PAT a valuable tool for supporting process scalability.

One other remarkable aspect of PAT is its ability to enable real-time release testing, effectively reducing cycle times. For instance, it allows for real-time release testing for dissolution. To establish such a test, it's essential to consider various inputs and create a successful design and innovative modeling. Some companies, like Vertex have successfully ventured into this space. Furthermore, universities often offer opportunities for development partnerships, where specific applications of PAT or different manufacturing configurations can be explored."

CPHI: What collaboration opportunities would you like to see to advance adoption of PAT a little bit faster?

SD: *"I think conferences such as CPHI Barcelona serve as excellent forums for collaboration among technology providers, innovators, regulatory agencies, outsourcing partners, and academia. These gatherings offer valuable insights into successful practices and the implementation of innovative approaches."*

Part 2

CDMO Strategies and Valuations

CPHI Barcelona 2023

2023 the year of re-alignment: yet all data points to green shoots ahead for 2024

An indpeth analysis on the health of the CRO/CDMO sector

Brian Scanlan
Operating Partner - Life Sciences, Edgewater Capital Partners

Introduction

In last year's CPHI Annual Report, the health of the CRO/CDMO sector was covered, and the question asked, "Has the bubble burst?" on the explosive growth observed in the years leading up to, and including, the pandemic. The prediction was for continued, but modulated, strength in demand for Pharma Services in the near and mid-term. Given that biotech funding levels appeared to be "bottoming out" at pre-pandemic (historically robust) levels, emerging pharma still sitting on 2-3 years of cash reserves, and the amount of cash sitting in big pharma's war chest, demand would remain relatively strong, albeit somewhat muted versus the past two years. As long as global pandemics and geopolitical tensions were in check, the sector appeared to be weathering the storm.

This year, we will look at the past 12 months, and update our predictions on both the near and long term health of the sector. Generally speaking, with the pandemic mostly behind us, global geopolitical tensions appearing in check, the level of demand has generally not lived up to expectations. With some exceptions, CRO's and CDMO's are seeing a softening in demand (particularly from emerging pharma and in earlier phases of development) which we believe will extend well into 2024. In spite of the current softness, the underlying demand drivers remain very strong for the sector. As such, the years 2023 and 2024 are viewed as a period of re-calibration or re-alignment. So what has happened since CPHI last year? Let's take a look.

Demand for Pharma Services and the Long-term Outlook

Before we look at the current demand for CRO/CDMO services, it is important to understand the long-term growth drivers for the industry. Over the past 10 years, the number of molecules in the R&D pipelines has more than doubled (Figure 1), with growth rates for small and large molecules around 5% and 12% CAGR respectively. The split between small and large molecules in development pipelines is approaching 50-50. Generally speaking, with the average drug taking over 10 years to go from

discovery to commercialization, the molecules in the development pipelines of today represent a key demand driver for the CRO/CDMO industry for the next decade, and both small molecule and large molecule services will be required to progress these new therapeutics.

Number of Molecules in R&D Pipelines Globally

Figure 1: Piper Sandler & Co.; IQVIA

One of the major contributors to growth in the CRO/CDMO sector is the emerging pharma / biotech community. By definition, these companies need to outsource most, if not all, of their R&D and manufacturing requirements to service providers, many of whom are attending CPHI Worldwide this year. Figure 2 demonstrates the importance of emerging pharma to the current and future success of the global pharma industry's innovative new therapeutic development.

Emerging Biopharma's (EPB's) Contribution to Pharma Pipelines

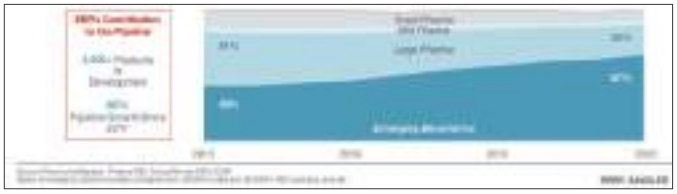


Figure 2: Piper Sandler & Co, IQVIA

What's Going on with Emerging Pharma?

A proxy for the health of the demand for CRO/CDMO sector is funding levels into the biotech / emerging pharma sector. After a period of significant decline (vs 2020/21), funding into the sector seems to have stabilized over the past two quarters at levels seen just prior to the pandemic (Figure 3). Q2 2023 saw funding into the sector of $12.0 billion which was down only 3% y/y. Many in the industry have been asking when/where the funding "trough" would bottom out. If, in fact, we've reached the bottom, then one level of uncertainty (risk) will be reduced, and more predictability can be factored into the future spending habits of emerging pharma. Will a belt loosening ensue?

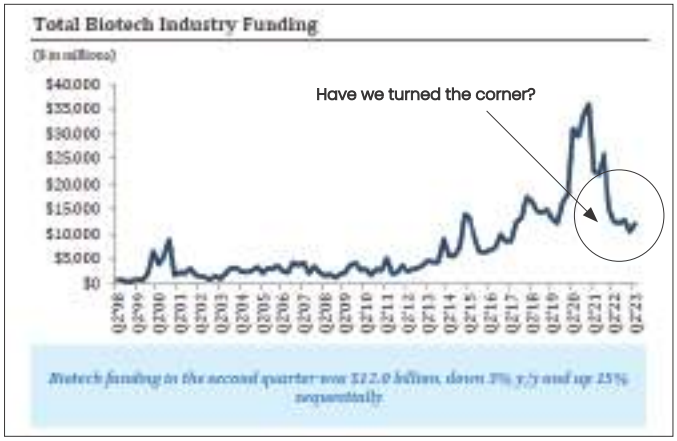


Figure 3: William Blair Equity Research. July 2023

Taking a closer look at funding into the sector (Figure 4) shows a mixed bag with VC, Follow-ons, and PIPE's all resuming near normal growth trends, albeit starting from pre-pandemic levels (2019). However, IPO's remain anemic through the first half of 2023 down 6% y/y. Total funding into the sector through July is $30.2 Bn and full year 2023 is trending ahead of 2022.

Figure 4: Piper Sandler & Co. September 2023

Too Many Companies, Too Little Capital:

Although non-IPO funding appears to have stabilized, there are still too many emerging pharma companies vying for too little capital. The number of companies with active R&D pipelines globally has grown from nearly 4800 in 2020 to over 5500 in 2023 (Figure 5). That's an increase of nearly 15%, while funding levels have dropped to nearly half the 2020 levels during the same period.

Figure 5: Piper Sandler & Co. September 2023

As a result of this, two things have happened:

1. Emerging pharma companies are reassessing their R&D product pipelines and will need to evaluate their approach in order to continue, or pause, slower growth programs to maintain a financial cushion to ensure that their lead compounds take the lions share of the resources. This equates focusing cash burn on fewer programs – reducing CRO/CDMO demand.

2. Emerging pharma valuations have become subdued. Since the second half of 2022 and extending through the first half of 2023, the prevalence of down rounds has accelerated dramatically (Figure 6) with at least one-third of venture growth-stage companies and over 10% of late stage companies in down rounds.

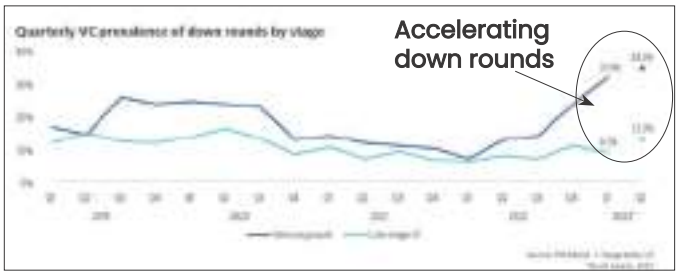


Figure 6: Pitchbook. June 2023.

The capital supply and demand dynamic is out of balance. According to Pitchbook, the demand for capital at late-stage biotechs is nearly 3x the supply, and demand for capital at venture growth-stage companies is 1.3x supply.

IPO Exits are Clogged:

Contributing to the challenge is the IPO market is clogged (Figure 7). Investors who saw a pathway to exit just two years ago are now stuck until the valuations come back. There is some evidence that IPO's are starting to pick up, but it will take time until the structural imbalances work their way through and get back to a more robust opportunity for IPO exits. For now, the system is clogged.

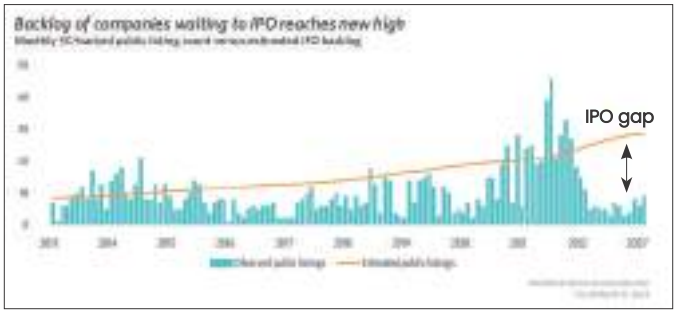


Figure 7: Pitchbook NVCA Monitor. March 2023.

To cure this, any combination of three factors has to happen: 1) VC/non-public funding needs to increase; 2) IPO's need to increase; 3) the number of biotechs need to decrease (fold, M&A, reverse merge). The result for now is an investor's market.

How Long is the Cash Runway for Biotechs?

Given the biotech funding environment mentioned above, CRO's and CDMO's are left wondering how much cash runway is remaining within the emerging pharma sector should the anemic funding environment continue on a protracted basis. Last year, we reported that emerging pharma was sitting on about 2-3 years of cash. According to KPMG and CapIQ (Figure 8), the US emerging pharma cash runway is just under two years (20 months), down from over 36 months in Q1 2021.

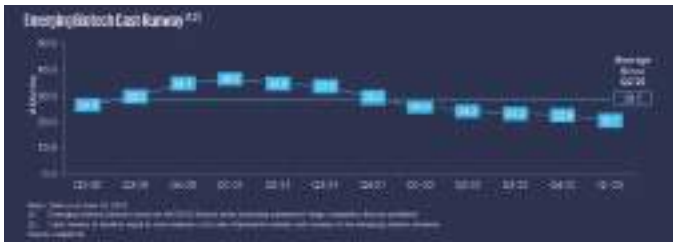


Figure 8: KPMG Corporate Finance and CapIQ. US Biopharma Services Industry Update H1 2023

Implications for CRO/CDMO's:

The protracted, weaker VC funding environment, and a clogged IPO exit funnel has led emerging pharma companies to continue to focus on managing cash burn. According to Pitchbook's European Venture Report for H1, 2023, they have seen VCs work with their portfolios to restructure operations in-house and extend cash runways as far down the line as they can given current funding environment. This has translated into a continued softening in demand for pharma services, particularly in the early and mid phases of development where most emerging pharma companies engage with the pharma services sector. With some exceptions, the general consensus among most of the CRO/CDMO's we've spoken to is a broad softening of the market, with most citing a softening in demand from emerging pharma.

What's Going On at Big Pharma?

While much attention has been paid to VC funding and emerging pharma, big pharma has been going through its own reinvention. Big pharma is operating against backdrop of continuing inflationary pressures, rising capital costs, patent expiries, ongoing Federal Trade Commission (FTC) transaction scrutiny, and the impact of the Inflation Reduction Act (IRA) in the US. In a recent survey by PwC, 90% of executives said they were worried about the macroeconomic environment, with many already taking action to adjust strategic plans.

M&A Picking up:

In last year's CPHI report, I predicted M&A to likely increase significantly as big pharma's balance sheets were robust, patent cliff's coming, and value buying opportunities with emerging pharma accelerating. What's happened thus far in 2023?

According to Goldman Sach (Report July 6, 2023), pharmaceutical companies are sitting on $700 billion for acquisitions and investment. Larger strategic consolidations have picked up in the past year, with a number of notable deals including Pfizer-GBT, Amgen-Horizon, GSK-Bellus, Merck-Prometheus, and Pfizer-Seagen. It is likely that these larger consolidations will continue for the foreseeable future. As big pharma continues to shore up gaps in therapeutic areas, and as it looks for new technology areas emerging earlier in the discovery pipelines.

Big pharma's M&A of smaller emerging pharma companies (values <$1Bn) has been more muted than expected for the past year, although there are signs of acceleration over the first two quarters of 2023. With IPO exits clogged, M&A activity should continue to increase, and value-buying opportunities of pre-IPO emerging biopharma should accelerate given the capital supply/demand dynamic currently ongoing in the private funding market.

Streamlining for the Future:

As big pharma deals with increasing costs, recent government intervention around mega M&A deals and drug pricing controls, and a changing macro environment, it is beginning a phase of structural change to ***proactively*** get in front of the changing dynamic. One area gaining much attention this year is announced layoffs within the industry. According to a Fierce Biotech analysis, as of mid-August 2023, layoffs industrywide (119) have eclipsed all of 2022. While understandable for emerging pharma, several big pharma companies including Novartis, Biogen, BMS, J&J, Genentech, Takeda, Novo, Eisai, Merck KGaA have all announced planned layoffs in 2023. A notable example is Biogen's "Fit for Growth" program where President & CEO Christopher A. Viehbacher mentioned, "We have taken a bottom-up view to shift our resources to the areas of greatest value creation." In August, Biogen announced ~11% reduction in workforce (~1000 employees) over the next three years.

Implications for CRO/CDMO's:
Big Pharma Streamlining - Enhances Demand for Services: As big pharma streamlines its resources to areas of greatest value creation (shedding people and assets) the need for outsourced providers of research, development, and manufacturing services will be needed more than ever. We should bolster demand for CRO/CDMO's.

Big Pharma M&A - Enhances Demand for Services: Increasing M&A volume provides an outlet for the clogged IPO funnel currently observed in the emerging pharma sector. This keeps the flow of capital to support development programs and commercialization of new therapeutics innovated by emerging pharma, and bolsters demand for CRO/CDMO's. This also helps fix the capital supply/demand imbalance in the emerging pharma sector by reducing the number of companies. Currently there are too many companies are chasing too little cash.

Government Regulatory Environment and The Inflation Reduction Act:

While government price controls have been the norm in many countries around the globe, the pharma industry in the US has relied on the ability to fuel the heavy cost of innovative drug development (now >$2Bn per new drug launched) by playing in an environment of limited price controls. This has enabled an environment of hyper-fueled re-investment of pharma profits back into R&D or M&A, and many argue has been the catalyst for the explosive decades of innovation centered in US.

The Inflation Reduction Act

In August of 2022, the Inflation Reduction Act (IRA) was passed in the US. Among other things, the IRA requires the US government to negotiate prices for the top-spending Medicare drugs. In August 2023, the first 10 drugs up for price negotiation were announced, and notably, number of drugs eligible for government price negotiations will increase to 60 drugs by 2029. The law sets the drug price ceiling at between 25% and 60% of its list price, with no price floor.

Another element of the IRA is the timing of when a drug will be eligible for government price negotiation. Under the IRA small molecules can be selected for government price negotiations 9 years after approval, while biologics selected for price negotiation will be implemented 13 years after approval.

It is estimated that 10's - $100's of billions of future profits could be wiped out based on the passing of this law alone. Industry trade groups like PhRMA and big pharma have pushed back on the IRA citing its potentially negative impact on drug innovation, given the billions in future profits that could be wiped out as a result. It is unclear how this will all shake out, but generally this will put negative pressure on demand for CRO/CDMO services should the price controls lead to a slowing of investment in future

innovation.

Enhanced Government Oversight of Mergers

Over the past year, the US Federal Trade Commission (FTC) and Department of Justice (DOJ) has signaled deeper scrutiny of merger activity in the pharma industry which could slow down or halt certain mergers going forward. In the US Omnibus Spending Package passed in 2022, increased filing fees for M&A will be used by FTC and DOJ to increase enforcement actions in mergers deemed anticompetitive. The fees went into effect in 2023.

As part of the increased scrutiny, the FTC and DOJ may consider changes to how they define "anticompetitive behavior" for pharma which will extend beyond competition as it relates to specific drugs or therapeutic indications. They are also considering to review mergers that span across markets, as well as impacts on future innovation. Scrutiny could also extend to clinical trial design, drug delivery and how platform technologies could have wider applications in field beyond what they are currently being used for.

One high profile example of enhanced scrutiny is Amgen's merger with Horizon which was halted in May 2023 with a lawsuit filed by the FTC. The case against Horizon and Amgen did not hinge on claims of competition (current or future), but rather focused on the possibility for Horizon's blockbuster drugs to be included in Amgen's rebate program. In a settlement on September 1, 2023, the FTC dropped its case and the merger was allowed to proceed.

Implications for CRO/CDMO's:

Price Controls and the IRA – Potential to Decrease Demand for Services: Increasing government pricing controls generally puts downward pressure on CRO/CDMO demand since the fuel for innovation in new therapeutic development has largely come from profits from commercial drug sales. This ultimately impacts negatively on future demand for pharma services.

Increased Government Scrutiny of Mergers – Neutral Effect on Services: Increased government scrutiny on mergers can cause more uncertainty, slow down the process, and cost billions to litigate which is money/resource not spent on pharma services and innovation. On the other hand, the true intent of anticompetition laws is to help foster an environment of diverse innovation and competition which can have a positive impact on demand for pharma services.

Regional Capacity and The On-shoring Conundrum

In last year's CPHI Annual Report, we reported that the on-shoring phenomenon had been maintaining the momentum gained from the pandemic due to additional geopolitical concerns surrounding Russia/Ukraine, China/Taiwan, and growing political tensions between the US and China. In the past 12 months, those concerns have been dampened somewhat, and generally speaking, the momentum towards on-shoring seems to have lost some steam. While on-shoring continues to be a significant topic for discussion, with few exceptions our conversations with many CRO/CDMO's in the US and EU have not revealed widespread evidence to support a consistent and material increase in business attributed to on-shoring. This is particularly true in our discussions with smaller pharma services companies, and those participating earlier in the drug development process. Hyperbolic talk of widespread on-shoring does not seem to match the reality on the ground. Why is this?

The current on-shoring climate is really a battle of competing forces. Those forces that originally ignited the supply chain re-alignment surge (Covid, Geopolitical tensions, other risk mitigation) have been partially offset by calming geopolitical tensions, easing supply chain disruptions, and the current funding challenges prompting renewed focus on cash management (ie re-considering lower cost regions for outsourced services). There is also the realization that disentanglement from off-shore sources such as China is exceptionally complex, and many supply chains ultimately lead back to China-made raw materials.

In spite of this apparent softening in the on-shoring rhetoric, a recent report from Cytiva (***2023 Global Biopharma Resilience Index***) cited just under half (44%) of pharma leaders feel that their supply chains are more robust than they were one year ago, and only 19% of pharma executives say that increasing supply chain resilience is a domestic priority for the next two years.

What is clear from this report is that if supply chain realignment (on-shoring) is going to systemically take hold, there needs a sustained, long-term industry and governmental prioritization to create a climate that supports such a complex initiative. Otherwise it ebbs and flows with the political cycles.

CRO/CDMO Valuations and the M&A Climate

CRO/CDMO's have generally seen valuations continue to modulate over the past year, but appear to be at, or near a trough (Figure 9), and flattening out around levels seen just prior to the pandemic which is about 20-25% below the peak

seen in 2021. TTM July 2023 shows only marginal declines in public valuations versus 2022.

Figure 9: William Blair Equity Research, Pharma Services Update, July 2023

According to Bain Capital's Global Private Equity Outlook 2023, private equity managed to post its second-best year ever in 2022, riding a wave of momentum coming off the industry's record-breaking performance in 2021. However, inflation and related interest rate hikes caused a sharp decline in deals, exits, and fund-raising in the second half of 2022.

The number of private equity healthcare services platform deals (LBO's) saw a steep decline starting in Q4 2022, extending through Q1 2023, and modestly picking back up in Q2 2023 (Figure 10). Interestingly, according to KPMG (Biopharma Services Update H1-2023), while overall PE deal counts are down, the sector has continued to witness strong participation from the private equity community as nearly 68% of all M&A deals were PE-backed. This level is consistent with the level seen in 2022 70% and represents a marked increase from the 2019 (pre pandemic) level in which 44% of transactions were PE-backed.

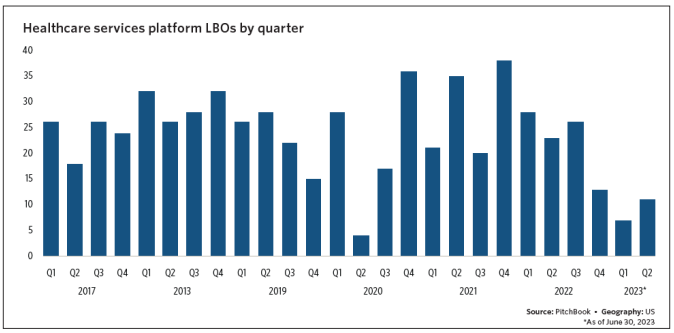


Figure 10: Pitchbook H1-2023 US PE Mid-market Report

It should be noted that while there has been a significant decline in the number of deals executed in the past three quarters, the amount of PE dry powder continues at historically high levels and the need to deploy capital remains high. However, given the broader economic landscape, and dampening valuations, sellers continue to sit on the sidelines awaiting for the right time to go to market. We have heard consistent feedback from the investment banking community that they expect deal volume to pick up later in 2023 into 2024. This will coincide with continuing improvement in biotech funding/valuation climate, and a stabilization/improvement in inflation and interest rates.

Summary on the Health of the CRO/CDMO Sector

The long-term demand drivers for the pharma services sector are strong, driven by strong pipelines of both small and large molecules across the entire drug development cycle, and a macro environment that favors more outsourcing. However, since last year's CPHI the CRO/CDMO sector has gone through a period of realignment. While pandemic and geopolitical pressures have subsided, inflation, higher interest rates, a capital supply/demand imbalance in emerging pharma, and a clogged IPO funnel have marshalled in a period of softening demand for services generally across the industry. Resultantly, emerging pharma generally have migrated towards cash preservation mode. There are signs of an improving VC funding environment, but this needs to coincide with increasing pharma M&A and a more healthy IPO environment. We believe softer demand, particularly from emerging pharma and in earlier phases of development, will extend for a period of 12-18 months.

Concurrently, CRO/CDMO valuations have modulated a bit, but appear to be stabilizing at levels prior to the pandemic (versus the highs of 2021). PE-backed deals and exits have slowed in the sector due to market conditions and buyers waiting on the sidelines. Noteworthy is that PE is participating in nearly 70% of the deals getting done, and the investment banking community is signaling a pickup on deal activity likely starting late 2023 into 2024.

Additional Questions and Answers

Are market forces and outsourcing costs now likely to be the main trend in the next 18-months – i.e. 'putting a pin' in the much talked about reshoring for now?

"With capital somewhat tight at emerging pharma now, there has been a shift towards more cost containment and limiting cash burn. We are hearing from CRO/CDMO's that this had manifested itself in the form of: 1) more scrutiny on proposal pricing; 2) limiting scope of proposals to smaller milestones before releasing future phases of work; 3) emerging pharma focusing spend on fewer programs."

Similarly, with a more stable geopolitical environment (compared to China [and the recent

Canada/Trudeau issues aside]) is India the likeliest CRO/CDMO 'winner' of the recent macro trends for the next 18-months?

"Yes, we have been hearing from both western and Indian CDMO's that the on-shoring momentum in India has been particularly consistent and strong over the past couple of years. That consistency has not been felt as much in the Western regions."

Both Catalent and Lonza have had fairly negative press around their most recent growth figures and CEO changes. Yet in the latter case some growth (4%) was recorded – do you think the largely negative reaction was perhaps overblown, or is it indicative of potentially falling sales in the next 12-months and this what the market is really about warning (falling share price)? (i.e. weakness in early stage outsourcing as alluded to in your article).

"Again, the long-term fundamentals for CRO/CDMO's are excellent given the number of compounds sitting in all phases of development, and continued market dynamics that favor increases in outsourced penetration rates in the coming years. The current funding/IPO climate in the emerging pharma has to sort itself out which will be a near term challenge over next 12-18 months."

Do you think the next 12-18 months perhaps represent a period of excellent value buying for CDMOs – particularly for biologics CDMOs, which until recently were trading at very, very high multiples. With emerging biopharma now 67% of pipelines and nearly 50% of R&D drugs now biologics does this points to excellent growth for these firms in the medium term?

"Yes, there are very good growth prospects for these firms in the medium term which will help keep valuations strong. For good quality CRO/CDMO businesses coming to market, I'm not sure we'll see value buying opportunities either. Public CRO/CDMO trading comps have shown some softening in valuations over the past 12-18 months, and private company valuations have softened a bit as well, but generally speaking both public and private firms are still trading at relatively high multiples versus historical levels. Many business owners have continued to sit on the sidelines this past year waiting for the right opportunity to go to market. Because the number of actionable M&A in CRO/CDMO is down somewhat, there is scarcity value in those deals that have come to market, and good quality assets have maintained good multiples."

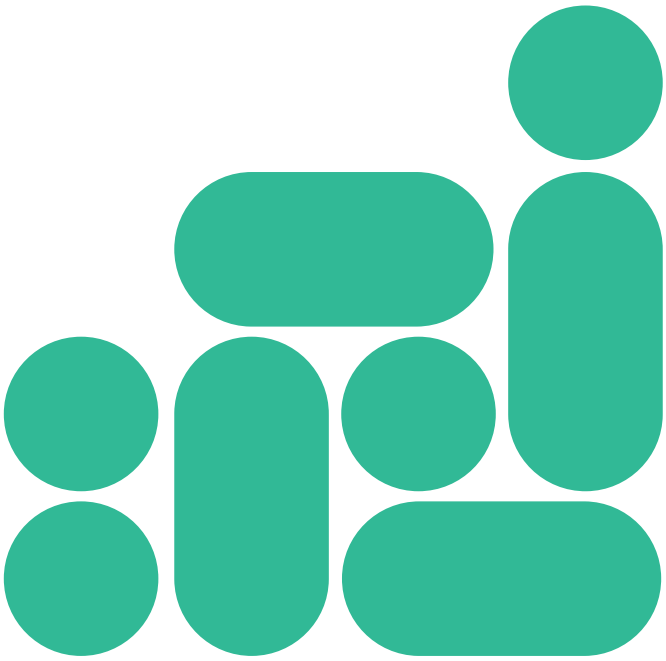
Question about Figure 4: Piper Sandler & Co. September 2023

Looking at the data for this year to date (of $30.2bn for Q1/2) we are on course [if this rate continues] for a year end figure of above $50-60bn, which is equal to or slightly in excess of 2019 figures [even when accounting for inflation]. Data like this is nearly always lagging (see central banks are most often behind the economy as an example) so can you envisage a 2024 with a return to the normal/increasing funding pattern ahead – i.e. $50+bn in biotech funding?

"Yes it does appear that private biotech funding has effectively bottomed out at around 2019 levels which is a good sign. I think many were looking for where the floor would be, and it seems that we are at that point. The IPO environment and pharma/biotech M&A also need to show continued improvement before we know what the new normal looks like in the sector."

When would your estimate be on when the 'record levels of PE dry powder' are released – do you think we might see a trigger event [just a hypothetical example e.g. a change of presidency and a reversal or partial reversal of IRA] or will it just be a reflection of gradually returning confidence?

"Generally speaking there will likely be a gradual increase based on continued signs of confidence in the macro environment. Business owners have been more hesitant to go to market during the past 18 months which has led to fewer deals. We are hearing from the investment banking community that activity level is likely to pick back up 2024 based on their pitch volume and the number of known deals sitting on the sidelines."



The road ahead for CDMOs in 2024: Whether it's an imminent supply chain reckoning or a raft of new modalities, excellent opportunities still abound for the 'right' CDMOs

Gill Roth
President, Pharma and Biopharma Outsourcing Association

Whether it's an imminent supply chain reckoning, or raft of new modalities excellent opportunities still abound for the 'right' CDMOs

The last several years have been tumultuous for the CDMO sector. Some companies benefited from a surge in demand for COVID vaccine and therapeutic manufacturing capacity, while others struggled to maintain supplies of key components and materials, and the drop in COVID-vaccine demand and therapeutic obsolescence due to virus variants have caused further disruption. The decade-plus of low interest rates gave way to inflationary pressures that impacted biopharma pipeline funding and workforce hiring and retention. Trade issues and generic market erosion have created opportunities for some while shutting out others. And the promise of new modalities has been tempered by slow regulatory reviews, manufacturing hurdles, and other obstacles. And then there's AI . . .

These and other factors affect the CDMO sector just as they do the larger biopharma industry. Let's look at some of them and see what they may portend for the next several years ahead. Please note that when it comes to predictions, there's an awful lot that can derail them, like a pandemic, a natural disaster, or an unexpected election result (there are also surprise boons, like a potential $50 billion market for weight-loss drugs springing up virtually overnight!). Also of note: my role as President of PBOA means I spend most of my time involved in policy advocacy — both regulatory and legislative — rather than market-driver-watching; between that and my vast overlapping network of NDAs, there are some trends I can allude to without naming names, as it were.

No matter how much we act like the pandemic is behind us, COVID and Operation Warp Speed (OWS) continue to reshape the world. Lockdown and export bans created an instant stress-test of global supply chains. CDMOs had to adjust to delays in critical materials while also protecting their workforce. As the months progressed and Operation Warp Speed led to unprecedented acceleration in vaccine development and

production, CDMOs who were not part of that effort had to contend with government reallocations of resources via the Defense Production Act to prioritize vaccine manufacturing. This (semi-) artificial supply chain constraint further tested production timelines at CDMOs and the viability of global manufacturing networks.

What came from this was a heightened awareness of supply chains, which will have a major impact on the CDMO sector in the years ahead. (The OWS initiative and the role of CDMOs like Catalent, Grand River Aseptic Manufacturing and Lonza in the pandemic response also created a heightened awareness of CDMOs among the public, which I generally consider a good thing.)

The desire to restructure supply chains through onshoring, nearshoring, friendshoring, etc. will only gain steam in the US ***and*** elsewhere — repeat after me: ***everybody*** has a shore — though it's unclear how extensive those changes can be. The 2020 publication by the US Department of Health & Human Services (HHS) of a Critical Medicines list has become a jumping-off point for initiatives aimed at refashioning the US pharma supply chain.

Some parties are trying to determine which medicines are ***really*** critical, and how can their supply chains be better protected from system shocks and trade wars. This has led to the realization that, even if APIs and dosage sites are located in "friendly" nations, key starting materials and excipients are likely sourced from "not friendly" nations and can't readily be made elsewhere.

So, even though globalization has put hard limits on it, various nations and regions are developing similar priorities for 'domesticating' their supply chains to a greater or lesser extent. Canada, for example, realized it had no scaleable vaccine manufacturing capacity during COVID, and has made significant investment in building it domestically, albeit without changes in some of the regulations and policies that may have led to the decline of domestic manufacturing in the first place. The EU and India both have initiatives to boost local API production. But as we've pointed out to legislators, regulators and other stakeholders, manufacturing on smaller, local scales can actually lead to ***greater*** fragility.

At the same time, one can't ***reimagine*** a supply chain without ***understanding*** that supply chain. In the US, we saw the Congress empower FDA in 2020 to require all API and Finished Dosage Form (FDF) facilities to report the amounts of product they make annually. As I write this, more FDA reporting authorities are being debated in the House and Senate, potentially requiring dosage facilities (including CDMOs) to report the source of each API they use and the amount of each drug product manufactured from that particular API. This has been framed as a means to battle drug shortages, but it's no stretch to see this as a mechanism to better understand dependence on certain countries for API supply. With trade tensions high between the US and China, a clearer idea of "what comes from where" will create a map of what's at stake. (Again, don't sleep on excipients and KSMs.)

When it comes to China, CDMOs, and the larger pharma sector, my Magic 8-Ball is murky. The most recent US rhetoric has moved away from talk of 'decoupling', but there are still trade barriers that both countries are exercising. Combined with China's recent economic slowdown and corruption crackdowns on some business sectors, it's unclear if the CDMO market in China will primarily be for in-China drugs and biologics, rather than global supply.

As mentioned, pharma-neighbor India is trying to jump-start its domestic API market — again, ***everybody has a shore*** — to reduce its reliance on China. Other high-tech industries are expanding investment in India as a hedge, so it's possible the Indian pharma industry — and especially CDMOs — will shift toward high-value biopharma manufacturing, while managing its reputation as the hub of low-cost generic drugs.

Those aforementioned FDA reporting regulations contain confidentiality rules so that the public will not have access to sensitive manufacturing information, but they will still require CDMOs to report out customer data in new ways. In some cases, this may require mass rewrites of quality agreements, and likely will also require added staffing at CDMOs to handle these new reporting duties. Some CDMOs may have to alter or install IT systems to better manage manufacturing data; with increased technology and workforce investment comes increased operating costs. Areas that are extremely cost-sensitive — such as commodity generic oral solid doses — could face new price pressures as these reporting requirements proliferate.

All of which is to say: Supply chain issues — whether they involve onshoring, transparency requirements, rated orders and export controls, or rerouting production due to drug shortages — will be critically important to the CDMO sector and its customers in the years ahead. For our part, the PBOA and its members have engaged with stakeholders to find ways to streamline the process of moving products to new sites or lines in order to mitigate against supply disruptions, and to incentivize investment in

new facilities in key dosage forms and areas.

Another aspect of COVID-hangover has been the impact on R&D. The lockdowns and uncertainty in 2020 led to slowdowns and shutdowns in clinical trials in many regions. The immediate result was a reduction in demand for development services but, cascading from that, this will result in "lost" commercial projects that were scuttled due to clinical delays from 2020-21.

This phenomenon may also occur as a result of the US Congress' 2022 Inflation Reduction Act (IRA), which permitted drug price negotiations by Medicare for the first time. Pharma companies large and small have made statements about canceling pipeline projects out of fear that, if successful, those drugs will be caught up in "price controls" and fail to recoup their R&D investment. In theory, such cancellations will trickle down to CDMOs losing out on associated projects, and even the loss of generics of such products years down the line.

(I'll note that some drug companies cited the IRA as the reason for pipeline-culls within days of its being signed into law, long before there was much clarity on how negotiations would be handled, which makes one (me) think those announcements were less a response to IRA and more an excuse to cancel projects while blaming outside forces.)

Related to this, the PBOA member companies I surveyed agree that the top CDMO business challenge is the slowdown in biotech funding, largely a result of higher interest rates that make investment less appealing than, say, buying a CD at 5%. Hesitation and yet *more* pipeline-trimming by virtual, emerging and small biopharmas can translate very quickly into reduced opportunities for CDMOs. No one has hazarded a guess as to when the finance-floodgates may reopen, but this has cast a pall over many CDMOs, both public and private.

One could argue that this slowdown is also tied into COVID, as inflation and interest rates were affected by government spending to keep economies afloat amid mass lockdowns/shutdowns. One could also argue that it's a bill-come-due function of artificially low interest rates following the 2008 financial crash. There are a multitude of other factors/stories to tell, but I'm no economist so I can't gauge the validity of them beyond my own confirmation bias. The upshot is that as funding becomes tighter, companies and investors have to make tough decisions about pipelines, and that trickles down (or floods) the CDMO sector, which must make capital-allocation decisions of its own.

Which brings us to another aspect of the "post-"COVID environment for CDMOs: the rationalizing of manufacturing capacity. CDMOs did a phenomenal job of keeping up with COVID vaccine and therapeutic manufacturing demands, helping save the world in the process. As a thank-you, once the demand shrank/fell off a cliff, some were left to their own devices to fill their expanded capacity.

In the early 2021 days of the vaccine rollout, I took part in a forum about vaccine production & future-pandemic preparedness where several participants noted that, without significant government investment, long-term contracts, and infrastructure/workforce commitments, the manufacturing capacity that was collectively marshaled to respond to COVID was not sustainable going forward, neither for CDMOs nor in-house pharma. The non-pharma industry participants declared that we were in a new world where many governments now had political will to support and sustain such capacity through public-private partnerships. I was skeptical at the time, and my predictions were accurate: governments have gone back to bickering over healthcare spending and pay lip service to "preparing for the next pandemic", while pharma manufacturing overall has been compelled to rationalize capacity.

That's not to say that the CDMO sector is shrinking. There's been plenty of non-COVID growth in the sector, and the various forms of -shoring have created opportunities for companies with capacity in strategic geographies. In addition, there's the promise of new/growing modalities: CGT, CAR-T, ADCs, mRNA (duh) and more. Of course, these new areas are not without risk. FDA is still racing to keep up with reviewing these new modalities, hiring staff and developing guidance to better treat CGT applications. Meanwhile, reimbursement for some of these drugs has proven difficult for insurers and national health systems. But CDMOs are positioning themselves in these areas, with some spending billions to build out capacity. As the agency staffs up and fulfills some of the commitments it made to innovator companies under the newest iteration of the Prescription Drug User Fee Act, we could see significant growth in new areas of drug manufacturing for CDMOs. But the lack of progress has some companies to pare back expectations in this space.

All of that said, there are realities of the CDMO sector that predate COVID and remain in place. It's still largely a world governed by private equity investment, notwithstanding several notable publicly-held CDMOs. PE funds have limited lifespans and that results in sales of CDMOs to other funds or mergers with other CDMOs or larger healthcare concerns. In the years leading up to the pandemic, we saw large valuations of CDMO

assets, seemingly driven by the notion that CDMOs would provide some of the steady revenue of pharma with little of the R&D pipeline risk (a Ph. II/III failure that leads to a startup shutting down). Those acquisitions continued into the COVID era, although they've slowed in the last two years, again due to this new world of real interest rates.

The industry saw a major and fascinating development when Thermo Fisher, which had acquired Patheon in 2017 to add CDMO offerings, bought PPD, a major Contract Research Organization. As someone who's seen a variety of combinations over a near-quarter-century in this field, I'm quite interested to see how they integrate CRO offerings into their CDMO portfolio and their larger healthcare services and equipment arsenal.

Even in a challenging economic environment, the CDMO sector will continue to play a vital role in supplying their customers with new and long-standing treatments for patients around the world. A supply chain reckoning may be coming, but there are limits to the changes that can be made and the very notion opens doors to CDMOs who are in the right place with the right capabilities. Governments will continue to explore ways to bolster manufacturing infrastructure, and at some point that aforementioned political will may come to bear in a way that makes manufacturing more sustainable and enables this sector along with larger pharma to be prepared for what comes next.

Oh, you want my predictions on AI and how it'll affect manufacturing (as opposed to R&D/discovery)? You're on your own with that one. . .

Gil Roth is the President of the Pharma & Biopharma Outsourcing Association (PBOA), a trade association advocating for the regulatory, legislative and general business interests of the CMO/CDMO sector.

What is the outlook for dose CMOs in 2024 and beyond: High Potency and Biologics Still Top Targets for CMOs Despite Difficult Borrowing

Adam Bradbury
Analyst, PharmSource, GlobalData

GlobalData's recent analysis shows that large CMOs are continuing to invest in specialist dose manufacturing despite difficult economic circumstances. CMOs such as Pfizer CentreOne and Catalent are still willing to spend heavily on valuable commercial-scale dose capabilities in areas such as high-potency manufacture and biologics. The other notable trend is that, while most marketed drugs are still oral solid dosage form drugs, a shift is underway. In fact, small molecule new molecular entity (NME) approvals by the FDA declined substantially during 2020–22. The FDA approved significantly more biologic NMEs in 2022 than small molecule NMEs (24 compared to 17). Another change affecting CMOs is that the most innovative therapies, which are often delivered by injection, have an even greater need for outsourcing – in part because these drugs require facilities that maintain sterility and other higher-value technologies. Large contractors have been making high-profile moves in the M&A space to significantly add to their cell and gene therapy manufacturing capabilities during 2021–22. On February 17, 2021, Charles River Labs acquired Cognate BioServices and its gene therapy division Cobra Biologics for $875 million. The transaction allows Charles River to expand its scientific capabilities in the high-growth cell and gene therapy sector. CRL acquired Vigene Biosciences Inc, a gene therapy CDMO providing viral vector-based gene delivery solutions, for $350 million. We predict that biologics and specialized capabilities will continue to be acquired and/or constructed by innovative CMOs in 2024 and beyond, often for high values as marketed and pipeline drugs continue to become increasingly complex and as smaller sponsors struggle to develop and produce these drugs solely in-house.

Company acquisitions in 2022

In 2022, there were 17 acquisitions of CMOs with a commercial dose service offering. Large CMOs LTS Lohmann and Catalent continued to add to their commercial dose capabilities, with LTS Lohmann acquiring Tapemark in August and Catalent acquiring Metrics Contract Services from Mayne Pharma in October for $475m. Tapemark, a US-based contract development and manufacturing organization (CDMO), specializes in transdermal

drug delivery systems and oral thin film, while Metrics Contract Services is a full-service CDMO with high-potency capabilities for oral solids

All the tables and figures below have been extracted from an analysis included in GlobalData's *Contract Pharmaceutical Dose Manufacturing Industry: Composition, Size, Market Share, and Outlook – 2023 Edition* report.

Delving deeper into the most popular acquisition targets, we see that specialized capabilities (containment and controlled drug manufacturing) and biologic production have been most sought after during 2018–22.

Facility acquisitions in 2022–23

From September 2022 through to September 2023, we observed that CMOs acquired three finished dose manufacturing facilities during, which is an annual rate similar to other years over the last decade, with the exception of peaks in 2017 and 2019. These sites had a diverse array of dose capabilities, with one European site.

Table: Summary of CMO acquisitions of dose facilities, 2013–22

Acquisition types	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Total facility acquisitions	4	2	5	5	9	3	11	5	4	3
Acquisitions of facilities in Europe	2	1	2	1	6	2	8	3	2	1
Acquisitions of facilities worldwide by European CMOs	3	1	2	2	5	2	4	3	3	1

Source: GlobalData, Pharma Intelligence Center Deals database (Accessed August 11, 2023) © GlobalData

Note: Dose facilities sold by bio/pharma companies and CMOs to dedicated contract CMOs are included in the table.

- Astellas Pharma announced that it will sell a manufacturing plant in Meppel, Netherlands, to Delpharm Industrie SAS. Delpharm will continue to manufacture the products that are currently manufactured at the plant in Meppel, using the same staff, and will deliver these products to Astellas.

- Pfizer acquired Abzena's manufacturing facility in Sanford, North Carolina, US. The site can produce biologics drug substances and provides additional manufacturing capacity for Pfizer.

- Unither Pharmaceuticals acquired Novartis's plant in Sao Paulo, Brazil, allowing the expansion of the company's ophthalmic multidose capabilities in Latin America.

The proportion of acquisitions involving European facilities or acquirers, compared to other regions, was relatively low in 2022, which was in stark contrast to the 2013–21 period, when most deals involved a European target or acquirer.

US dose manufacturing

The US has the most commercial-scale contract dose manufacturing facilities in the world at 214. About one-third of US dose sites offer either containment or controlled substance manufacture. The five major European markets (5EU) – France, Germany, Italy, Spain, and the UK –, Japan, and India form the next seven nations with the most commercial dose facilities.

In terms of which manufactures have the most sites, Pfizer and Catalent currently gave the largest number of commercial dose facilities in the US.

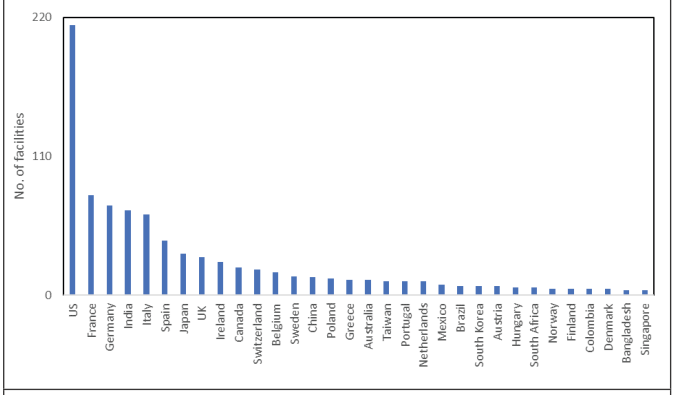
What is notable about manufacturers in the US is that approximately 35% of US commercial dose manufacturing facilities have containment capabilities and 36% have controlled substance manufacture, which is comparatively high globally, suggesting a high level of specialization. Other countries with a high percentage of facilities with containment are France, Germany, and Japan.

Although acquiring specialist capabilities in North America and Europe remains a high priority, CMOs value increasing the geographic reach of their production capabilities to markets in Asia and South America.

Geographic Distribution of Commercial Dose Facilities

The US also has 102 solid dose, 89 injectable, and 66 non-sterile semi-solid and liquid dose manufacturing facilities, giving it the largest number of sites for these individual dosage forms (a single facility may have multiple service types.) The fact that India still ranks among the top five countries for dose facilities shows the country's appeal for commercial dose manufacturing [because there are also many other Indian CMOs that only supply domestic drug companies and do not have approvals to supply to the US, Canada, Europe, and Japan, which is a requirement for inclusion in this analysis]. CMOs headquartered in nine of the top 10 countries will, by default, have at least one of the regulatory approvals to supply their domestic markets.

Figure: Geographic distribution of commercial dose facilities, 2022



Source: GlobalData, Pharma Intelligence Center Contract Service Provider database (Accessed August 11, 2023)
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Note: This graph shows CMOs that manufacture pharmaceutical finished dosage form for the US, Canada, the EU, the UK, and Japan.

What we also see is that India's commercial dose production continues to see investment and to name just a few from the last 12-months:

- Adcock Ingram Holdings built a facility in Bengaluru, India, with annual production capacity of 750 million tablets, 75 million sachets, and 4 million bottles within 8,000m³.

- Hetero Drugs will invest INR10 billion ($120 million) to expand its manufacturing in the Indian state of Andhra Pradesh over the next two years, adding 3,000 jobs, said Managing Director Vamsi Krishna Bandi on March 2, 2023 at the Global Investors Summit 2023.

- SAI Life Sciences opened a 16,000 square foot highly potent API (HPAPI) manufacturing facility at its Bidar, India site that can handle molecules requiring less than 1µg/m³ containment.

Injectable Demand

Globally, there are substantially more CMOs and facilities for solid doses than for injectables, because orally administered medicines remain far simpler and cheaper to manufacture. Injectables tend to be formulated for higher-value products and the delivery form is used for the majority of biologics. This means CMOs require a higher level of expertise and capital entry point for injectable drug manufacturing, as these products are more difficult to manufacture while retaining sterility, which requires techniques such as terminal sterilization, aseptic filtration, and aseptic formulation. Most injectable oncology drugs will also require containment for manufacture. High-containment capabilities are a specialist offering requiring special equipment and expertise, adding a further layer of cost and complexity. Contract injectable manufacture become increasingly important as the COVID-19 vaccines were approved, manufactured, and distributed globally, but their outlook due to falling COVID-19 demand has become less certain.

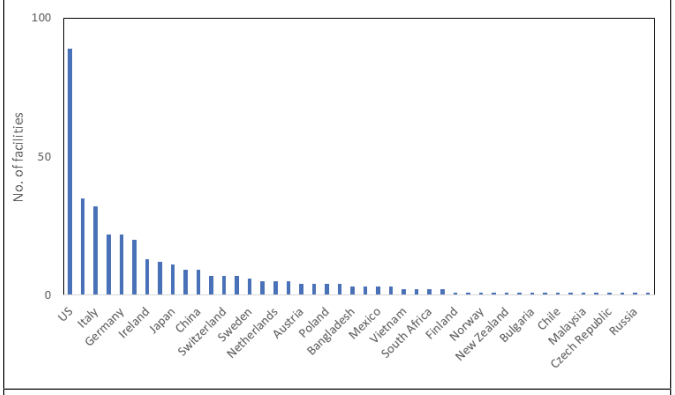
The US, India, and the 5EU feature heavily in the top 10 countries for commercial dose injectable facilities. The US has more than double the commercial injectable facilities of any other country, with Italy seeing the second highest facility count. A total of 42% of contract dose manufacturing facilities in the US offer injectable manufacture. What is notable is that investment into injectable facilities continued into 2023 and therefore beyond the height of the COVID-19 pandemic.

- DelSiTech opened a 100 square meter cleanroom facility in June 2023 for aseptic manufacturing including sterile injectables. The facility will be available for contract manufacturing in Q3 2023.

- PCI Pharma Services plans to open a second 200,000 square foot facility in Rockford, Illinois, US for injectable drug-device combination products, both biologics and small molecules. This facility will house 20 suites for the assembly and packaging of vials, pre-filled syringes, auto-injectors, and pen-cartridge combinations. Additional capabilities include on-site cold storage, high-speed vial labelling, assembly, and packaging of multiformat autoinjectors, serialization, testing, and drug product release. The $50 million investment will add 250 jobs in the next two years, the company claims, and the facility is expected to be operational in H2 2024.

- Carbogen Amcis AG opened a 9,500 square meter facility in Saint-Beauzire, France, for sterile injectables. The facility can handle highly potent compounds, antibody drug conjugates, and freeze-dried products. The site will manufacture for preclinical and clinical trials, as well as small-scale commercial use. It currently employs 100 people, and Carbogen expects to add another 50 employees by the end of the year.

Figure: Geographic distribution of commercial dose injectable facilities, 2022



Source: GlobalData, Pharma Intelligence Center Drug database (Accessed August 11, 2023)
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Note: This graph contains CMOs that manufacture pharmaceutical finished dosage form to the US, Canada, the EU, the UK, and Japan.

1. https://www.ltslohmann.com/en/press-releases/lts-takes-next-step-in-its-growth-journey-with-the-acquisition-of-tapemark-inc/
2. https://www.catalent.com/catalent-news/catalent-to-acquire-metrics-contract-services-for-475-million-to-expand-high-potent-capabilities-and-oral-development-and-manufacturing-capacity/

Part 3

CDMO Biologics Capacity, Sustainability and Bio in China

CPHI Barcelona 2023

Supply and Demand Trends: 2022-2027 Mammalian Biomanufacturing Industry Overview

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Trends Overview 2022-2027

1. Demand for biologics manufacturing capacity by volume is projected to reach nearly 4,400 kL, a 5-year growth rate of nearly 11.5% per year (just over 2,500 kL in 2022).

- If certain high-dosage and frequently dosed products for large population indications such as Alzheimer's, diabetes and cancer checkpoint inhibitors are approved by regulators and reimbursed by most insurers, demand for capacity could be much higher resulting in capacity constraints.

2. Global biologics manufacturing capacity will increase to nearly 8,400 kL by 2027 from nearly 6,500 kL in 2023.

- CMO and hybrid companies are projected to increase their control of capacity from just over 35% in 2023 to just over 45% in 2027 with capacity growth rates in Asia exceeding 10%.

3. Nearly three quarters of the recombinant products currently in late phase development (Phase 2, Phase 3) can be met by a single 2,000 or 5,000L bioreactor.

4. In the short term, BPTG predicts manufacturing capacity will not be constrained but may tighten after 2027. While the majority of capacity currently remains in-house, companies performing contract manufacturing are expanding their capacities which, in the coming years, may lessen the difficulties companies without capacity may have experienced in accessing capacity at the right time and under the right terms.

Abstract: Biologic-based drugs continue to be an important part of the portfolio growth strategies for pharmaceutical and biopharmaceutical companies, and these companies face key issues such as the current and future state of biomanufacturing capacity, the availability of that capacity, and technologies impacting upstream and downstream bioprocessing. This article provides a high-level overview of the current state

of the supply of and demand for mammalian-based biopharmaceuticals and details a forecast of where the industry is heading and how manufacturers are keeping pace.

Article:

Mammalian-based biopharmaceutical product sales have continually increased over the past three decades and represent a thriving sector in the overall growth of pharmaceutical company revenue. In 2022, the top five selling recombinant proteins generated nearly $71B in sales, four of which were antibody-based products (Humira, Keytruda, Stelara, Eylea) with sales totaling nearly $62B. The fifth product, the microbiallyexpressed glucagon-like peptide-1 (GLP-1) receptor agonist Ozempic/Wegovy, posted just over $9B in sales. For antibody product revenue, a group which includes naked monoclonal antibodies, Fc-fusion proteins, antibody fragments, bispecific antibodies, antibody conjugates, and other antibody related products, the compound annual growth rate was 16.9% from 2005 to 2015. Although this growth has remained in the low teens in recent years due to the maturation of many products and emerging alternative therapeutic modalities, it far exceeds the 4.5% growth rate of traditional pharmaceutical (i.e., small molecule) sales from 2005 to 2015 or the low single digits in recent years.

To provide context around this growing segment of the pharmaceutical market, BDO's proprietary bioTRAK® database of biopharmaceutical products and manufacturing capacity estimates that there are over 1,600 biopharmaceutical products in some stage of clinical development in the United States or Europe. The majority, approximately 88%, are produced in mammalian cell culture systems. We evaluated the distribution of mammalian products by product type and phase of development to further refine the biopharmaceutical manufacturing market. **Figure 1** shows the distribution of product types, including antibody products, blood proteins, cytokines, enzymes, fusion proteins, hormones, and other recombinant proteins, by phase of development. Antibody products are the dominant commerciallymarketed product type at nearly 70% and the largest product type for all phases of development, including the early-stage pipeline which consists of nearly all antibody products. It is important to note that many of the early commercial biopharmaceutical products, such as growth hormones, insulins, and interferons, are produced in microbial systems, and are not included in this analysis.

Whether commercially approved or in development, the manufacture of each of these products requires access to mammalian production capacity.

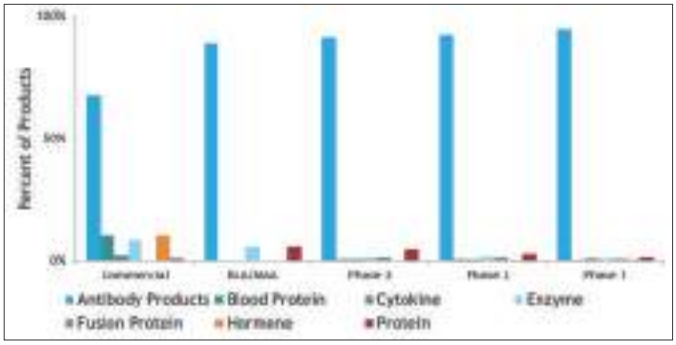

Figure 1: Distribution of Mammalian Products by Product Type and Phase of Development

For current commercially approved biopharmaceutical products, future demand is estimated from each product's reported annual sales data, along with estimates of each product's future growth rates. Our future product growth estimates take into consideration a product's age, as sales growth typically slows as a product matures, while newly approved products often do not reach full market penetration for several years.

With a projected treatment population size estimate, based on price per mg and sales for 2022, we combine the estimated population with the yearly per patient dosing, allowing us to forecast the kilogram quantities required to meet the projected demand of each product for the next five years. These kilogram quantity forecasts can be converted to liters of manufacturing capacity for each product using cell line expression level and overall purification yield estimates. These estimates are based on product type, industry benchmarks at the time the product was being developed and the maturity of the company developing the process. For example, the commercial process for a product launched more than ten years ago will likely have a lower expression level assigned in our forecast algorithm than a product currently in clinical development. For products in development, future commercial demand is estimated based on the market penetration of currently approved products or, in some cases, proxy products with similar indications. Additionally, for products in development, we employ a phase-based commercialization probability assumption when calculating future demand.

Figure 2 depicts the projected kilogram quantities of product needed to meet annual commercial and clinical demand for all product types produced using mammalian production systems. In 2022, a total of just over 37 metric tons of product was required. As more products enter the pipeline and products in development receive commercial approval each year, the overall kilogram requirements needed to meet product demand increase from just over 37 metric tons in 2022 to nearly 85 metric tons in 2027. During the pandemic, demand for COVID-19 related products had a unique demand algorithm and

were not included within the typical forecast, which is shown below. However, given that the pandemic has waned, products related to COVID-19 will be included in our standard analyses in the future and will be grouped with other recombinant products for infectious diseases.

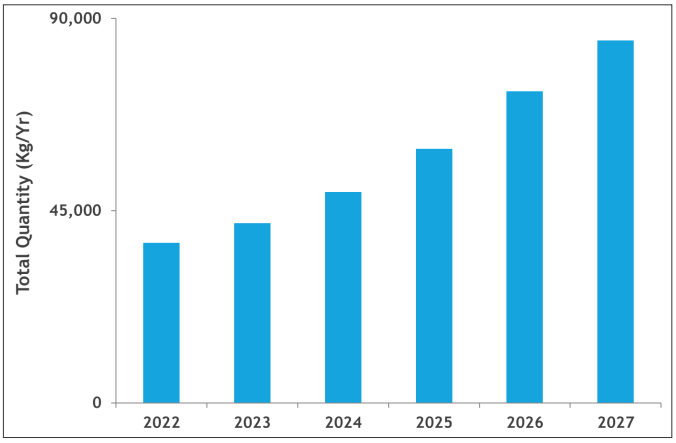

Figure 2: Estimated Quantity of Bulk Kilograms Needed to Meet Product Demand

The projected volumetric capacity needed to meet annual commercial and clinical demand for all product types using mammalian production systems is depicted in **Figure 3**. In 2022, the annual volumetric requirements were just over 2,500 kL, while in 2027, the volumetric requirement is projected to be nearly 4,400 kL, a 5-year growth rate of nearly 11.5%. Similar to the kilogram demand, volumetric demand for COVID-19 related products is not included within this forecast analysis.

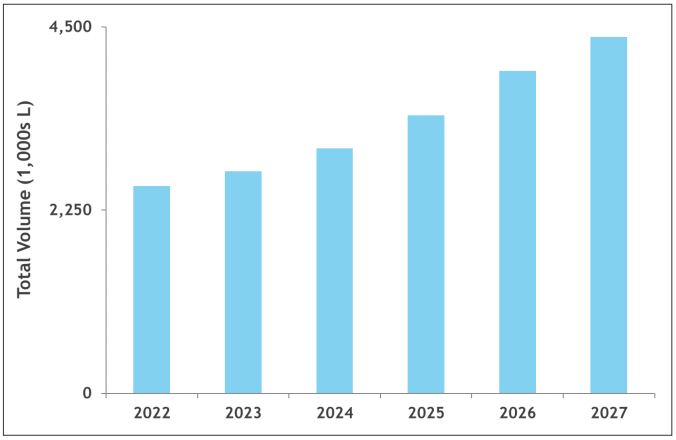

Figure 3: Estimated Volumetric Capacity Needed to Meet Product Demand

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

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

To understand how the industry is positioned to meet these product demands, we estimated the 2023 mammalian cell culture supply to be nearly 6,500 kL and predict it to grow to just over 8,400 kL by 2027, with a 5-year growth rate of nearly 6.5% per year (**Figure 4**). However, not all capacity is equally available throughout the industry. As of 2023, product companies, defined as companies focused solely on product development, control nearly 65% of the installed mammalian cell culture capacity.

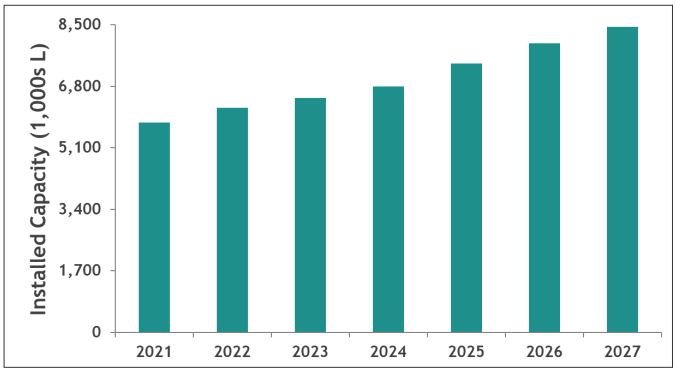

Figure 4: Mammalian Manufacturing Capacity

CMOs (strict fee for service manufacturers) and hybrid companies (those companies that are not only developing products but are also selling or making available any excess manufacturing capacity) control significantly less capacity. This

distribution of capacity changes in 2027, with Product companies controlling just over half of the installed capacity, while CMO capacity increases 12%, with Hybrid companies remaining stable.

While Product companies control the majority of cell culture capacity, the distribution of this capacity is highly concentrated within ten companies, as shown in **Table 1**. Capacity for companies not ranked in the top ten is distributed among 131 companies in 2023, and 140 companies in 2027. Currently, 54% of the capacity is controlled by ten companies shifting slightly to 57% in 2027. Most of the top ten capacity holders in 2023 are also present on the 2027 list, however, based on substantial capacity investments, FujiFilm Diosynth Biotechnologies and Celltrion will displace Novartis and Sanofi from the top ten.

Table 1: Control of Manufacturing Capacity

2023 Rank	2027 Rank	Company	Company Type
1	1	F. Hoffmann-La Roche	Product
2	2	Samsung Biologics	CMO
3	6	Boehringer Ingelheim	Hybrid
4	5	Lonza Group	CMO
5	7	Johnson & Johnson	Product
6	4	WuXi Biologics	CMO
7	8	Amgen	Product
8	10	Biogen	Product
9	-	Novartis	Hybrid
10	-	Sanofi	Product
-	3	FujiFilm Diosynth Biotechnologies	CMO
-	9	Celltrion	Product

Figure 5 Illustrates the geographic distribution of the manufacturing facilities. In 2022, nearly 40% of all mammalian capacity is in North America, followed by Europe and Asia. In the prior five years (2017-2022), there has been minimal capacity growth in North America and significant growth in both Europe and Asia which is projected to continue into 2027. By 2027, with growth rates projected in Asia of 10%, Europe of approximately 7% and North America at 3%, Europe will surpass North America in total liters of capacity.

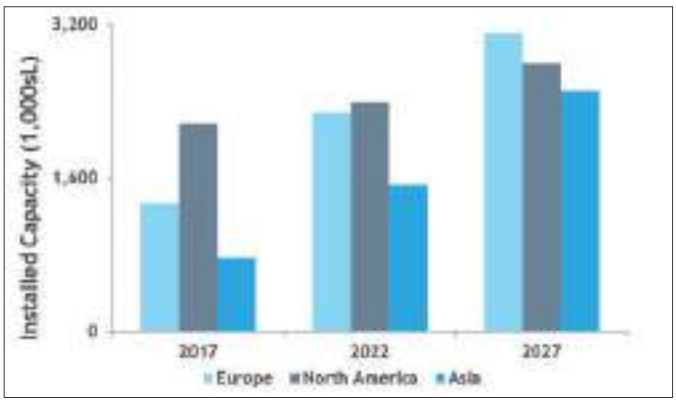

Figure 5: Geographic Distribution of Capacity

As described earlier, different products require different capacity. For example, the kilogram demand in 2022 for the top four selling antibody products totaled approximately 2.1 metric tons while the demand for the nearly 165 remaining marketed antibody products, combined was approximately 28 metric tons (an average of ~197 kg each, and a median of 34 kg). For antibody products still in development, in a best-case commercial scenario where market success and maximum market penetration are assumed, projected demand for over 65% of these products in development is expected to be less than 100 kg per product per year. Just 8% of the products within our forecast are each projected to require over 750 kg per year. Typically, these projected high kilogram requirements can be attributed to sizable dosage requirements, high frequency of dosing and indications with significant numbers of patients including Alzheimer's disease, Parkinson's disease, diabetes, and some cancer-related products.

A closer review of future projected commercial manufacturing demands for products in Phase 2 and Phase 3 clinical development reveals nearly 75% of the products in development can likely be met with a single 2,000 or 5,000L bioreactor assuming 18 batches per year per bioreactor and a 90% success rate for batch manufacturing (**Table 2**). However, this does not mean that large scale capacity is no longer needed. Our model predicts that the remaining products will need bioreactor capacity of 10,000 L and greater to meet the forecasted demand. Increasing the number of bioreactors able to service a single product increases the manufacturing capacity and not surprisingly, causes a shift in the percentage of products whose projected demand can likely be met. As an example, a single 2,000L bioreactor is capable of manufacturing 60% of the products in Phase 2 and Phase 3 while a trio of bioreactors at this scale would be capable of manufacturing over 75% of the products in development.

Table 2: Percentage of Product Demand Met by Bioreactor Scale

No. Bioreac-tors	2,000 L Bio-reactor	5,000 L Bio-reactor	10,000 L Bio-reactor	> 10,000 L Bioreactor
1	60%	13%	11%	16%
2	68%	15%	8%	9%
3	76%	11%	7%	6%

If we analyze the number and scale of bioreactors online and projected to be online between 2022 and 2027 at the < 2,000, 2,000, 5,000, 10,000 and > 10,000L scale (**Figure 6**), it is evident that during this time span an average of 50% of the bioreactors will be at the 2,000L scale with nearly 20% at a scale of 10,000 L or greater. While manufacturers understand the capacity demand scenarios and are installing capacity to meet these anticipated demands, it is likely that the current and future demand for a certain subset of product will likely continue to add pressure to manufacturing networks with large scale capacity.

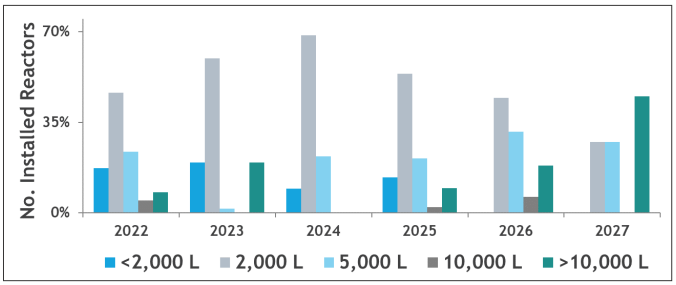

Figure 6: Percentage and Scale of Future Bioreactors

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

While the supply of capacity will increase over the next five years, demand for capacity, is projected to increase at higher rate. In prior years we have noted both periods of capacity constraints at the clinical scales due to very high clinical demand, as well as short-term loosening of capacity constraints, and the industry has responded in kind with a wave of facility expansions.

Year to year, while the numbers vary, we continue to see and would expect that this cyclical constraint and loosening to continue and view it as a status quo for the industry. However, more so now than in the decade prior, the type and scale of capacity being installed will also be important, as the demand for a significant portion of the products in mid- to-late-stage development (met with 5,000 L of capacity or less) has increased over time. While the remaining products will require larger capacity to meet future demand, the industry has responded to this demand as evidenced by the majority of new bioreactors are smaller in scale yet has continued to meet the need for large scale capacity for legacy and novel products with potentially high yearly demands. We will continue to monitor the current and future state of the supply and demand for mammalian-based biopharmaceuticals and will continue to track how the industry is responding and rising to the challenge to meet the typical and additional demands for capacity, without creating a significant situation of over-capacity, as it is critically important to ensure current and future products are available to patients.

Innovation in China's BioPharma: Finding the Next Driver

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The last two decades has witnessed strong growth for China's biopharma industry. China has grown into the world's second largest pharmaceuticals market, and regulatory reforms at the national level have encouraged and enabled domestic developers to invest more in research and development. As a result, China has made rapid strides in innovation, with top companies including BeiGene, Hengrui Pharma, Innovent Bio, and others[1] that are actively engaged in innovative biological developments. Areas in which China has made significant achievements include ADC drugs, PD-1 and cell therapy, and some domestic industry insiders predict that in these subsectors domestic developers can catch up with their Western peers[2]. Chinese developers, known for developing pipelines for established targets, are now often following their Western counterparts in working on drugs and therapeutics with innovative mechanisms of action/targets.

Innovation Comes at a Price

China's industry has most definitely advanced in terms of moving from a biogenerics producer to focusing on innovation and R&D. From BioPlan's 20th Annual Report, we find that China now is seeing higher costs for production. In our Annual Survey, we asked respondents to consider the average cost per gram for protein/mAb, not the finished product. The average cost per gram of primary recombinant proteins in China until recently used to be significantly cheaper than in the US or Europe. This is no longer the case, with the cost of primary proteins now more in China than in the US ($294.00 in China to $255.29 in the US). This may be due, in part to, the rising demand and labor costs in China. For example, while government subsidiaries may help Chinese developers to control costs for facilities, wages a major cost in biologics production, will continue to rise in the coming year. Another factor is the increased costs may also be due to the rise in the percentage of mAb therapeutics, which are more expensive to produce among primary recombinant proteins, as these mAbs are getting BLAs at an accelerated pace.

This change represents a significant shift for China – which may now have difficulties in promoting itself as a low-cost manufacturer of biologics –

especially as costs for consumables increase, and greater wage parity begins to develop [verses the West]. This shifting dynamic may then force Chinese companies to look at alternatives, for example, investing in cutting edge technology or other niche production strategies to differentiate themselves in this ever-growing and highly competitive industry.

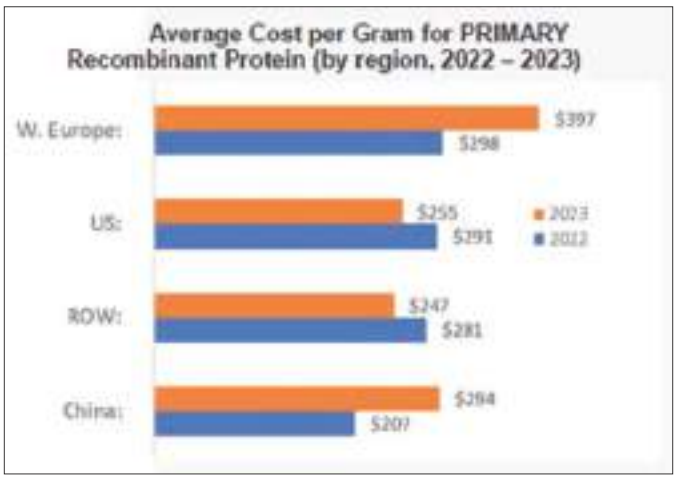

Fig 1: Average Cost per Gram for Facilities' Primary Recombinant Protein (By Region, 2022-2023)

Yet the perception of China as a low-cost biomanufacturing producer remains pervasive, as one head of a biologics CDMO put it, 'a global biotech/biopharma company can develop two projects in China at the cost of one in other markets'. So the question is, as competitive environments change, can China maintain this image and reality.

Source: 2nd Annual China's Position in Global BioManufacturing: A Comparison of China's Emerging Position vs. Established Regions' Manufacturing Capacity and Production; BioPlan Associates, Inc., Rockville, MD USA https://www.bioplanassociates.com[3]

China Improvements in Innovative Drug Development

According to China's National Medical Products Administration (NMPA), in the past decade the organization has approved 130 innovative drugs and 217 innovative medical equipment, and in the first half of 2023 24 innovative drugs and 28 innovative medical equipment were approved[4].

Significantly, applications for IND Class I (innovative) drugs increased by 360% in four years, from 208 IND submission in 2017 to 944 in 2022 – as a percentage of all biologics the growth was equally impressive rising from 17% in 2017 to 49% in 2022[5].

Figure 2 Number of Class I IND in China 2017-2022[5]

Further, the number of clinical trials for innovative drugs doubled in 5 years, from 744 in 2017 to 1444 in 2022. Broken-down by development stage, the number of Phase I trials increased from 337 in 2017 to 744 in 2022, Phase II clinical trials increased from 137 in 2017 to 377 in 2022, and number of Phase III trials increased from 270 in 2017 to 323 in 2022[5].

International licensing deals, both 'in' and 'out', have increased more than 10 fold in the past decade. In-licensing projects have been pivotal to the growth of China's pharma innovation, while it is also now common for domestic developers to license out innovative projects to pharma MNCs (multi-national corporations). In 2013, China based companies in-licensed 14 innovative projects, by 2022 that number had risen to 92, while the number of out-licensing projects has increased from 2 in 2013 to 60 in 2022[5].

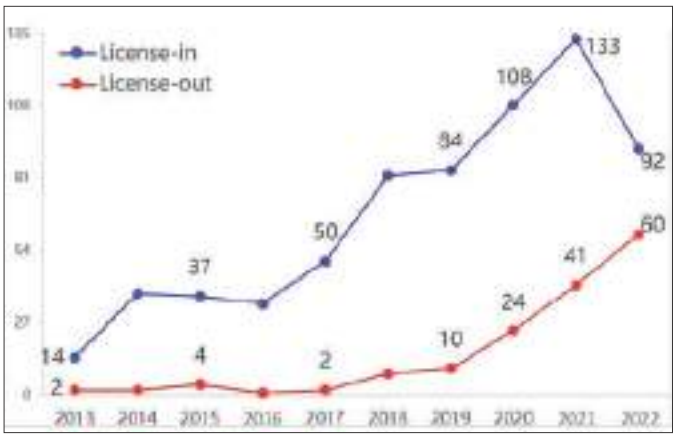

Figure 3 Cross-border Licensing Deals for China Biopharma[5]

The drivers of the progress in innovation

Perhaps the single largest transformational shift began in 2015 as the regulatory authorities introduced pro innovation policies that accelerated the transformation from a bio-generic dominated industry into a more diversified one. Most significantly, the regulator redefined the definition of 'innovative drugs': whereas in the preceding

years any drug launched in China for the first time was regarded as an innovative drug, now only those which are launched for the first time globally would be defined as an innovative drug. A further change that year saw the introduction of an 'authenticity investigation of clinical trial data', which enabled developers to withdraw submissions if they felt the quality of data might be an issue. Consequently, just 10% of applications passed the authenticity investigation, the majority of which were from MNC developers[6] – with the remainder either rejected by the newly stringent regulator or withdrawn. The metaphorical goalposts for the standards and integrity of data ever since have been far higher.

Then in 2017, China was also accepted into the ICH, a sign that country has become formally integrated within the international drug regulatory system. In 2018, CFDA released the Technical Guidelines for Accepting Clinical Trial Data from Overseas, which also opened the door for standardized bridging studies for innovative drugs from MNC developers while encouraging international multi-center clinical trials. In August 2019, the updated Drug Administration Law gave green light to the outsourcing of drug manufacturing via MAH (market authorization holder) system.

New Exit Routes in China

A recent development in response to these changes, has seen 'new exit route' planned and this has attracted substantial investments into the sector, often enabling companies to develop their innovation capabilities in house. For example, in April 2018, the Hong Kong (HK) Stock Exchange updated its IPO guidelines, allowing biotech companies without profits to go public in Hong Kong.

Another boon saw the Science and Technology Innovation Board; STAR Market, launched in Nov 2018, which allows innovative companies without revenues to raise fund via IPO at STAR. Then finally in the spring of this year, HK stock exchange announced its updated IPO guidelines would allow tech companies without profit or revenue to IPO in HK. These reforms have provided exit routes for investors before the launch of innovative drugs from companies they invested in – which naturally provides far greater investment flexibility and strategy options. The investment criticalities in terms of deadlines and funding are far reduced and ultimately this has enabled biotechs to focus solely on innovation knowing there are options out there as projects develop.

For example, to take a very well-known biotech, BeiGene has raised over RMB 30 billion (USD$4.5 billion) via multiple IPOs since 2016 and yet the company is still to achieve profitability today. In the past this approach would have been unsustainable but thanks to the aforementioned investment flexibility BeiGene has 23 projects under clinical development, making it China's top biopharma innovator. With high profits highly likely to follow in the near future. This means that, taken at a national level, companies in China can now scale their innovation operations far more quickly.

Attracting Investments

The booming biopharma industry in China has attracted tens of thousands of returnee scientists, many of whom have started biotech start-ups or are now working with pharma's MNC R&D centers [until recently these centers were closed as MNCs tended to prefer partnering with local biotechs].

These returnee scientists are propelling the country forward as it means biotechs in the Country now have access to highly experience R&D personal familiar with the full western approval pathway but coupled with China's massive chemistry services and lower development costs. It's a very compelling combination. For example, Zhang Xiaolin, the CEO of Dizal Pharma, stated the company spent only four years developing Sunvozertinib from preclinical stage to NDA. The company attributes the fast development speed to the team's prior expertise in EGFR accumulated during their work at AstraZeneca's China R&D site[3]. Besides returnee scientists, China also has a large pool of domestic scientists with life science and medicinal chemistry educations, providing the industry with relatively cheap and qualified labor. The big patient population also makes clinical development less time consuming. As a result, the costs incurred during R&D stages for an innovative drug is far less than in the US or EU. For example, Toripalimab, the first PD-1 in China, developed by Junshi Pharma cost just RMB 4.73 billion (USD$700 million), and both Hengrui and Henglius only spent around RMB 2 billion (USD$300 million) for their respective PD-1 mAb development programmes. Similarly, Chang Biopharma stated it spent less than RMB 900 million for each of its two mAb biotherapeutics (Telitacicept the TACI-Fc fusion protein and Disitamab Vedotin the Her2-ADC).

Famously, development cost in both Europe and the United States are estimated at circa USD$1 billion or more for one innovative drug[7].

China's Biopharma Industry Faces Challenges in Further Innovation

However, the country still has challenge and China is still relative weak in some of the basic life science research capabilities needed for innovative drug development – i.e. target identification and

validation, mechanism of action, etc.

Similarly, the public research institutions and universities, are still adapting to make the significant improvements needed to offer comparable breakthrough similar to many of their Western. The relative weakness here has meant domestic developers looking at first-in-class drugs will more often stick to 'me-better' strategy.

Another issue is how fund innovation in the biopharma industry, with most domestic developers investing in 'me-better' drugs and thus far the NMPA has been relatively lenient in granting approval for and NDA. The net result is that China's biopharma market is flooded with innovative drugs with the same targets and little differentiation. So if we take 2021 statistics there were 657 clinical trials on PD-1/PD-L1 mAbs from circa 150 developers, and the 183 projects Phase III clinical trials do not differentiate much from each other[8]. One PD-1 developer stated that though the cost of developing a PD-1 in China is only around RMB 2-3 billion, NMPA has granted approval for product launch to more than a dozen projects. Then challenge is that the reference price offered is less than 10% of the price in western markets, making it extremely difficult to make profits[9]. Meanwhile the Chinese government initiated National Healthcare Insurance Access Negotiations and Volume-based Procurement Program, which cut profit margin of drugs significantly. This reduced likelihood of profits is therefore causing a significant drag factor on capital inflows for many biotech star-ups as investors seek more certain and larger returns in other sectors.

Looked at in data form, we see that in 2022 there were 1516 investment deals in China's biopharma sector, which is 37% less than in 2021. These deals totaled RMB 123.1 billion, which is 48% less than in 2021, and the average deal size was down 18% to RMB 810 million[8].

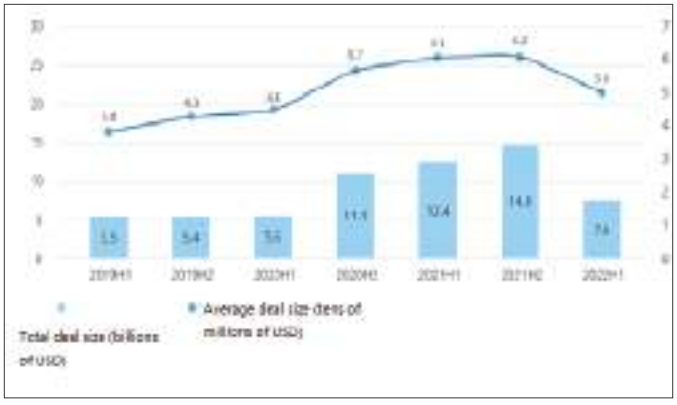

Figure 4 Investment Deals in China's Biopharma Sector in 2019-2022[10]

Next Generation Innovation in China's Biopharma

It is hard to imagine that China's national healthcare insurance program will give innovative drugs any type of incentives, as policymakers focus on making broad insurance coverage and cost effectiveness their priorities. Therefore, for domestic developers to make profits from their innovations, industry insiders believe one of two possible strategies must be applied:

Strategy 1: Merger, Acquisition and Differentiation. The current over-crowded competitive landscape, with many domestic developers chasing just a few 'trendy' targets, is certainly not conducive of high profits for all. Regulatory authorities in China are aware of the problem and are making policy changes accordingly. In 2021, NMPA announced Guidelines on Clinical Value Oriented Clinical Development of anti-cancer drugs, which tries to solve the issue of over-crowding of drugs within the same target classes. Since the announcement of this guideline, the speed of NDA granting to PD-1 drugs has slowed significantly. And, to give just one example, in June 2023, Genor Biopharma announced its NDA application for Janozumab had not been approved by the NMPA. This is the first PD-1 mAb to be rejected for NDA approval in China. It is widely expected that more PD-1 NDA applications will be rejected by NMPA. This policy trend will drive merger, acquisition and differentiation in the domestic developer landscape. In the next decade, China may have fewer biopharma and biotech companies around, but the remaining ones will be more specialized and sophisticated in their own area of strength.

Strategy 2: Exploring overseas markets. It is gradually becoming a consensus that overseas regulated markets, especially the USA, present far more lucrative options for domestic drug developers. BeiGene's Zanubrutinib has already paved the way forward, entering the US market in 2019, and generating RMB 2.52 billion (USD$380 million) in revenues in the first half of 2023[11]. More domestic developers have successfully out-licensed their pipeline to multinational peers in recent years[12], and though there are recent setbacks industry experts are optimistic about the prospect of domestic developers turning to oversees markets as their primary profit drivers.

Conclusions

Looking ahead five years China's biopharmaceutical landscape is likely to have undergone significant transformations driven by its ongoing commitment

to innovation and strategic adaptations. The industry, having evolved from a low-cost biomanufacturer to a research and development powerhouse, will have successfully carved out a much larger niche for itself in the global market. Regulatory reforms, which have already shaped the industry's trajectory, will continue to influence its direction, prompting domestic developers to pursue mergers, acquisitions, and differentiation strategies to overcome challenges of overcrowding within specific drug classes. This regulatory drive will culminate in a more streamlined and efficient drug development pipeline, marked by a reduced but highly specialized pool of biopharma companies with focused expertise.

As China's biopharma players mature and further deepen their research capabilities, they will increasingly set their sights on international markets, particularly the lucrative opportunities presented by the United States initially but with Europe's market an increasing target. One prediction we can make then, is that it is highly likely that we will see China's growing innovation industry attempt to buy or build local resources to further their ambitions in Western markets.

Learning from the success stories of pioneers like BeiGene, Chinese companies will continue to see increasing numbers of regulatory approvals in international arenas, leveraging larger patient populations and premium pricing potential to drive greater profits. Geopolitical considerations and factors will of course therefore need to be a much greater part of China's biopharma strategies. Therefore, brand and comms and advocacy expertise will likely be needed to achieve bigger markets breakthroughs and acceptance.

Another approach will be to explore collaborations and licensing agreements with multinational corporations, and this will play a pivotal role in many companies' expansions for the remainder of this decade.

Appendix

Table 1 Out licensing or Co-development Deals by Domestic Pharma Developers in H12023[10]

Domestic Developer	Product	Stage	Overseas Partner	Deal Size
Domestic Developer	Product	Stage	Overseas Partner	Deal Size
Impact Therapeutics	IMP1734/PARP inhibitor	IND	Eikon Therapeutics	na
XtaiPi	AI small molecule drug discovery platform	na	Eli Lilly	Upfront plus milestone totaling USD 250 million
Nona Biosciences	Fully humanized mouse platform	na	ModeX Therapeutics	na
Lanova Medicines	LM-305 (GPRC5D-ADC)	IND	AstraZeneca	Upfront payment USD 55 million, milestone payment USD 545 million, and sales commission
Zion Pharma	ZN-A-1041 (HER2 inhibitor)	ph1	Roche	Upfront payment USD 70 million, milestone payment USD 710 million, plus sales commission
Bliss Biopharma	BB-1701 (HER2-ADC)	ph1/II	Eisai	Upfront payment unknown, milestone payment US 2 billion, plus sales revenue
CBMG	C-CAR039, C-CAR066	ph1b	Janssen	Upfront payment USD 245 million, milestone plus sales commission
Gene Quantum	GQ1010 (TROP2-ADC)	preclinical	Pyramid Biosciences	Upfront payment USD 20 million, milestone payment USD 1 billion plus sales commission
Duality Biologics	DB-1303 (HER2-ADC), DB-1311	ph2	BioNTech	Upfront payment USD 170 million, milestone payment USD 1.5 billion, plus sales commission

Domestic Developer	Product	Stage	Overseas Partner	Deal Size
HighlightII Pharma	TLL-041 (TYK2/JAK1 inhibitor)	preclinical	Biohaven	Upfront payment USD 20 million, milestone USD 0.95 billion, plus sales commission
Biocytogen	RenLite@ platform	na	Janssen	na
Anji Pharmaceutical	AJ201	ph1b/2a	Avenue Therapeutics	Upfront payment USD 3 million plus equity, milestone payment USD 250 million
Keymed Bioscience	CMG901 (CLDN18.2-ADC)	ph1	AstraZeneca	Upfront payment USD 63 million, milestone payment USD 1.1 billion plus sales commission
Harbour Biomed	HBM7008 (B7H4x4-1BB bi-specific mAb)	ph1	Cullinan Oncology	Upfront payment USD 25 million, milestone payment USD 0.6 billion plus sales commission
Hengrui Pharma	SHR2554 (EZH2 inhibitor)	ph1	Treeline Biosciences	Upfront payment USD 11 million, development milestone payment USD 45 million, sales milestone payment USD 650 million plus sales commission.
Shijiazhuang Pharma	SYS6002 (Nectin4-ADC)	ph1	Corbus Pharmaceuticals	Upfront payment USD 7.5 million, development milestone payment USD 130 million, sales milestone payment USD 550 million plus sales commission.
Hutchison Pharma	Fruquintinib	launched	Takeda	Upfront payment USD 400 million, milestone payment USD 0.73 billion plus sales commission
Mabwell	9MW3011 (TMPRSS6 mAb)	ph1	Disc Medicine	Upfront payment USD 10 million, milestone payment USD 0.4 billion plus sales commission

Additional Questions and Answers

Looking ahead to 2028, how many international licensing deals do you think we might see (and could in licensing and out licensing swap positions – i.e. out licensing is growing very quickly while in licensing fell in 2022. As an example, could we see the current rate of increase maintained and 2028 we might have say circa 200 out license deals and maybe still around 100 in license?)

"I think both in-licensing and out licensing will grow, but out-licensing might grow faster. However, the current rate of increase may not be sustainable if we see a recession in the sector within China."

In 2030 do you predict that the majority of IND/BLAs files will be for truly innovation biologics (i.e., with novel modes of action)…. Or by when might this happen looking at current trends? What percentage of these do you think will be primarily targeting the USA/EU market verses domestic? Are there any other markets that China base companies might target for increased profitability?

"I think in 2030 the majority of IND/BLA files will not be truly innovation biologics, as China lags behind in MOA research. It is hard to predict when China will be generating many first-in-class biologics, because it depends on many factors, including geopolitical issues (at current stage China's innovation in biopharma sector relies on returnee scientists). Many domestic developers want to explore US/EU markets, but to what extent they can be successful we need to wait and see. Chinese developers are also targeting south asian and Latin American markets."

How do you see geopolitical concerns (particularly in the USA) affecting prospects for China's biopharma industry over the next 12-18 months. What strategies do they need to adopt?

"I think geopolitical concerns have not affected China's biopharma industry to a significant degree, and I do not expect it to have a significant impact in the next 12-18 months. However, if sino-US relationship does not improve, there might be less scientists interested in going back to China to work in China's biopharma industry."

Could Chinese companies seek to use greater branding, PR, public affairs services etc., to try and temper geopolitical concerns in western markets – i.e., might events like CPHI become more integral to these internationalisation efforts.

"I think Chinese companies would be interested in CPHI events; but most domestic developers are relatively small and they would naturally have a 'wait and see' attitude."

Is a logical next step for Chinese companies to invest in overseas manufacturing facilities – will this be CDMOs, innovators and where might they be looking for targets – will they be looking this year or longer term?

"I think it is a logical next step, but they will be looking at a longer term, i.e., only when they get BLAs from FDA."

Biotech capital and access to VC funding is widely believed to be down globally this year as caution have come into the market/. How do you see the funding environment in China for the next 12-18 months (is the country suffering a slowdown and/ or is it better able to withstand this than biotechs in Europe or the USA).

"I think China is suffering a slowdown, particularly after the recent crackdown on bribes/kick-backs in the pharma sector."

Do you think interest in using China's large R&D workforce to drive early stage for innovation has cooled from big pharma?

"I think if you think the interest only in having R&D centers in China, then it has already cooled down. Multiple MNC pharma have closed their R&D centers in China. But they are leveraging China's R&D workforce via other routes, such as co-development or licensing deals."

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2024 will see leadership redefined in the drive for sustainable bioprocessing

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Sustainability: a term that resonates in almost every industry, representing the future we hope to build. This concept, while straightforward, embodies a holistic approach to long-term viability, ensuring that actions today don't compromise the prosperity of the future. Such is the ethos presented by the World Commission on Environment and Development (WCED) in 1980[1].

For the biopharmaceutical sector, the path to sustainability has been convoluted. Strict regulations, an uncompromising demand for safety, and immense market pressures meant that product quality often overshadowed sustainable practices. However, a paradigm shift is currently in motion. A review spanning the last 14 years shows a significant increase in the industry's commitment to sustainability, waste management, and stewardship[2].

Sustainability and process efficiency are interconnected. For many in the bioprocess industry, this should involve:

- "Reduce" process steps as this also – by definition – reduces waste and is more than an eco-friendly gesture; it's a strategic business decision that can yield both environmental and financial dividends.
- "Reuse" whatever we can, as this will have a multiplier effect compared to recycling. However, the challenge in bioprocessing is that reusing single-use equipment can have severe negative impacts.
- "Recycle" as a last contributor to sustainability, recycling allows the last bit of value to be recovered from a system.

Although recycling is often considered by some to be synonymous with sustainability, in this industry recycling's contributions are often considered lower in the long-term picture. Despite this, we can use the segment's interest in recycling as an indicator of interest in broader sustainability initiatives.

The challenges associated with single-use systems in the biopharmaceutical industry are brought into stark relief when comparing industry opinions on what constitutes 'proper disposal' verses the actual practices in facilities. The glaring disparity between the "should-be" and "is" scenarios underscores a profound cognitive dissonance within the sector. A telling instance of this is the overwhelming sentiment favoring the recycling of single-use devices by sending them back to manufacturers; nearly half of the respondents (48.1%) believe this should be the norm, yet a meager 4.9% of facilities implement such practices. This vast gap echoes across other preferred methods like third-party recycling and incineration for power generation.

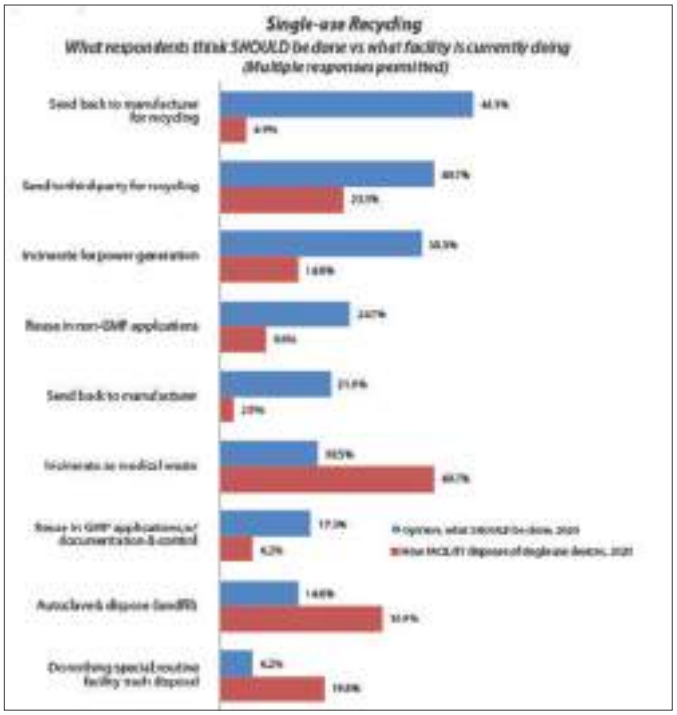

Fig 1: Single-use Recycling; Respondents' Desires for Disposal vs Actual Disposal Process (2020 Data)

Source: 20th Annual Report of Biopharmaceutical Manufacturing and Production. April 2023, BioPlan Associates, Inc. www.bioplanassociates.com/20th

Furthermore, while the industry shows a notable inclination toward eco-friendly and sustainable solutions, the existing infrastructure and operations contradict these aspirations. The data reveals a concerning reliance on less sustainable methods: for instance, a staggering 40.7% of facilities resort to incineration as medical waste, despite only 18.5% of respondents seeing this as an ideal practice. Also troubling is the fact that almost one-third of facilities have no choice but to use landfill disposal after autoclaving, with only 14.8% believing this should be the approach.

This divergence between industry sentiment and on-ground actions highlights a pressing need: While awareness of sustainable disposal methods is present, systemic changes and infrastructure investments are imperative to bridge the existing chasm and align actual practices with the collective vision for a greener biopharmaceutical future.

A silver lining has emerged, though. An increasing number of vendors have warmed up to recycling programs. This is more than a mere trend; it's a testament to the evolving value system of the biopharma supply chain.

Leadership Needed

Leadership is, without doubt, the linchpin of sustainability in this industry. The FDA and EMA have of course set the standard for product quality and, in some cases, this makes sustainability initiatives difficult to implement. Managing that balance creates challenges for leaders. At a recent CDMO summit in Copenhagen, June 2023, BioPlan surveyed 44 global CMC consultants regarding the challenges they saw leaders facing when advocating for sustainable initiatives. The single most daunting challenge is "Demonstrating an ROI," followed by the related, "Convincing board to invest in sustainability initiatives."

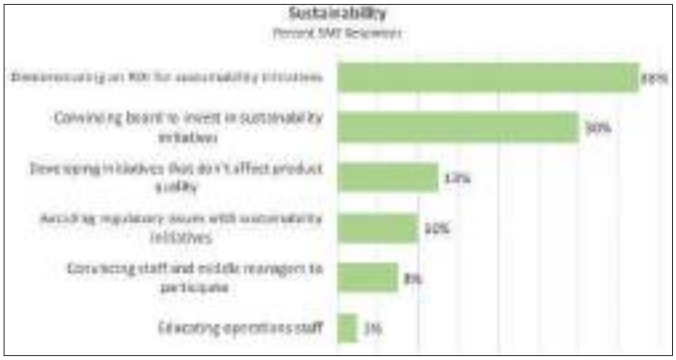

Fig 2: #1 Challenge Bioprocessing Leaders Face when Advocating for Sustainability

Source: BioPlan's survey of 44 biopharma CMC consultants at a CDMO Summit, Copenhagen DK, June 2023.

Sustainability Requires the Ability to Measure Progress

The Leadership Thesis to be considered is that "Sustainability" requires positive outcomes and the ability to measure success. Real sustainability

is not just about incremental improvements, e.g., implementing a recycling program, or PR around planting trees or installing solar panels. It is about changing mindsets and that requires organizational change.

To accomplish this, the data suggest that "Sustainability" will occur in biopharma segments when the focus ***includes***:

- Revenue-positive outcomes (profitable)
- *And* the ability to measure initiatives' results (revenue, productivity or efficiency)

Essentially, successful sustainability initiatives will require that leaders demonstrate intent to:

- Change organizational mindsets – in a biopharma facility, that requires leadership
- Demonstrate revenue positive outcomes can significantly improve an initiative's chances for successful implementation
- Measure outcomes of initiatives to ensure enduring change, not just for an annual report, or PR 'greenwashing'

True sustainability hinges on the presence and commitment of visionary leaders. It is these leaders who understand the need to prioritize sustainability initiatives that not only drive positive environmental but also generate favorable financial returns. Their leadership establishes well-defined metrics that show tangible impact of sustainability efforts, ensuring they're more than just superficial gestures.

Leaders play a pivotal role in cultivating a pervasive culture of sustainability within the organization, making it an intrinsic part of its ethos. The real litmus test? Delving into the depths of a leader's commitment to sustainability and gauging their long-term vision for a more sustainable future.

A long-term model of sustainability in biopharma can be distilled into two key elements:

Profitable outcomes derived from sustainable initiatives. The ability to quantify the results of these initiatives can be measured through improved efficiencies, which can lead to profitability.

Operational success is often a function of middle management's ability to act within the bounds of regulations. Empowering these individuals with the right tools and mindset to adopt practices like reusing, repurposing, and recycling can have ripple effects throughout the organization, setting the stage for a brighter, greener future.

The undercurrent in modern sustainability is economic viability. When operations are fine-tuned to minimize waste, there's an inherent reduction in costs. Such economic incentives are now central to sustainability narratives, blending fiscal responsibility with ecological stewardship.

The mandate for leaders is clear and challenging. It's not just about oversight but active transformation. This entails securing the commitment of the board, developing a compelling sustainability narrative, and converting overarching strategies into day-to-day operational tactics. The aspiration is to seamlessly integrate economic performance indicators with green initiatives—a balancing act that demands unwavering focus and innovation.

In the final analysis, biopharmaceutical manufacturing requires leaders armed with vision and pragmatism. By developing a metrics-driven, economic, and environmental strategy that maintains the segment's quality imperatives, the industry can ensure a future that's both prosperous and green.

Additional Questions and Answers

Looking ahead to when do you foresee that sustainability desires might = sustainability real world practices. Are we just turning a slow-moving ship, and by when (year) might we start to see real traction on best practices industry wide?.... could 2024 be the year we see bigger shifts underway or does your data suggest a longer more drawn-out period of change? (could the year ahead see a merging of 'metrics driven process improvements' and sustainability goals – perhaps these can encouraged via three pressure points: from financial, manufacturing and sustainability leaders)?

"Sustainability desires are changing slowly, consistent with the general public's interest in doing better. However, making actual impactful changes in bioprocessing that don't impact product safety or quality will require doing things differently. There are some things that can be done that don't involve changing the process, but the real impacts will come from streamlining new processes, reducing usage of materials and energy, etc. This will require innovative thinking from suppliers, as well as from process developers. We have seen that strides can be made rapidly, base on what we've seen during COVID. But can a similar level of focus be brought to bear on

reduction in process inputs?"

Historically, Europe has been ahead of the USA in environmental concerns, where do you think greener bio manufacturing is going to advance fastest in the next 18-months (though until 2025) and what might change at these pioneers.

Is this the year we see a switch from a focus on recycling to the bigger real term gains we can see in reduction of materials used.

"18 months is a short timeframe, bioprocessing-wise. Change will likely come when the regulators EMA and FDA indicate a greater interest in green strategies. However, this is unlikely to occur if it impacts drug safety or quality in any way. That will be a high hurdle."

We have seen EU implement changes for bioprocess components like PFAS that may actually result in unintended changes. For example, even where such plastics-containing chemicals have been shown to have no impact on human health, an all-out ban could shift bioproduction from EU to elsewhere. Further, if re-importing such life-saving biologics becomes a problem, then there may be drug shortages. The resultant increase in mortality may exceed the potential impact of exposure to certain chemicals.

For biologics could titre and process improvements (as deliver cost and environmental improvements) be the low hanging fruit that help bring in faster improvements. Respondents to the Bioplan Survey all cite proof as ROI and access to board investment as the biggest challenges to implementing improvements.

"Definitely—titer improvements have a direct impact. Doubling titer from 2 to 4 grams grams per liter can cut upstream production consumption in half. While it doesn't impact downstream purification much, new chromatography technologies that reduce WFI and buffer usage could be the next advance. Clearly, in addition to the sustainability impact, such a process improvement focus would drive reduced costs, and increased profitability."

Looking ahead to 2025 or beyond you think there is scope for a new type of single use materials or reactors – what might be possible here. Alternatively, could sustainability concerns move certain processes back toward batch or what might be ahead here. Can you foresee any solutions to this intractable problem in the next 18-months?

"Yes--In 2 years, we may see many different SUS devices, bioreactors, etc. However, simply getting such devices into a commercial platform, regardless how effective, efficient, or green, could then take 5 years or more. Further, because it would only be applied to new production lines (existing lines are hard to change for regulatory reason), growth for such innovations would be dependent on the new biologics pipeline."

Do we need greater regulatory flexibility around process parameters or changes after approval to encourage continual innovation?

"That would certainly support implementation of innovative technologies. But as has been seen, very few drug innovators want to be the first in line with the FDA to propose introduction of a new, untested device on their new biologic. Investors and innovators invariably take the path of least regulatory resistance. So an innovative green solution would likely need to be proven to regulators to be as safe, if not safer than existing products. And that takes years."

Your report predicts some of the fastest changes are likely to be driven from the top down – by CEOs and leaders that embed a culture of continual improvement. Do you think we are only at the beginning of how might deliver improvements using 'reusing, repurposing, and recycling'?

"CEOs and boards establish the corporate culture. If leadership rewards making no waves and taking the safest course, then little will change down to the bioprocess level. But if leadership clearly rewards innovation that supports greener bioprocessing that targets reducing consumption (which at the same time shows ROI), then operational changes can at least be proposed without fear of running afoul of regulatory issues."

What sustainability outcomes do you foresee for bio manufacturing in 2024/2025 and 2030

"Frankly, not much progress will be made in the next 24 months. Perhaps in 5 years internal programs will be in place to facilitate consumables and energy reduction as well as address overall process improvements that impact sustainability. But this will take change at the leadership level. Otherwise mid-level managers will remain focused on their primary roles, including product safety and quality production."

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Part 4

The Outlook from Spain

CPHI Barcelona 2023

Spain and Navigating the Biotech Landscape in a Post-Pandemic World

Raúl Martín Ruiz
Partner at Ysios Capital

We might have almost forgotten, but the COVID-19 pandemic highlighted society's susceptibility to global health crises, triggering an unprecedented focus on healthcare investments. As the dust settles, biotechnology has significantly improved its standing globally contributing enormously to the many vaccines, therapies and diagnostic tools used to overcome the pandemic. The industry now stands out as a key strategic sector from both a social and economic point of view, having proven its performance and potential during the pandemic.

If we look deeper at the data, we see 2021 was also a landmark for biotech IPOs, and the performance and perspectives of biotechnology during and immediately after the pandemic had a positive impact on the whole ecosystem. However, investment in the sector considerably slowed down in subsequent years due to the convergence of high inflation and elevated interest rates. This trend was common to other capital-intensive industries and looking ahead to the remaining of 2023 the situation is still uncertain. Inflationary pressures may also release somewhat in 2024, but the present challenges are also not felt evenly by all stakeholders in the biotech value chain.

The number of Initial Public Offerings (IPOs) remains limited – valuations are down – and the prospects for fundraising and achieving liquidity in the public markets will be uncertain until those markets stabilize. Raising inflation rates and macroeconomic uncertainties have decreased the global investment activity in high-risk sectors.

Yet, despite this, licensing and merger and acquisition (M&A) activity between pharmaceutical and biotech companies has not suffered that much in terms of overall numbers – which many outside the sector may find surprising.

However, high-growth sectors like biotechnology have seen a decline in valuations. This downward trend has inevitably trickled-down to private funding rounds, prompting venture capital managers to focus on capital preservation and management of portfolio companies to ensure their viability in an uncertain funding environment.

One of the foremost challenges we currently face are escalating costs, which subsequently affects margins and the constrained availability of capital for new financing rounds. This represents a substantial hurdle for companies striving to reach milestones initially set within a significantly different macroeconomic context. A pivotal lesson learned from our adaptation to these economic shifts underscores the necessity for a stringent corporate discipline. Companies have responded by prioritizing development programs, among other capital-conservative strategies, to align with the current macroeconomic landscape. To understand this, it is crucial to remember that the nature of venture capital investments entails long investment cycles, often spanning a decade or more, with firm commitments for this extended duration.

On the positive side, recent data from BioCentury reveals that from July 2022 to June 2023, the industry witnessed 25 M&A deals and 154 collaboration and licensing agreements between biotech companies and major pharmaceutical entities. Despite representing a modest dip from prior periods, these figures are still more favorable than other sources of funding or liquidity for biotech's and their investors.

A further positive is in the continual rise share of GDP from Healthcare companies. The industry is a cornerstone of the economy, representing 9.7% and 9.6% of GDP in OECD countries during 2020 and 2021, respectively. This surge, in part influenced by the pandemic, surpassed the previous benchmark of 8.7%-8.8% range seen from 2015 to 2019. Moreover, the horizon for prescription drug sales also looks optimistic in both the medium and long term. Data from Evaluate Pharma suggests that global prescription drug sales could experience an annual growth rate of 6.4% from 2021 to 2026, providing a significant boost to the biotech sector. Several factors support this anticipated growth:

- **Addressing Unmet Needs:** Numerous diseases still lack adequate treatments, presenting significant opportunities for innovation in healthcare.
- **Advancements in Science:** Progress in basic science, the discovery of new therapeutic targets, and innovative treatment modalities expected to help to address those unmet needs.
- **Patent Concerns:** Pharmaceutical companies facing patent expirations, have exiguous pipelines and seek external innovation.
- **IPO Market Prospects:** Anticipated reopening of IPO markets and a robust pipeline of companies poised for public offerings when interest rates go down.

Ysios Capital, a venture capital firm based in Spain, specializes in investing in innovative life sciences companies focused on therapeutic products for high-unmet medical needs on a global scale. With over 15 years of active involvement, we have witnessed the sustained growth of the life sciences sector in Spain and are therefore, as a key part of the value chain, we are well placed to envisage what might be ahead for the industry in the next few years.

When we began our operations, the situation was quite different compared to the current one. Despite the presence of leading research institutes, hospitals and pharmaceutical companies with internal R&D activities, there was a limited number of entrepreneurs and biotech companies. Since then, we have seen an exponential growth and today the Spanish biotechnology sector has all the necessary elements to be an essential economic engine of the country.

The Spanish Bioindustry Association (AseBio) report, referred to 2021, provides a clear snapshot:

- **Number of companies:** 4.362 companies carry out biotechnological activities, of which 898 are biotech.
- **Talent:** Biotech companies have the highest number of researchers, and 60% of the total employees are women.
- **Investment:** The biotech sector attracted 142 million euros, with an increased participation of international investors.
- **R&D expenditure:** The biotechnological sector invested 1.038 billion euros
- **Impact:** Biotech companies contribute 1,1% to the GDP and provide 118.000 jobs.

By way of an illustrative example, 24 international specialized investors have co-invested with us providing 4 times the capital invested by Ysios. Furthermore, companies like Ona Therapeutics, SpliceBio, Minoryx and Sanifit have raised financing rounds between € 30M and € 72M in the period 2019 – 2023, confirming the interest of international investors in Spanish biotech companies. Also, several companies have completed the cycle and were acquired by larger players or out-licensed

programs at an international level after having raised funds from Spanish and international investors.

- STAT Diagnostica: acquired by Qiagen
- Cellerix: merged with TiGenix and eventually acquired by Takeda
- Sanifit: acquired by Vifor Pharma
- Minoryx: European rights licensed to Neuraxpharm

Venture capital and startups play a pivotal role in fostering innovation in high-value industries. Spain confronts the challenging task of maintaining sector stability during less favorable investment periods, ensuring the consolidation of significant progress achieved over the past decade.

Looking forward, Spain is expected to follow the trends seen in other developed countries, with a venture capital sector that, while potentially decelerating compared to previous years, remains solid. Given the capital-intensive nature of the life sciences sector, maintaining investment momentum is critical to consolidate the sector's advances and making it a relevant contributor to the economy of the country.

Additional Question and Answers

Predictions for access to VC funding in 2024. Do we see early-stage biotech waiting out the year waiting for capital from VCs, while perhaps private equity funding may not be as constrained, will the number of mega mergers and acquisitions decrease (i.e. between very large pharma companies)?

"It is difficult to predict if the life sciences VC sector will rebound. Whereas there is a significant number of firms that raised new funds before the high inflation and elevated interest rates arrived -and even in that challenging context- it is true that many other firms are struggling with the fundraising. Should the inflation rate and interest rate come under control, private capital should be mobilized into VC funds, and a rebound might happen as early as 2024."

What sort of demand do to anticipate from 'international specialized investors' for co-investments with partners like Ysios Capital for Spanish biotech companies? What advice would you give to biotechs looking to access funding in 2024?

"As a background, when we started operations there were no Spanish biotech companies funded by international investors. We made our first investments in the country in parallel to the first international ones, and we realized that it was difficult to bring international VCs to Spanish deals in the first rounds of financing. With one single exception, all the first financing rounds of our Spanish portfolio companies from our first fund were co-funded by Spanish VCs. Once some international VCs worked with us on international deals they decided to invest in second rounds of Spanish companies. The situation changed with the second and third funds, where we managed to incorporate international VCs in the first investment rounds. Moreover, these days we see some international VCs look at Spanish deals without the involvement of Spanish investors in the syndicate. This is clearly a sign of maturity of the sector, that is now much more international. Several international investors are now familiarized with the sector in the country, whereas others are not and prefer to invest with a local VC. This is not an issue particular to Spain and we have seen it in other countries as well. What the VCs want to see is the same for Spanish deals or in other countries: good science, an interesting project, a committed team willing to incorporate key positions if needed, a solid development plan and a clear exit strategy. The advice that we typically give is that they should start pitching their project early on to those VCs that are open to it. They will receive invaluable feedback for free."

The CPHI report pointed to Barcelona as the second top ranked biotech investment destination in Europe (behind just the London region) – what is your perspective on the region's growth in 2024 and access to capital (e.g. is it more constrained in Catalonia despite a very large bank of biotechs in the region. Or access still good etc etc). Do you think the region will out- or under- perform the wider global biotech industry? (our own data suggests we think Spain more generally should outperform the wider pharma sector – at least in Europe)?

"Spain has escalated in the European biotech map in the last years, with Barcelona clearly leading the game. I am positively surprised with Barcelona ranking second behind London, because I thought that other cities like Amsterdam, Zurich, Basel or Copenhagen were more attractive and strong. My perspectives for the mid-term are positive based on the rate of creation of new companies, the increasing entrepreneurial spirit among the scientists and international exposure of the companies. I tend to agree with your outperformance expectations of Spain compared to the close peers in general, but I don't think it will be the case for biotech start-ups in the short-term.

In terms of the conditions needed to make this happen, well we still need incentives to foster innovation and a clear political leadership through to secure regulations, as well as measures to support science and innovation. Together this will provide Spain with an R&D system in line with its economic potential."

Do you see any underlaying trends in the Spanish or Catalan region – i.e. are there any specific products classes or technology areas we think the region will benefit significantly from in 2024 or might drive its growth (oligos, cell&gene, diagnostics, oncology, high potents, traditional small. molecules etc etc)?

"The historical strength of the country is around small molecules. However, a number of companies have been created around more "sophisticated" modalities including antibodies, cell therapy for regenerative medicine and oncology, gene therapy, RNA therapeutics, oncolytic virus. However, there are also now some initiatives to foster advanced therapies, but they are still too incipient to know if they will consolidate and become a driving force for the sector."

Spain has continued to improve its reputation for 'pharmaceutical manufacturing' in the last year's (CPHI Survey data), do you think CDMO growth in Spain will help deliver wider biotech growth and innovation?

"Indeed, we are aware of this and have learned that many European biotechs are working with Spanish CDMOs. Also, some of them have been acquired (Idifarma and Viralgen, to list a couple of examples). In general, I would say that Spanish CDMOs provide a high-quality service at a reasonable cost and I believe that it is a sector that will continue growing."

Predictions for global M&A activity in 2024?

"According to a recent report from Deloitte, the M&A perspectives for the second half of 2023 in the life sciences sector are optimistic and we agree with that. Pharma has been and is expected to lead the show, and this trend is expected to continue in 2024. There is a significant number of potential acquirers with dry powder ready to be invested in acquisitions, as well a significant number of targets."

I'm interested Ysios Capital's strategy moving forward. Given the current challenging conditions, are you considering a "wait and watch" approach for the first half of 2024 before deploying capital?

"We are actively investing with our current fund and we plan to continue deploying money in new opportunities that have a fit with our portfolio."

Part 5

The Convergence of Nutraceuticals and Personal Care Ahead

CPHI Barcelona 2023

Nutraceuticals, personal care and pharma converging over the next 5-years as the biology of health & wellness science accelerates.

Sara Lesina
General Manager, Sirio Europe

A few years ago, we authored a predictive CPHI trend analysis, in which we explored the growth of large pharmaceutical brands increasingly looking to new consumers in the nutraceuticals space. This year, perhaps the first truly post Covid period, what we see is there has been an acceleration of wellness globally and we discuss what that means for consumers – with a more considered and longer-term approach now taken.

The move to wellness may well have been built upon trends that were already in the market, or it might have been a logical response to the fact that general health was often a factor in who became sick with Covid. However, coupled with the extra time much of the world spent at home, a focus on wellbeing and general fitness is an idea that has not only gained traction but continued as a lasting-legacy. Fast forward to today and what we are seeing is very interesting and categories – like personal care, OTC health, wellbeing, and natural health – are expanding and continuing to merge with each other. So the boundaries, range and delivery forms of products is growing extremely quickly. Yet not only are consumer trends changing, what we are also seeing is an increased focus on advancements in delivery formats across nutraceuticals, with an improved consumer experience the panacea we are searching for. For example, bioavailability enhancement tools – like liposomal technologies – and increased use of enzymes to improve productivity, as well as continual dosage innovation for probiotics.

If we start with our predictions ahead for personal care over the next 2-3 years. Here, we are seeing many brands now exploring adding complementary gummy products to existing topical ranges and this could well be a growth segment in the next 18-36 months. Collagen is a classic example of an ingredient that has traditionally been applied topically as cream or powder, but we see many personal care companies now launching nutraceutical products with collagen combinations via a gastrointestinal route. This is a really interesting area of biology around what are the benefits of going this route verses via a topical application that has to overcome the biological barrier of the skin. In the next few years this could be a huge trend where we see increasingly symbiotic or synergistic

products come in to the market. The interesting aspect is that we are also seeing a convergence of different consumer types and therefore how brands are looking to market products. To give just one example, we are seeing marketers come into the industry from personal care backgrounds to explore how we can market 'beauty from within' gummies to consumers – and we are even starting to see this trend at the point of sale with complementary gummies sold alongside creams or powders as packaged collagen combinations. With innovations in the gummy format, this trend is here to stay and will blur the lines even further: an indulgent moment, offering guilt-free pleasure literally sitting at the sweet spot of supplement, food and personal care. The 'winners' will be those who understand all three worlds and can create the formulations that will resonate the most with consumers while leveraging the latest ingredient science.

One good way to think about this trend is in selling both the short-term and long-term benefits – with topical products applied for only immediate gains, but nutraceuticals can be used to deliver long term benefits as well from the inside out. It's still very much a 'white space' around the possibilities both in terms of complementary combinations and marketing. The other interesting aspect is the complementary demographics of consumers – although traditionally sold separately – and we do believe that consumers buying beauty and personal care products are likely also interested in general wellness and in taking supplements. To date as an industry, we have not really explored these trends and we can expect an explosion of marketing ahead. The holistic approach to beauty and nutrition together is right on trend with these type of consumers who are growing in numbers.

We haven't seen a significant step yet where current gummy brands are transitioning into personal care. Initially, it's more likely that premium personal care brands, with higher profit margins, will start offering add-on products in their range. One emerging idea is that we might also see special vegan and health brands target 'inside and outside care' through more wellness, health, and organic focussed supermarkets alongside 'natural cosmetics' – again for consumers that, on average, have a higher disposable income.

In terms of specific beauty ingredients, on the more commodity side Vitamin C with collagen, and collagen combinations (i.e. multiple types of collagen in one product) are gaining popularity, but also probiotics and prebiotics are going to be the 'hot' areas. In fact, probiotics are currently a massive area of research, not just in nutraceuticals but across whole segments of pharma and healthcare, as it's such a virgin area scientifically – and the effects probiotics can have on the skin and the microbiome in terms of skin and hair1. Not only from how different strains can support the microbiome and have effects both inside and out. But also, in terms of how to make these bioavailable and delivered in a live state through to the target area of benefit. With mode of action within the body around the microbiome still at an early stage of understanding, we can expect further breakthroughs, personalisation of strains, and tailored delivery formats. One other area where we could see innovation is in 'solid probiotic drinks,' which is a new method for establishing a healthy microbiome. We are currently exploring this as an improved delivery form to populate the gut with live probiotic strains.

However, going back to collagen, the suppliers of this ingredient have only recently started considering the chemistries that apply with different delivery formats. So we also expect technical differences in how these active ingredients are now supplied to manufacturers and we might see them launched with slightly different chemistries. The other area we expect to see some development is in the male side of the market perhaps extending out of the lifestyle brands we see in men's grooming, gym-based health brands or perhaps male moisturising segment.

The range of products in the beauty category has also expanded to include not only hair, nail, and skin gummies but also more specialized products like hyaluronic acid gummies and injectable forms of moisturizing agents. This trend reflects a growing interest in personalized and targeted skincare solutions. People are increasingly looking for innovative ways to address specific skincare concerns and are willing to explore different delivery methods beyond traditional topical products. Hyaluronic acid is a popular ingredient known for its hydrating properties, and the availability of hyaluronic acid gummies suggests a convenient and tasty way to incorporate this ingredient into one's daily routine. However, we envisage this standard product' being elevated to something unique perhaps with the addition of herbals – that have centuries of use and chime with the 'back to roots' trend – for example, ingredients like turmeric, paprika, astaxanthin, aloe and zeaxanthin among others all of which an evolving scientific base[2].

Bioavailability is also going to be the consumer breakthrough word in the next 3-years, as the general public becomes more aware and

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7916842/#:~:text=Hence%2C%20dysbiosis%20in%20the%20skin,dandruff%2C%20and%20even%20skin%20cancer
2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10364564/

educated,[3] that taking a tablet does not always mean all of the ingredient is absorbed by the body in the way you intend. Alongside this, we will see the rise of technological applications – and this is a little chicken or egg – as part of the reason for the shift is that, as an industry, we have made tremendous progress in properly evaluating and improving bioavailability.

Lipid delivery, for example, has been used in pharmaceuticals for some time for poorly water-soluble drugs[4]. But what we now see is nutraceutical brands exploring how lipid technologies like liposomes[5] can help protect vital nutraceutical payloads via micronized encapsulation though the harsh environment of the gastrointestinal track and increase transmucosal (oral) uptake and absorption. For example, a liposome encapsulated Vitamin C – widely known as a poorly soluble substance – will help deliver greater bioavailability with lower dose in each gummy. We have currently introduced a patented technology into two production lines, but this is just one example of the direction of travel we see with more pharmaceutical dosage form science now translating through into nutraceutical applications. In fact, we expect all major nutraceutical companies and CDMOs to start evaluating product development along three scientific key metrics:

- **health benefits**: exploring a more rigorous approach to its safety, stability and bioavailability and targeted delivery
- **dietary patterns**: can we deliver actives in formulations that also made using more natural methods and materials
- And how can we continue to improve the **consumer experience** of our products – especially important given the high growth products like gummies

One greener production method we now see coming through is the increased use of enzymes and biocatalysts in the production of nutraceuticals and we expect this to be a major growth area perhaps in the medium term. It's still a nascent trend but consumers are starting to look for greener processes in the products they purchase. Similarly, greener ingredients or plant derived sources are also increasingly desired and we are seeing an acceleration of science into how we improve the functionality and stability of functional ingredients from plants.

Overall, the nutraceutical industry is on the verge of a transformative journey as it converges with personal care [as well as increased use of pharmaceutical methods], a transition substantiated by the growing emphasis on holistic well-being in today's consumer landscape. A survey conducted by Grand View Research, Inc. reveals that the global nutricosmetics market is expected to witness significant CAGR of 21% through to 2030[6], underscoring the potential of this evolving trend. In an era marked by heightened health awareness, individuals are adopting a deliberate and comprehensive approach to their overall health. This evolution is driving the expansion of various product categories, including personal care, well-being, and natural health, effectively erasing traditional boundaries. What's most significant about this is, that large multinational companies are looking increasingly at adjacent areas of their consumers' behavior and purchasing life. Moving forward, brands will explore how they can develop deeper partnerships across multiple segments that were previously sold in isolation. The consequential impact of this is that they are likely to garner deeper and more personalized engagement with their consumers, leading to improved brand loyalty, frequency of purchase, and the lifespan of the relationship.

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