CPHI
Milan

ANNUAL INDUSTRY REPORT

2025 is expected to continue industry's pre-pandemic stellar trajectory

Key Themes: The rise of biologics, GLP-1s and advanced therapies, BIOSECURE and the much-awaited return of the funding

CPHI Milan 2024

CPHI Annual Industry Report & Survey

The eighth **CPHI Annual Survey** will explore the perspectives of over 280 pharma executives, evaluating the likely trends in 2025 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 12th 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 Milan 2024**

Produced by defacto

Table of

Contents

CPHI Pharma Survey and Industry Rankings 2024

BIOSECURE; bio innovation and processes; VC funding return; the pharma league tables and the quiet rise of Lombardy

Methodology

This is the eighth CPHI Annual Survey and explores the insights of nearly 280 industry executives from every region of the globe – survey completed in September 2024. 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 other survey questions – culminating in overall scores for each country. In addition, this year we have launched the European Manufacturing Hub index for both solid dose and biologics.

Respondent Breakdown: Europe 25%, Latin America 3.5%, North America 14%, India 25%, Africa 3%, Middle East 4%, Southeast Asia 7.5%, China 8%, Rest of the World 10%
Top Firms Involved: Pharma Company Innovator 49%, Biotech 5%, CROs & CDMOs 10%, Government Academia 3%, Distributors 9%, Ingredients Manufacturer 4% , Consultancy 9%, Wholesale 3%, Financial Institutions 1%, Other 7%

When we reviewed industry prospects and looked at the primary issues de jour at this time last year we saw four major uncertainty's affecting prospects, namely: funding, inflation, war and reshoring. The first question was when will funding return to biotech and how quickly this would transfer through to CDMOs. The answer to this first question appears to have been slower than expected and Brian Scanlan will give his full funding predictions latter in this report. The second issue of inflation last year's analysis correctly identified as 'falling back in 2024', yet at the time of writing, the nadir of a slowing US economy has wobbled stock markets. The war in Ukraine, while not resolved, and certainly still having the potential for global disruption, has become a known uncertain, and as such, has dissipated from pharma media narratives. Which leaves finally the elephant in the room that has unsettled drug discovery and development paradigm – reshoring, near shoring and stability in supply chains – and in particular the continuing tensions between the United States and China. Few will have failed to notice the BIOSECURE Act and along with a change of President in the White House – if not necessarily party – what is the direction of travel for US-Sino relations. The pharma industry is, of course, incredibly global and starting materials are primarily sourced from Asia markets – mainly China. As we will discuss later in this piece, the industry is ambivalent on what comes next, with even the most clairvoyant of analysts scrambling to anticipate how this debate will resolve, and what the short-, medium- and long-term implications are.

The positives however are also again accelerating, and we saw a continued glut of FDA approvals, with rates equivalent to the record levels seen pre-pandemic. In 2023, there were 55 drug approvals, which is just four shy of the all-time high reported in 2018, and significantly 28 (54%) were for Rare Disease indications and 17 for biologicals[1,23]. So far in 2024 the rate of innovation has remained strong, the FDA has approved a further 29[4] drugs including notable breakthroughs like Donanemab – a drug to treat the underlying biology of Alzheimer's – and Casgevy the first approval of CRISPR/Cas9 gene editing technology (which famously won its inventors the 2020 Nobel prize)[5,6,7]. The latter two potentially herald the emergence of new era of drugs. For Alzheimer's we have long sought for any effective treatment options that could address the underlying disease progression and so we it marks the begging of a new era in which we can begin preventing and potentially one day reverse decline. For Casgevy the effects are no less impressive as the beginning of the next 30-years of gene editing. Already new variations of CRISPR are being developed, such as base editing, which allows changes to be made to individual letters inside DNA, and prime editing – which replaces the CRISPR 1.0 'molecular scissors' with enzymes and genetic instructions to insert, delete or rewrite short segments of DNA[8].

GLP-1 (Ozempic, Wegovy, Trulicity, and Mounjaro) and PD-1 (e.g. Keytruda and Opdivo) drugs have also continued their meteoric rise and Globaldata predicts they will be worth a staggering $156bn in annual sales by just 2029 – with GLP-1s growing at nearly 20% (CAGR) and reaching $105 billion and PD1s returning figures of 5% and $51 billion. The question is therefore do contract services firms have the right mixture of capabilities and capacities for the developments to emerge in the pipeline over the next 2-3 years.

Pharma investments in the supply chain are typically reactionary and especially those in the contract services sector, which relies upon commercial contracts to fund investments, so the implications of large numbers of molecules in the development pipeline could potentially mean slowing timelines. Two of the largest five CDMOs – WuXi AppTec and Catalent – have obvious questions about the availability of resources moving forward, particularly in the medium term. WuXi has no issues regarding available capacity, however, the implications of some of its massive volume of customers attempting to move to other outsourcing resources will most certainly have an indirect impact on the wider market. While Catalent's acquisition by Novo Nordisk also creates some

1. https://pharmaboardroom.com/articles/2023-fda-drug-approvals-second-highest-count-in-30-years/
2. https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/2023-biological-license-application-approvals
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10856271/#:~:text=The%2055%20drugs%20approved%20this,so%2Dcalled%20small%20molecules%2C%20in
4. https://www.fda.gov/drugs/novel-drug-approvals-fda/novel-drug-approvals-2024
5. https://www.nature.com/articles/d41587-023-00016-6
6. https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapies-treat-patients-sickle-cell-disease
7. https://www.gov.uk/government/news/mhra-authorises-world-first-gene-therapy-that-aims-to-cure-sickle-cell-disease-and-transfusion-dependent-thalassemia
8. https://www.statnews.com/2023/11/16/crispr-vertex-sickle-cell-beta-thalassemia-casgevy-approval/

uncertainly as we await the outcome of the Federal Trade Commission's view on the potential takeover. Namely, whether it sees the ability of Novo to boost capacity at the potential expense of its rivals as fair. So the medium-term implications of this acquisition on the contract services space and likely supply side economics remain opaque[9].

Another new area of research for the Report in 2024 is to explore in detail the pharma manufacturing hubs across Europe in addition to the biotech centres added to our analysis last year. In particular with CPHI hosted in Milan – Lombardy being a major pharma hub – we rank the largest areas of production in Europe for best regions to undertake small molecule, device and/or biologicals manufacturing.

Additionally, the survey will deliver its usual global manufacturing rankings, while also exploring how many novel drugs the industry expects to be approved in 2025. As well as the ongoing implications of AI technologies on drug discovery/clinical trials and global efforts to reduce the costs of biologics production, notably through titre improvements and/or continuous manufacturing. The latter trend our report predicts will becomes increasingly intertwined with pharma's ongoing sustainability efforts, which increasingly include scope 3 emissions.

The other big trend from 2023 was the predicted revolutionary impact of Psychedelic drugs and, despite their strong efficacy potential, the last year has in fact been disappointing for its advocates. The potential we have seen and continue to see in trials has not yet been matched by a clear regulatory pathway with many companies failing to prove efficacy to the FDA. The two primary intractable issues remain 'how to blind studies effectively and show efficacy', but also, the added complexity of 'approving a drug/psychotherapy combination within existing rules'. Lykos Therapeutics failure in August – the FDA rejected its use of MDMA to treat post-traumatic stress disorder (PTSD) – is the indication's biggest setback to date but with other psychedelic innovators now hoping to learn the lessons with decisions pending on two further phase 3 trials for psilocybin use in combatting depressing[10,11].

Where does all of this leave the industry looking forward to 2025 and beyond?

This is perhaps the million, billion or even trillion-dollar question, the short answer is in a very good place to build from in 2025 through to 2030. Innovation has continued apace despite lagging VC funding, while the stock market has – despite a few wobbles remained impressively strong. So with both capital expected to be imminently deployed by Private Equity in 2025 for acquisitions and the almost certain surge in VC funding ahead (it cannot stay parked indefinitely) we are potentially on the brink of one of pharma's best ever years in 2025 with the medium term for both biotech and contract services firms looking incredibly robust. This report's long-term projection is therefore that both CRO and CDMOs will need to evolve more quickly than in the past to meet the next generation medicines now in early development, but also, will become more profitable and grow faster as a consequence.

The BIOSECURE Act

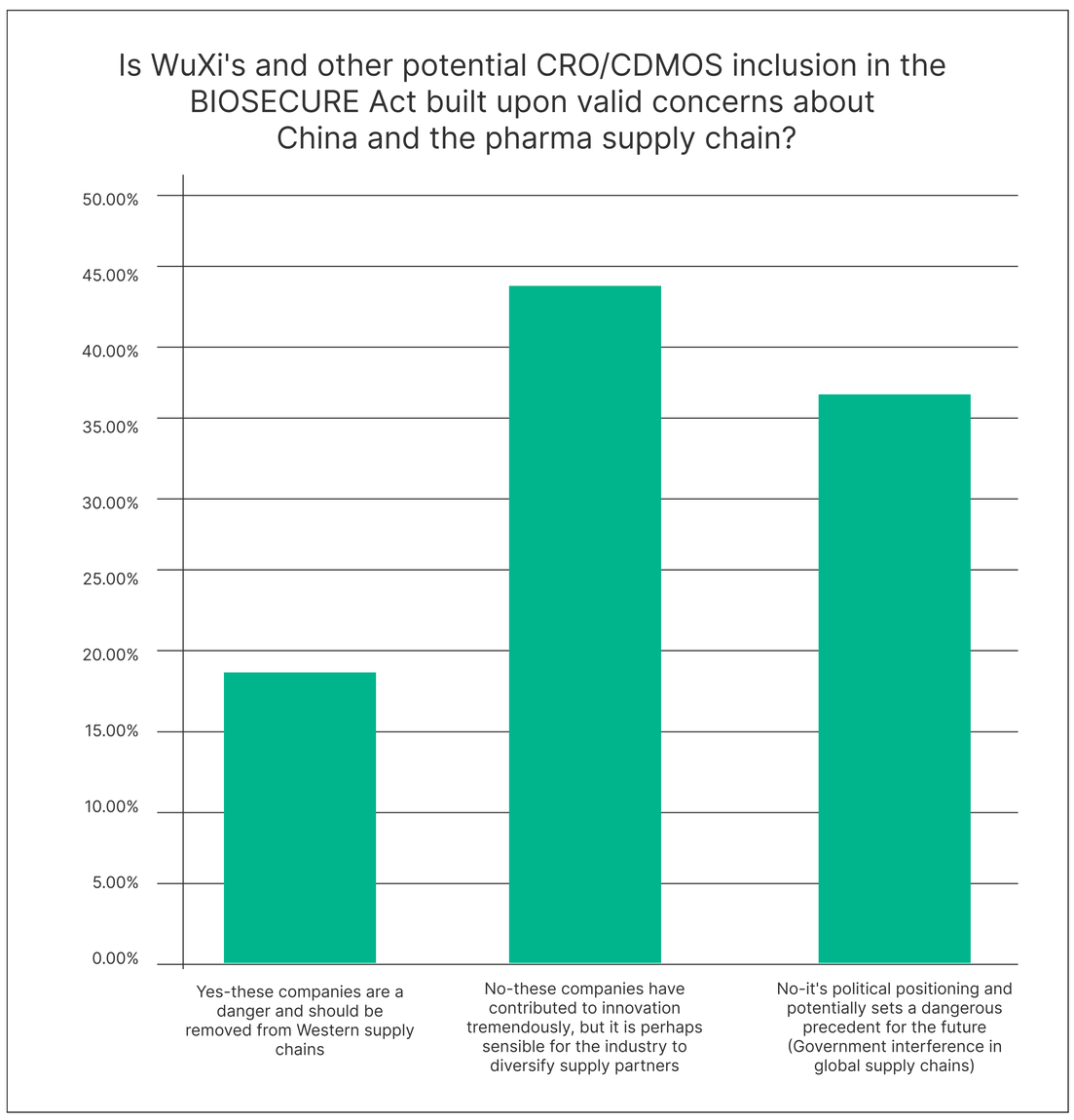
The Act had inauspicious beginnings late last December (2023) when a cross-party group put forward the legislation, with the Senate version passing to congress in January 2024. The original goal of which was a direct response to concerns about access to American patients' genomic data and allegations of involvement from the China Communist Party potentially accessing American innovation[12,13]. However, these explosive origins have evolved over the year into a form that seeks to broadly alley concerns in the United States around pharma supply side security. An update to the bill in May 2024[14] named 'companies of concern' – genomics companies BGI, MGI, and Complete Genomics and, perhaps most significantly, global CRDMO WuXi AppTec – and set a notional deadline of 2032 for US companies to remove or not renewal contracts with the companies[15]. Until just before the time of publication the bill had reached a, at least temporary, impasse as it was not included in the National Defence Authorization Act for the fiscal year 2025. However, that was most likely a result of parliamentary procedures rather than a distinct change of legislative direction, and it may simply mean a new bill is needed to take this forward[16].

Update: At the time of writing, we have just seen a major move forward as the Bill was passed on September 9th in the House of Representatives [the House] by 306 to 81 [i.e. greater than the two thirds majority needed to advance]. However, most analysts still predict the Bill will "need to hitch a ride" with another legislative vehicle to advance, especially as we enter the dead season between administrations[17]. The true litmus test of the way forward however will come on Senate review where individual law makers have much greater powers. It is likely the Bill will be modified in some form after further Senate scrutiny and could yet see Lawmakers set aside the legislation in light of recent opposition from prominent democrats [e.g. Rep. Jim McGovern (D-Mass.) and Rep. Jake Auchincloss (D-Mass.)][18]. Ultimately, if it does advance further the most likely route to become Law would be via a larger legislative bill such as the annual defence bill or government funding legislation. Putting aside the implications for the named companies, it still leaves both the innovators and wider outsourcing sector with significant uncertainty. For example, assuming it goes ahead in some form, are there opportunities for other global CRO/CDMOs, and/or do preclinical biotechs now need to be mapping and changing their journey to commercialisation much earlier – with competition for places rising if China's considerable discovery and development resources are likely removed from the equation.

9. https://www.statnews.com/pharmalot/2024/08/19/novo-nordisk-catalent-ftc/
10. https://www.nature.com/articles/d41586-024-02597-x
11. https://www.science.org/content/article/fda-rejected-mdma-assisted-ptsd-therapy-other-psychedelics-firms-intend-avoid-fate
12. https://cen.acs.org/business/outsourcing/House-bill-targets-Chinese-outsourcing/102/i4
13. https://www.reuters.com/technology/chinas-wuxi-apptec-shared-us-clients-data-with-beijing-us-intelligence-officials-2024-03-28/
14. https://cen.acs.org/business/outsourcing/Amended-BIOSECURE-Act-sets-new/102/i15
15. https://www.fiercepharma.com/manufacturing/wuxi-apptec-wuxi-biologics-shares-jump-after-BIOSECURE-acts-unexpected-exclusion
16. https://identity.biocentury.com/?redirect_uri=https:%2F%2Fwww.biocentury.com%2Farticle%2F652699%2FBIOSECURE-act-may-have-less-impact-positive-and-negative-than-anticipated
17. https://www.statnews.com/2024/09/09/house-passes-biosecure-act-targeting-china-biotechs/
18. https://www.biocentury.com/article/653505/biosecure-passes-house-but-senate-fate-uncertain

So with these great variables and winds of legislative change as our backdrop we asked global pharma what they felt was behind the BIOSECURE Act and their perspectives on potential outcomes in 2025. Not surprisingly, the industry has responded with tremendous ambivalence: yet only 19% have taken a very hard-line perspective that China based-CDMOs 'are a threat and should be removed from Western Supply chains'. Diametrically opposed to this position are 38% of respondent who argue that BIOSECURE is entirely a 'politically motivated issue that sets a dangerous precedent for the industry'. For example, while Indian CDMOs have chiefly reported a beneficial impact thus far, some analysts are postulating whether this might be the beginning of a much larger US protectionism and move toward near and or home shored options. These concerns are of course being monitored by the larger global players and it will be unsurprisingly to see further acquisitions of US sites by foreign owned outsourcing providers in 2025 – as they will then have the flexibility to offer a US based resource to customers.

The final 43% of the industry – and therefore the largest grouping – take a balanced view, which is both in support of 'WuXi's tremendous contribution to the industry', but also suggesting that it is perhaps sensible for the industry to 'diversify supply partners'. This position reflects the long-term debate – running as far back as the middle part of the last decade – on how much of the industry should be outsourced and to where for optimal discovery and commercialised supply chains.



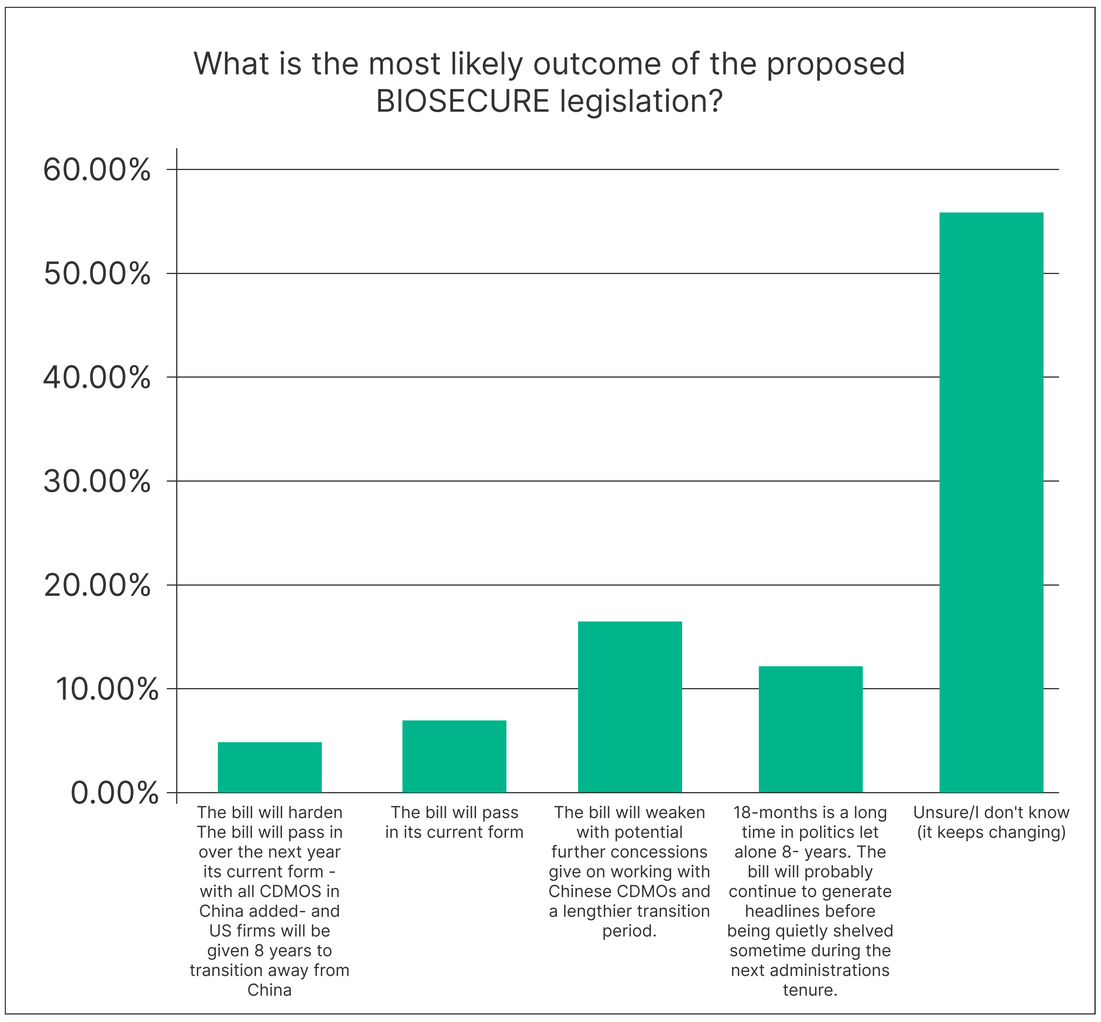
Where does the legislation go next…. Report update: as of September 9th - the Senate

Perhaps the bigger and more interesting question is, of course, what comes next and here the industry is at the mercy of both political winds of change as well as what form of legislation lawmakers in the Senate take, and how it potentially moves forward either as a standalone Bill or as part as another act.

For example, the prescriptive details of the Act have changed a few times already and many experts suggest it will change further as more legislators are made aware how disruptive a full or even partial decoupling will be [putting aside any thoughts of fairness and due process – which have been terms frequently used by the accused companies]

The ongoing debate has shone a special light on WuXi AppTec and taking just its small molecule [Chemistry] unit – excluding both its biologics and advance therapy companies – it was recently reported to be involved in a stagging circa 62 FDA approved drugs[20] during DCAT Week[21]. That means the company is responsible for manufacturing either the API, intermediate or finished dose of these drugs and, in many cases, all aspects the drug manufacturing. In fact, the CDMO supported 27% of all FDA small molecule drug approvals from 2023 – so its impact on commercial drugs is enormous, not even accounting for the thousands of molecules it supports in various phases of development[22]. To put these figures into context, India's contract services industry at present is believed to support around a dozen [novel] commercial FDA approved drugs from the country.

Emphasising the ongoing uncertainty over half (52%) of the industry said they simply did not know how it might unfold as the situation 'keeps changing' – however, it should be noted the survey question was asked prior to the September 9th House vote decision. Of those that did proffer potential outcomes the consensus is that the bill will likely be weakened or shelved at some point in the future (34%). In fact, just 8% of the industry believe the bill 'will pass in its present form' with even fewer just (6%) believing the legislation will be hardened before becoming law. So as we head into a new administration next year, the analyst consensus is that with so much of American drug development and innovation riding upon a global supply chain it may well be a self-inflicted wound to aggressively pursue the removal of China based CDMOs that contribute so much to therapeutic development. Especially, when so much of the industry's starting materials originate in China meaning that BIOSECURE will slow novel development hindering USA-based biotech, but without really tackling the biggest area of supply chain insecurity in chemical precursors and starting materials. What it has done however, is created a renewed optimism among Indian CRDMOs – who excel in the discovery to development paradigm thanks to large scientific workforces – but also CDMOs and CMOs in the West that are now potentially more attractive commercial supply options. Investors are already reportedly looking at opportunities in other Asian markets – mainly India and Korea – and in the West with leading CDMOs [e.g. Lonza, Recipharm and Thermo fisher et al][23]



One of the speculated 'side-effects' of the BIOSECURE uncertainty is whether this is slowing development decisions in the United States, as biotechs – the most likely effected group in a 'disorderly decoupling' – are re-evaluating partners and therefore taking longer selecting CRO and CDMO partners. In a surprising result earlier this, WuXi has reported only a 1% fall in US revenues [effects of Covid contracts removed], having gained a 5% uptick in revenues from Europe – with 500 new customers added in the last year[24].

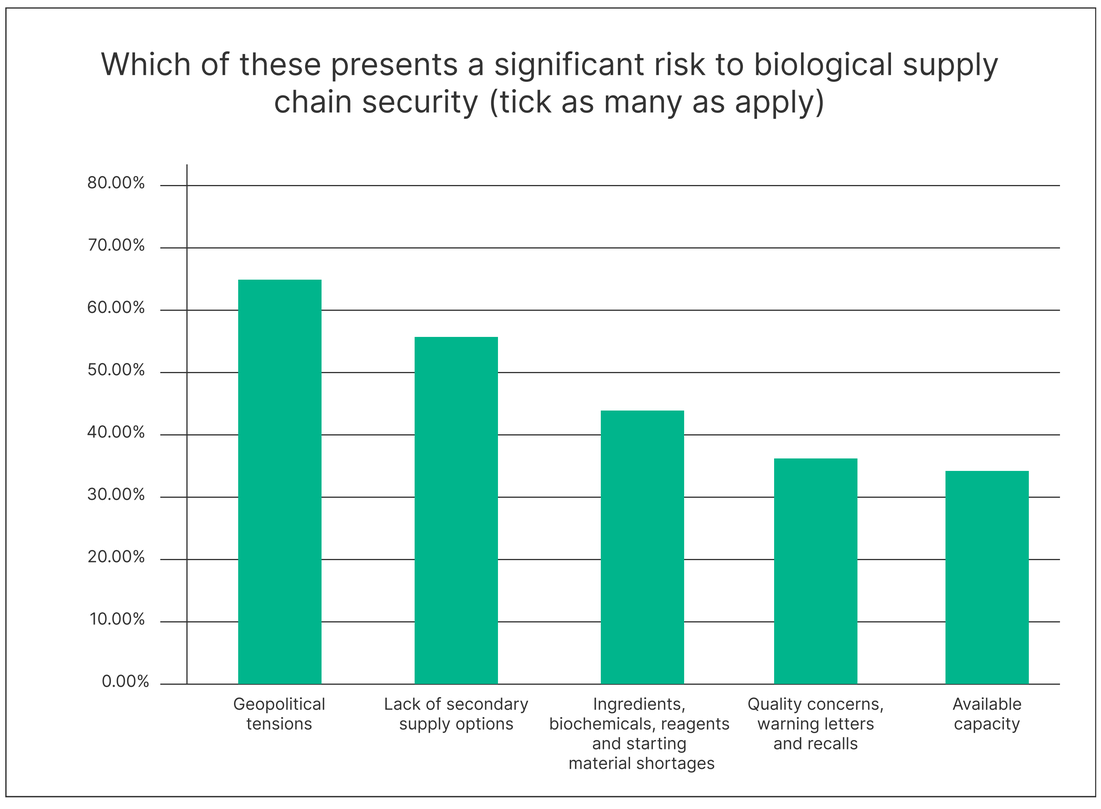
"One of the unintended consequences of this turbulence, is that biotechs in Europe should look at the instability of BIOSECURE as opportunity to advance more quickly than their US based rivals – with notably few places to outsource projects that transitions the CRO to CDMO pathway. Another potential unidentified issue is US-based VCs backers withholding investment decisions and slowing advancement while they wait and see where the chips fall. Better to go slow now, if your project team is working with China so that its less disruptive if a switch is need. These companies are the engine of innovation but under the radar in the legislative debate so remain unheard. No one wants to make a big 3-year decision they might regret in 6-months' time. So for the sake of US innovation, we must reach a consensus soon. It's a particularly acute issues for those of us used to working with CROs in China – it's difficult to get what we need elsewhere" commented a top twenty VC director on condition of anonymity.

In a further complication for early stage biotechs, Gil Roth, President of the PBOA notes within his article [in this report] that the funding recovery is not being felt evenly and it is indeed the early-stage projects – the "lifeblood of CDMOs" as he coined it – where investment dollars remain scarce, while for late-stage assets investment is now again flowing in.

So what are the biggest threats to supply chains?

Predictably [see paragraphs above], in a year of increased 'geopolitical tensions', this theme was identified by nearly 70% of the industry as presenting the biggest threat to biological supply chain security followed by a 'lack of secondary supply chain' options - the latter, of course, becoming a much more complex issue should geopolitical tensions arise within your primary partner. This is an existential threat faced by many biotechs currently advancing their clinical products in China – do they slow development and/or risk failure by attempting to move or mitigates with secondary supply options or stay the course and continue development in China and hope the political winds of change have shifted come approval in a few years' time.

Encouragingly for all of the industry, 'quality concerns and warning letters' were seen as a far less likely cause of supply chain disruption – with around only one third believing this presents a risk to security. What's unclear, is if this result represents improved confidence in quality standards across the industry or that simply other concerns are now more pressing.



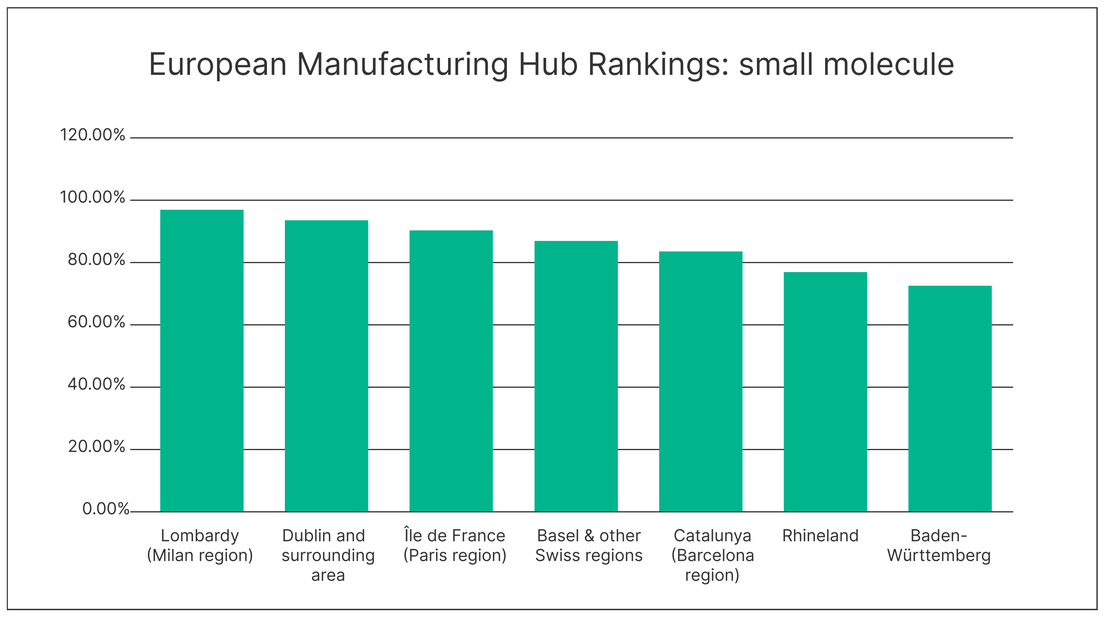
Lombardy and European Manufacturing Rankings

Last year we introduced a new index to the report which ranked the top biotechnology hubs – i.e. the most productive regions to launch a biotech – and following this success we have launched the inaugural **European Manufacturing Index [EMI]**. The EMI rankings will evaluate all the major manufacturing centres across Europe with three separate categories for small molecules, biologics and medical devices.

The small molecule ranking is designed to evaluate the most attractive destination to build a new manufacturing facility factoring- in 'the cost of plants, access to qualified personnel, and cost of on-going operations'. This category is particularly significant for the host region of this year's CPHI Milan, as Lombardy has historically vied with Germany (both Rhineland and Baden-Württemberg) as the continent's largest production centre by volume. Significantly, while Lombardy did emerge as the key winner, several other regions in Europe finished ahead of the major German hubs, with the Dublin region and Île de France

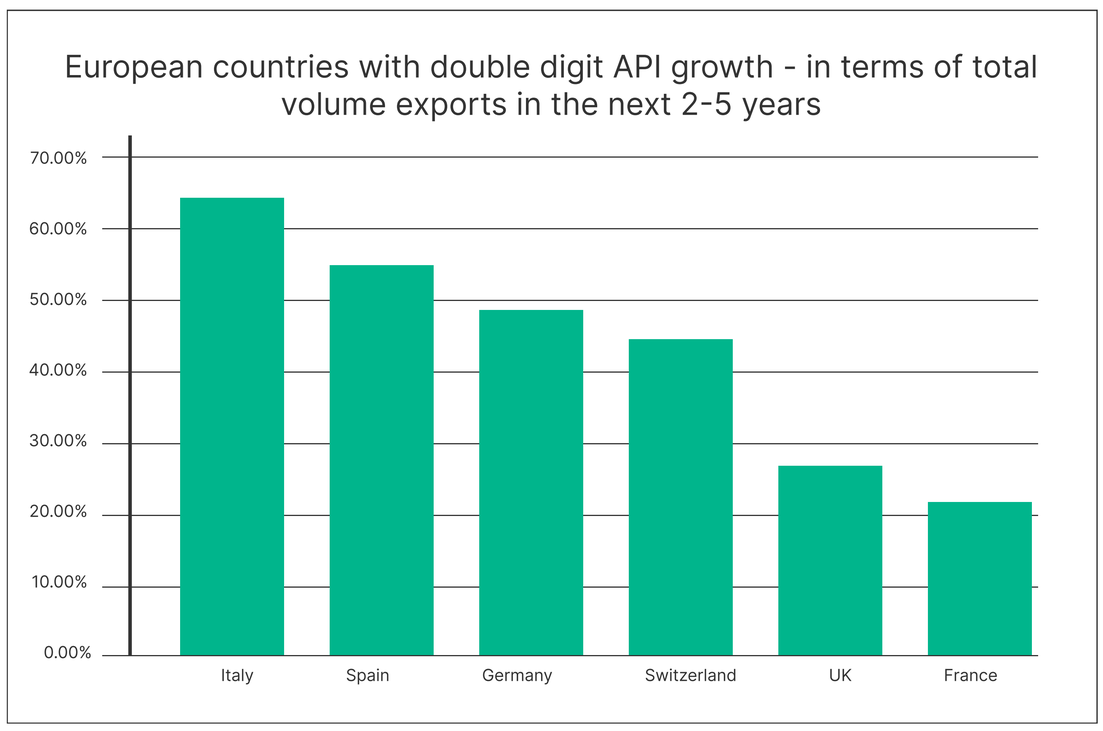
24. https://www.fiercepharma.com/manufacturing/bioseecure-act-looming-wuxi-apptec-shows-declining-revenue

(Paris region) scoring very strongly among respondents to the survey. Switzerland with its long-established innovative pharma industry and major international pharma companies unsurprisingly scored highly, but so did the newer Catalunya region, which has grown impressively in recent years[25]. For example, earlier this summer Esteve announced plans to invest over €100m in building a new API production plant in Girona[26], while Siegfried opened a global Development Center for Drug Products in Barcelona last year[27].



When we asked the same questions for biological manufacturing two locations ranked clear above all others in Europe. Namely, 'Basel & Swiss regions', perhaps unsurprisingly considering its long pedigree in advanced manufacturing, however, the 'Dublin region' also scored nearly identically. Ireland has become a major player in biologicals – perhaps originally driven by favourable tax rates – but increasingly by the ecosystem of companies and employees in the country. In just the last few years Ireland has seen large biological investments, hundreds of millions each from BMS, Eli Lilly, and MSD, while Pfizer famously committed €1.2bn[28] to its biological drug substance manufacturing site in Dublin.

In a further boon to the prospects for Lombardy in the next 5-years, Italy was selected as the top European nation in terms of API growth potential. In fact, 63% of pharma professionals expect the country will report 'double digit growth in terms of total volume of exports over the next 2-5 years'. Spain, a country that has seen fast improvements in its reputation for API manufacturing, finished second (56%), ahead of Germany (49%) and Switzerland (47%). Both the United Kingdom and France scored relatively poorly with just 24% and 21% respectively anticipating double digit growth over the same timeframe.



Lowering the cost of biologics production

The cost of biologics production has long been an industry issue but in recent years we have seen an acceleration of cost reduction technologies, and not just at lab scale as many manufacturers, biosimilar producers and even contract providers looking to break the symbolic $100/gram level, with several companies on record as aiming for sub $50/gram. For example, while the technology is still in its infancy with only a few manufacturers using it, continuous biologics processing was identified by the industry as the most likely (62%) technology to have the biggest impact over the next years years.

Significantly, outside of big pharma only two CDMOs are currently operating continuous biologics set-ups, namely, Just Evotec and Enzene Biosciences. Continuous biomanufacturing means fresh cell culture media is continuously added with less accumulated by-product, which means a higher degree of intensification and much greater yields. Just Evotec is on record as stating its J.POD® can hit the $50/gram[29] mark and Enzene are on record as aiming for below $40/gram with their next generation continuous systems EnzeneX™ 2.0/3.0.[30] Interestingly, traditional cell line improvements – the technology that has made the greatest contribution to lowering costs over the last five years – is only the third favoured option looking ahead five years. Perhaps signally the relative maturity in this area and that the next major step-changes breakthroughs in cost reductions will require newer technologies.

In a surprisingly result, 'AI and automation' finished only narrowly behind continuous bioproduction as the industry increasingly embraces its potential for process improvements, real-time monitoring and analysis.

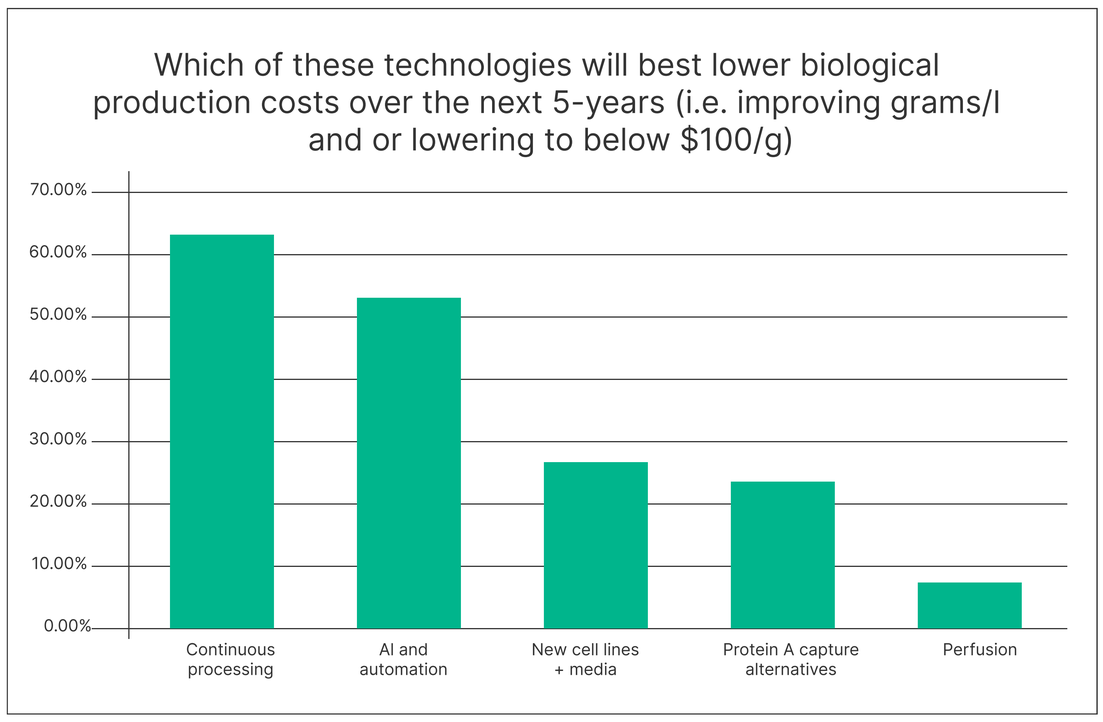
The ability to run bioproduction facilities more efficiently and with lower energy usage should not be underestimated and signals a new era in which we look holistically at the problem from all sides – so cost is no longer solely a yield-based issue, but rather, one of resources and achieving overall efficiencies. For example, 'digital twins' are now being routinely used to simulate production scenarios and optimise process before real world testing begins – however, with the addition of AI technology this can potentially be optimised in days or seconds rather than months.

Taking this a step further, AI can take forward the theoretical (digital twin) data and compare this in real time as live batches are produced – ensuring that any out of spec issue is identified, mitigated and or even improved during production[31]. In advanced therapies automation is also predicted to produce step change improvements in costs, as they empower greater scaling, integration of automated quality-control monitoring, and again, the potential to modify manufacturing conditions in real-time[32].

25. https://www.biocat.cat/sites/default/files/content/file/2024/02/08/2/2022_catalonia_bioregion_report_en.pdf
26. https://catalonia.com/w -invests-100-million-euros-to-strengthen-its-manufacturing-presence-in-catalonia
27. https://www.siegfried.ch/news-archive/?y=2023&tag=38
28. https://www.pfizer.ie/media/pfizer-announces-12-billion-investment-and-hundreds-of-jobs-at-grange-castle-site
29. https://sciencepool.evotec.com/j-pod-toulouse-revolutionizing-biologics-manufacturing-in-europe/
30. https://x.com/enzenebio/status/1805245009207103989
31. https://www.bioprocessintl.com/sponsored-content/ai-enabled-digital-twins-in-biopharmaceutical-manufacturing
32. https://www.genengnews.com/topics/bioprocessing/automation-and-standardization-will-cut-cell-and-gene-therapy-production-costs/

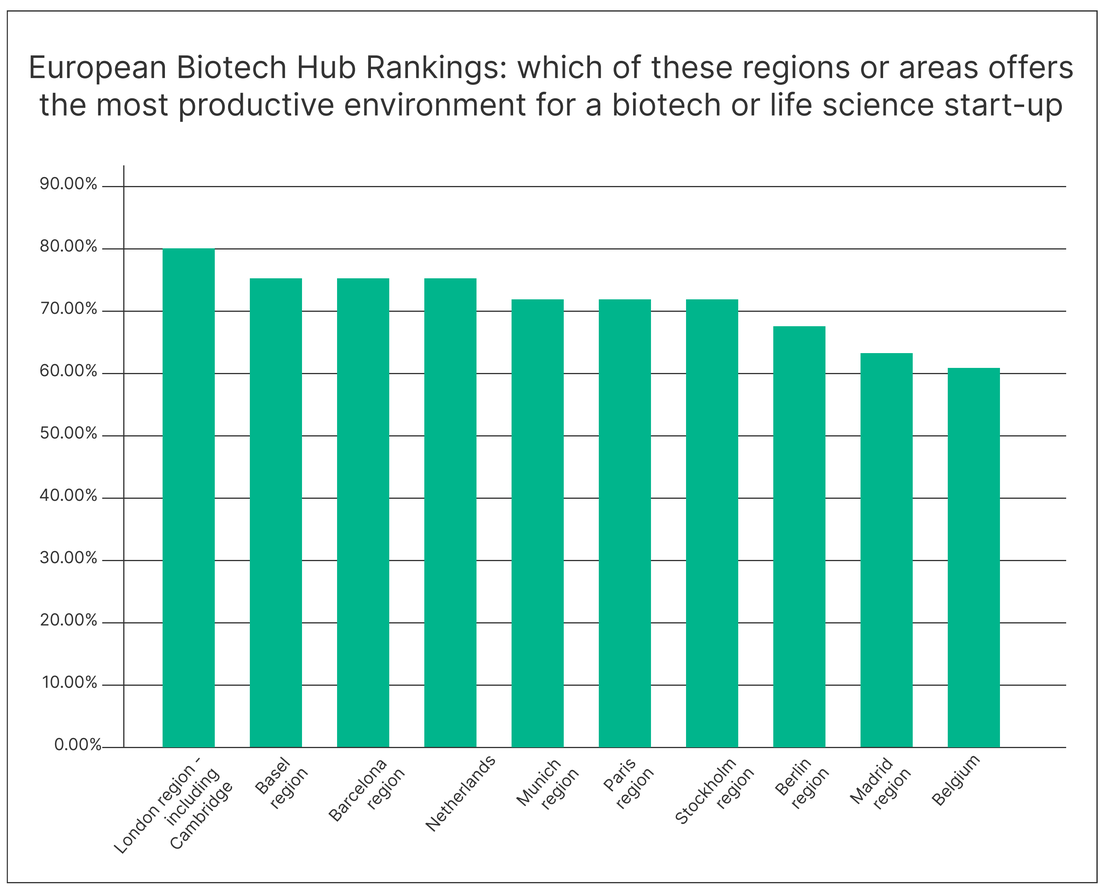
Additionally, there is now great interest in developing more standardized platforms for delivering gene therapies, to reduce both the cost and the regulatory burden. AAV-based therapies have advanced the furthest with common vector 'backbones' for multiple indications, into which a specific gene [depending upon the disease targeted] could be inserted[33].

In contrast, alternatives to the Protein A capture step – at present the most expensive element of production – and perfusion, which has greatly intensified processes in batch production were seen as less likely alone to drive change in the next five years. Perfusions very low score in particular, is quite surprising, especially at a time when so many biosimilars producers and CDMOs investing in this to lower costs. Our speculation here then is that the market believes the big gains have already been had using these technologies that are widely used.



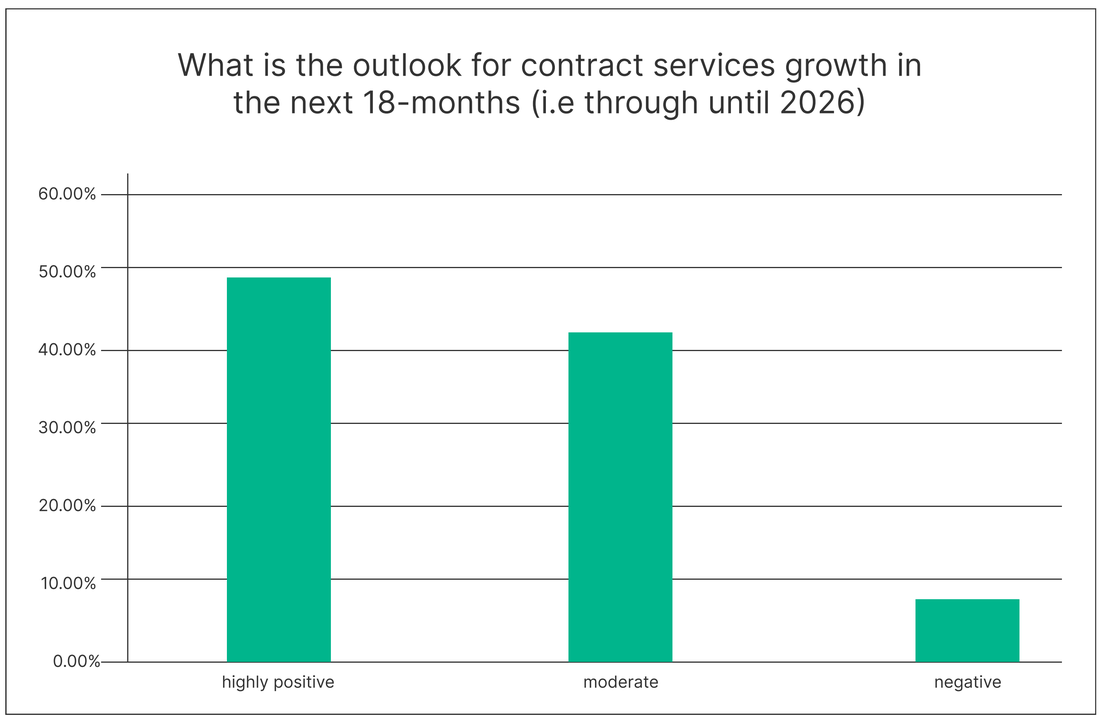
Biotech rankings

The European Biotech Hub Ranking returns for its second year, with largely consistent results as the best locations to launch a new biotech. London and the wider golden triangle has retained its top spot ranking for a second year, but Barcelona has fallen back narrowly behind Basel and level with the Netherlands. The overall trend here is for slightly lower year-on-year scores, but also, a much smaller spread between regions – suggesting that the European biotech landscape has become more competitive with smaller centres increasingly attractive.



Contract Services

Last year's report documented the shifting narrative, with the latter half of 2024 expected to see more rapid growth after a cooling in the first half of 2024, most analysts (see Gil Roth's piece) observe a recovery to growth has been slower than expected. However, this new analysis suggests this is now underway, as just 7% of the industry had a negative outlook for contract services companies over the next 18-months, with 49% 'highly positive' and 44% 'neutral'. With the staggering demand for PD-1 drugs and both WuXi and Catalent's capacity uncertain, it would appear certain this will raise demand for other providers. In a further data point of this trend underway, CDMO and non-clinical CROs saw surging support as the most appealing investment options, moving well ahead of last year's one and two: AI companies and late-stage biotech's respectively.

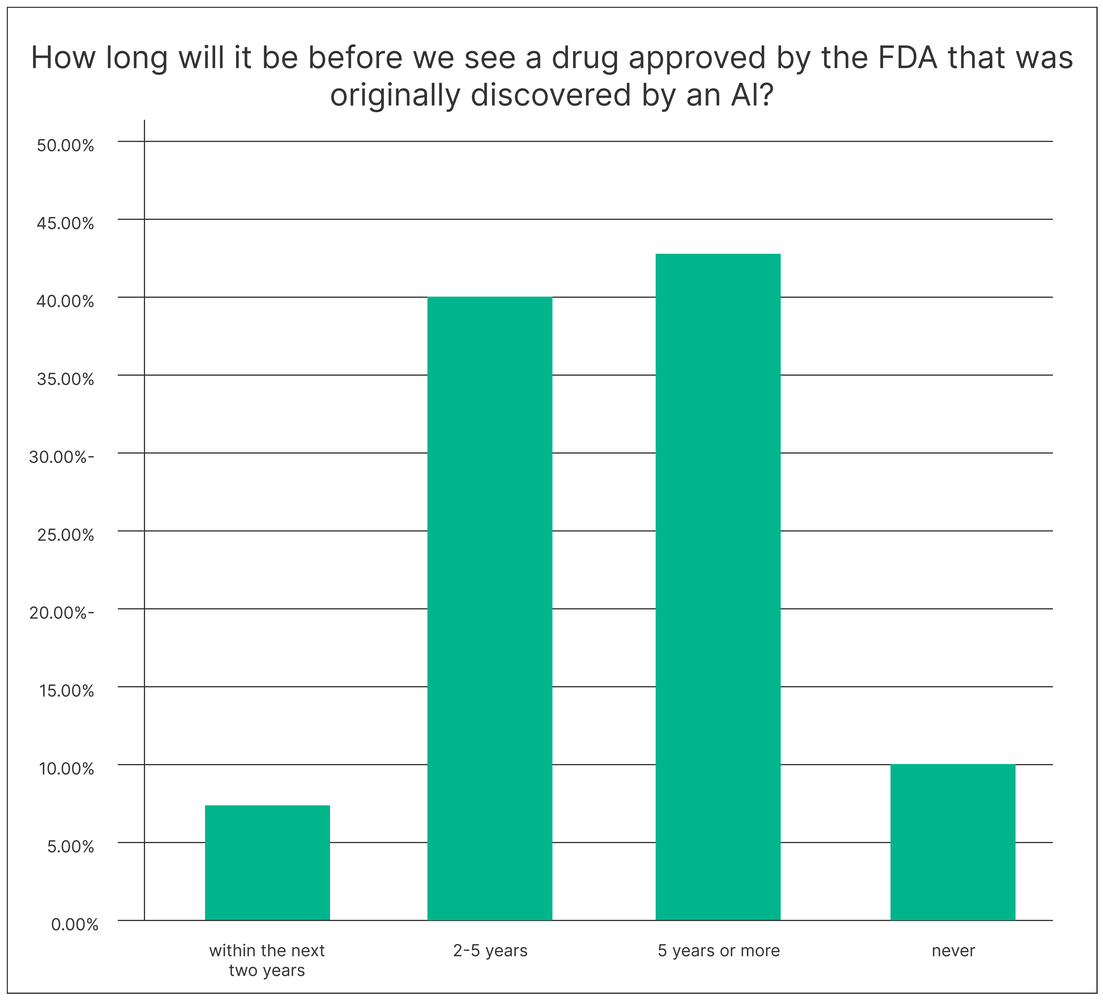


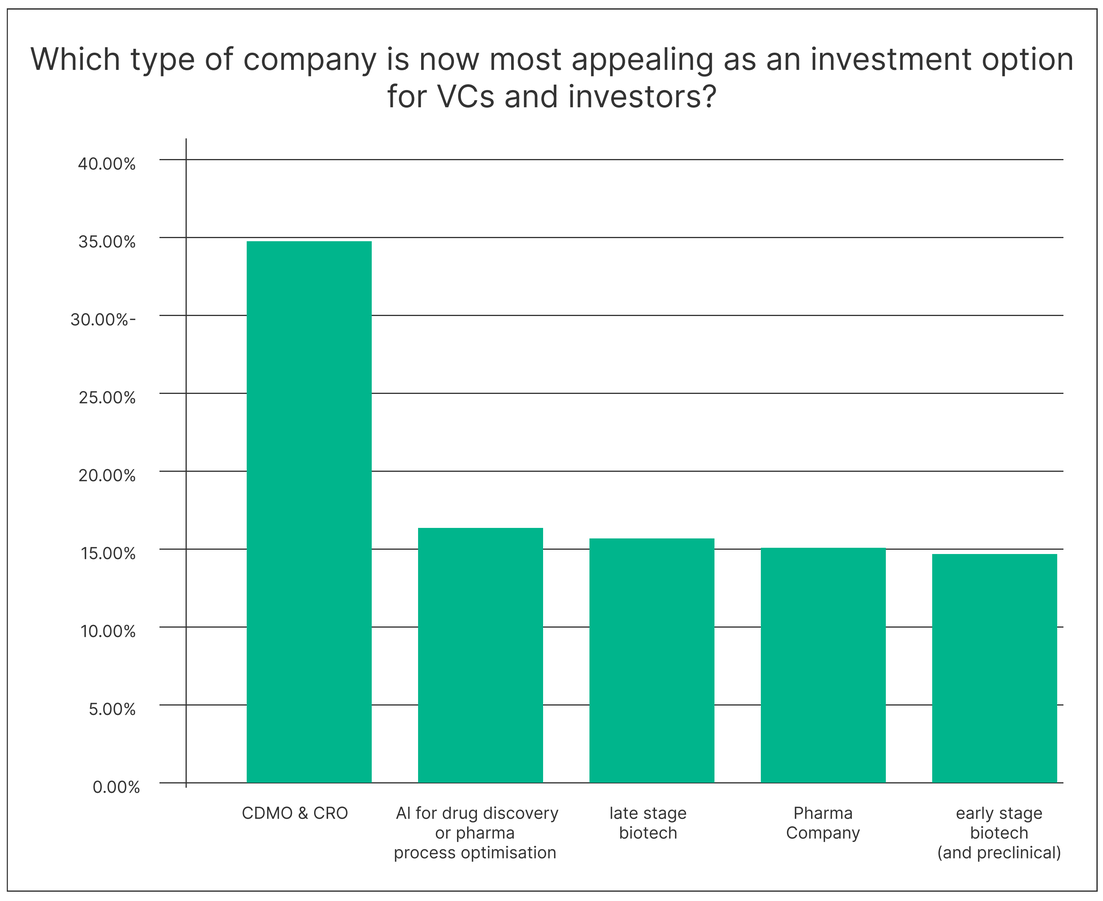
The fall of AI from being the golden child of pharma in 2023 perhaps reflects a more muted environment after the well-publicised failures of several lead candidates from Exscientia, BenevolentAI, and Sumitomo Pharma[34].

Following this downturn in AI both Recursion and Exscientia have lost much of their value since going public and merged in August 2024[35]. With even Insilico founder, Alex Zhavoronkov warning, that after billions in industry write-downs and consolidations we must be more careful as an industry to sperate 'real progress in AI' from 'dangerous financial hype'[3637]. What we have seen as a result is that the industry is much more reticent on a likely FDA approval, with just 7% of those surveyed believing this could come within two years. In fact, 43% believe its timescale of 2-5 years is most likely with another 40% believing it will be 5-years or longer – and 10% suggest we will 'never see an AI discovered drug approved.'

So confidence in the technology to power a new age of drug targeting and discovery has fallen back in particular among those predicting approvals within the next two years – falling from 20% in 2023 to just 7% this year [a notable shift as we are obviously also one year into that two-year survey and no approval has been forthcoming]

33. https://www.genengnews.com/topics/bioprocessing/automation-and-standardization-will-cut-cell-and-gene-therapy-production-costs
34. https://endpts.com/first-ai-designed-drugs-fall-short-in-the-clinic-following-years-of-hype/
35. https://www.biopharmadive.com/news/recursion-exscientia-merger-deal-artificial-intelligence-drug-discovery/723714/
36. https://www.genengnews.com/topics/artificial-intelligence/is-generative-ai-in-drug-discovery-overhyped/
37. https://www.unite.ai/beyond-the-hype-unveiling-the-real-impact-of-generative-ai-in-drug-discovery/





In terms of which types of contract services provider is expected to see the greatest growth in the next five years, we see another major trend underway – as biologics are identified as the modality most likely to be the most lucrative. We have seen a steady and continued rise in the number of new biological agents approved by the FDA with 10 in 2019, 13 in 2020, 14 in 2021, 15 in 2022, and a record 17 in 2023 – with a total of 22 BLA [Biologics License Application] approved by Center for Biologics Evaluation and Research (CBER) i.e. when accounting for therapies approved for multiple indications. Monoclonal antibodies unsurprisingly have led the charge with 12 new molecules and a further 5 enzymes and/or proteins based biological agent approvals.

Improved linker technologies and broadening payload options[38] have marked a coming of age for ADCs, which garnered much media coverage and interest during the last few years – with the 202339 CPHI Annual Report noting the large investments made by CDMOs. However, in 2023[39] for the first time since 2016, the FDA approved no new ADCs (antibody drug conjugates). It should be noted that three new approvals are expected in the 2024/25 – for Datopotamab Deruxtecan, Patritumab Deruxtecan, and Telisotuzumab vedotin[40]. The significance of this becomes apparent when we switch to look at Tides drug approvals – which although are classified as small molecules show many structural complexities similar to that of biologics – during 2023 where there has been a sudden glut of approvals, with nine approvals in 2023 (five peptides and four oligonucleotides) and a further three so far inn 2024 at the time of writing.

So looking ahead while small molecules [34%] & cell and gene therapies (37%] – which are hard to scale – are still preforming strongly, the industry now expects easily scalable advanced therapies either peptides [43%] or biologicals [53%] to be the best performing modalities for CDMOs [i.e. delivering the best marginal and overall returns]. As an aside to this, much of the attention of GLP-1 drugs has a focussed on the fill finish process – since the Catalent acquisition – but there are far fewer CDMOs currently specialised in the development and commercial production of peptide actives. So while, as previously discussed the role of WuXi AppTec is pervasive in commercial supply, what has also gone under the radar during the last few months of BIOSECURE turbulence is that they are also perhaps the largest CDMO in Tide's active production – for example, supplying the active for Eli Lily's blockbuster Zepbound/Mounjaro[41]. Taken collectively, if Tides are to remain a key modality moving forwards does this present a massive opportunity for CDMOs with cash to spare to invest – our CPHI analysts think yes.

Looking further ahead to the next generation of PROTAC (PROteolysis TArgeting Chimera) drugs – an emerging class of drugs that use a bifunctional molecule to target and degrade specific disease-causing proteins via the ubiquitin-proteasome system – while to date we are yet to see an FDA approval this is likely to be another 'growth modality' to watch closely in the years ahead. Analysts expects a first approval by the earliest in 2025 or latest 2027, with GlobalData predicting annual sales of $3.7billion by just 2030[42].

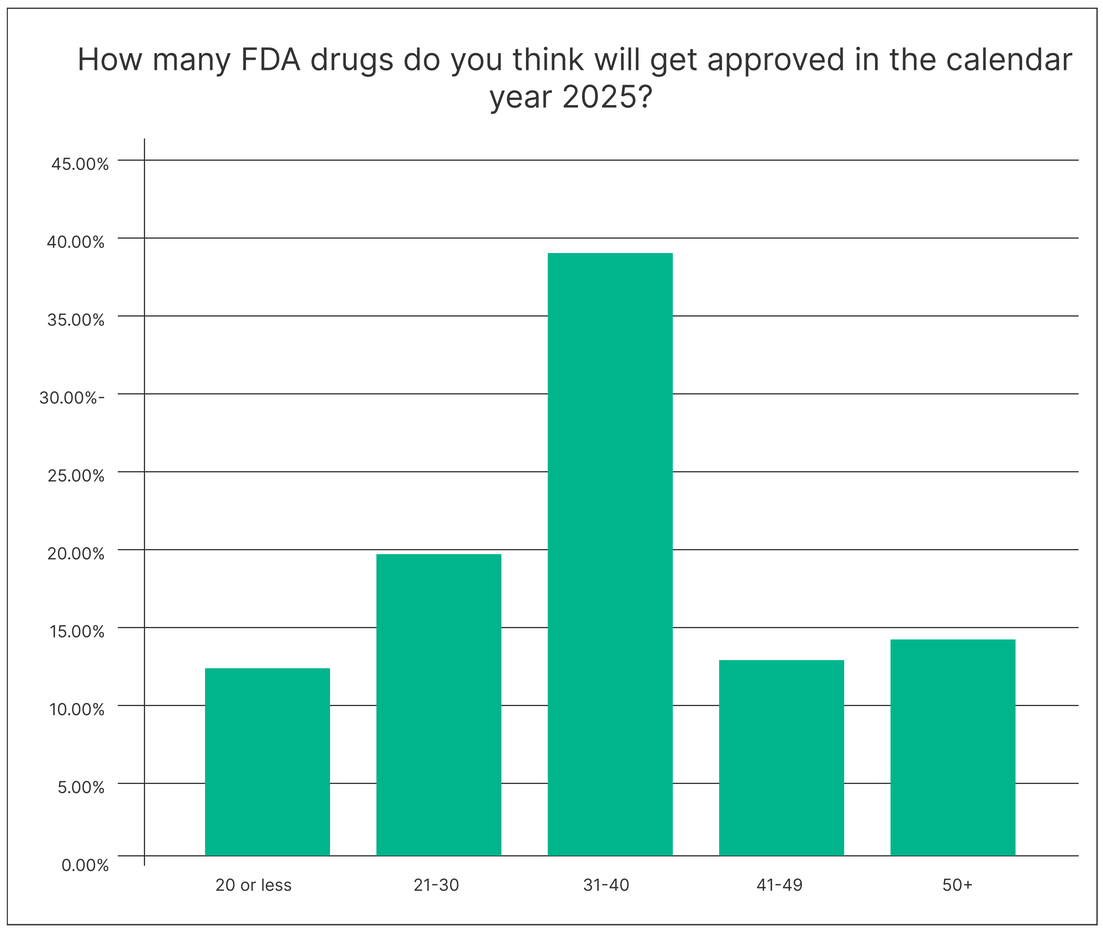
The CROs with current PROTAC teams included Charles River and WuXi AppTec along with Indian pair' Syngene and Aurigene, and we anticipate greater investment and the building of PROTAC teams at CDMOs over the next 2-5 years as more targets progress to late-stage development.

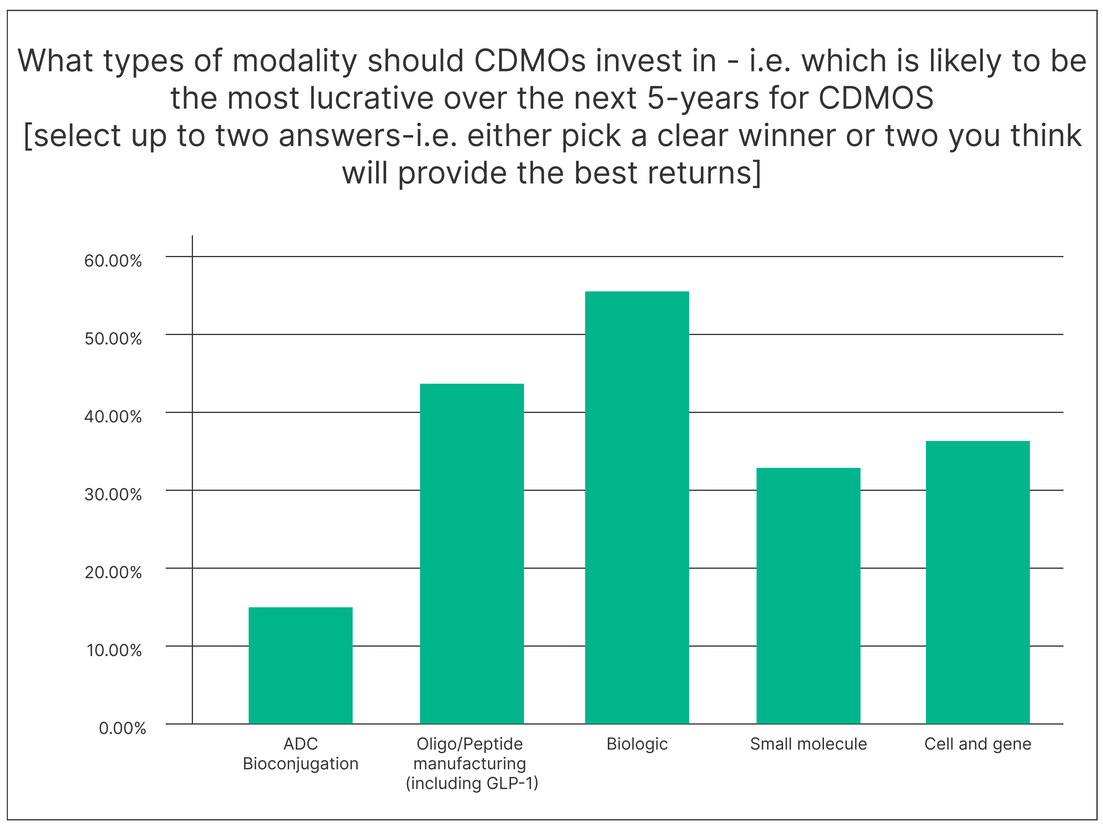
Prestigious rate of novel drug innovative to be maintained in 2025

The majority of the industry also expects the recent rates of innovation to continue in 2025, with a majority [67%] expecting that FDA approvals will again surpass 30 – of which 15% are expecting more than 50 approvals, 14% predicting 41-49, and the largest group expecting somewhere between 31 and 40 approvals [39%]. What we did not ask and might have proved enlightening, is by when the industry expects biological and advanced therapy approvals to overtake those of

38. https://www.nature.com/articles/s41587-024-02168-5#:~:text=Many%20development%2Dstage%20ADCs%20chase,patients%20with%20advanced%20urothelial%20cancer
39. https://broadpharm.com/blog/ADC-Approval-up-to-2023
40. https://www.biochempeg.com/article/397.html#:~:text=In%202024%20or%202025%2C%20three,vedotin%20(ABBV%2D399)
41. https://www.bloomberg.com/news/articles/2024-03-06/weight-loss-drugs-threatened-by-us-effort-to-contain-china?embedded-checkout=true
42. https://health.economictimes.indiatimes.com/news/pharma/pharma-industry/protacs-oncology-market-to-reach-3-7-bn-by-2030-despite-regulatory-challenges-globaldata/110698322

conventional small molecules. For context, while there were 17 approvals – of 59 – last year for pure play biologics, there were also however, a further nine Tides approved perhaps showing that for the first time complex molecules are now extremely close to parity. In fact, looking more closely at the approvals year-on-year small molecules have remained consistent over time and it is the growing rate of complex drug approvals that is driving the steady growth in numbers. So our report's experts now predict that within the next three years we will see the combined number of Tides, biological and cell and gene therapy approvals approved in a year surpass small molecules for the first time.



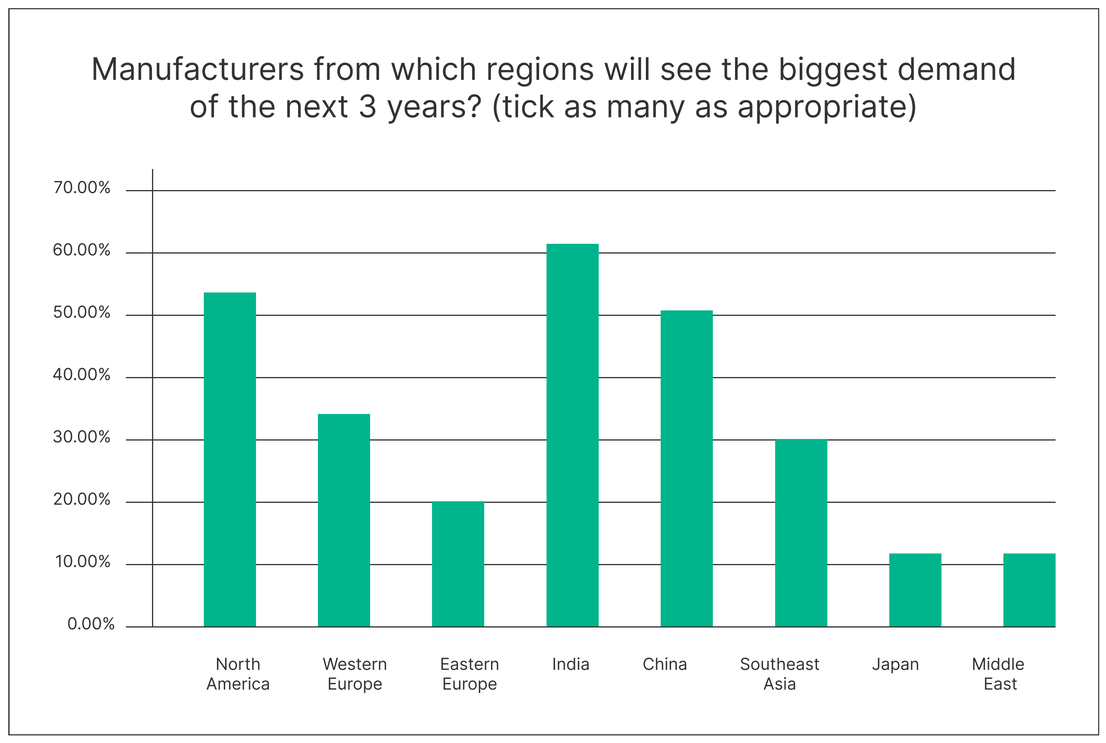


Geographical location of CDMOs?

The general trend globally, especially post pandemic, is to have manufacturing options in at least two continents for greater supply chain security. However, mirroring the industry debate running in a myriad of stories[43] throughout 2024, India is predicted to be the biggest medium-term beneficiary for CDMOs services. Yet beyond India, the industry remains ambivalent on prospects between the United States, China and India – in a perhaps surprising finding Europe remained a little adrift of these regions, with much fewer professionals predicting as good prospects over the next three years. A conclusion we can infer from this: is that while Indian and China remain unrivalled for chemistry and biology services – as the world's CRO powerhouses, where cost and access to scientific personal makes their leads unassailable – the United States is potentially the biggest beneficiary of drive for domestic production [as the biggest home market]. However, we temper this prediction with the reality this topic – 'made in the USA' – has been long muted now, and unless facilities are built and invested in, the rhetoric will remain just that[44].

In fact, US Government Analysis is underway to try and map the complete API and starting materials supply chains and perceived vulnerabilities to China – including across more than 2800 generic molecules[45].

The other aspect we did not explore and is covered in greater depth by Gil Roth in his piece, is the potential role of 'friend shoring' and 'near shoring' – so might we see more significant growth in Canada as well as the USA.



In terms of capacity challenges, perhaps unsurprising considering the shift – albeit gradual – we now see in approval numbers is that once again biologics CDMOs were seen by the industry as the ones with the most likely [54%] to see capacity shortfalls in the next year. Significantly and, perhaps a reference to the slow return of funding, all other CDMO types were seen as unlikely by most respondents to have industry-wide capacity issues.

Longer term (3-4 years hence) however, Dawn Ecker of BDO suggests – later in this report – that increased CMO capacity will help power a new age of MAb approvals from smaller companies that previously might have seen development slowed (due to a lack of available capacity).

Novel excipient creation

This is a question we have asked for three consecutive years. In the 2022 – around the time the FDA Novel Excipient Review Pilot[46] Program was first introduced and encouraged by the recent Covid successes the industry was much more confident of an approval within a year or two. Yet this year, like in 2023, the majority of industry respondents now believe 2027-2030 is the most likely timeframe for the introduction of an approved novel excipient.

43. https://cen.acs.org/business/outsourcing/India-seeks-seat-drug-services/102/i25
44. https://www.atlanticcouncil.org/blogs/econographics/the-us-is-relying-more-on-china-for-pharmaceuticals-and-vice-versa/
45. https://www.pharmamanufacturing.com/production/unit-operations/article/55042959/mining-the-reshoring-rush-targeting-government-spending
46. https://www.fda.gov/drugs/cder-conversations/cder-conversation-novel-excipient-review-pilot-program#:~:text=With%20this%20pilot%20program%2C%20FDA,and%20the%20facilitation%20of%20new

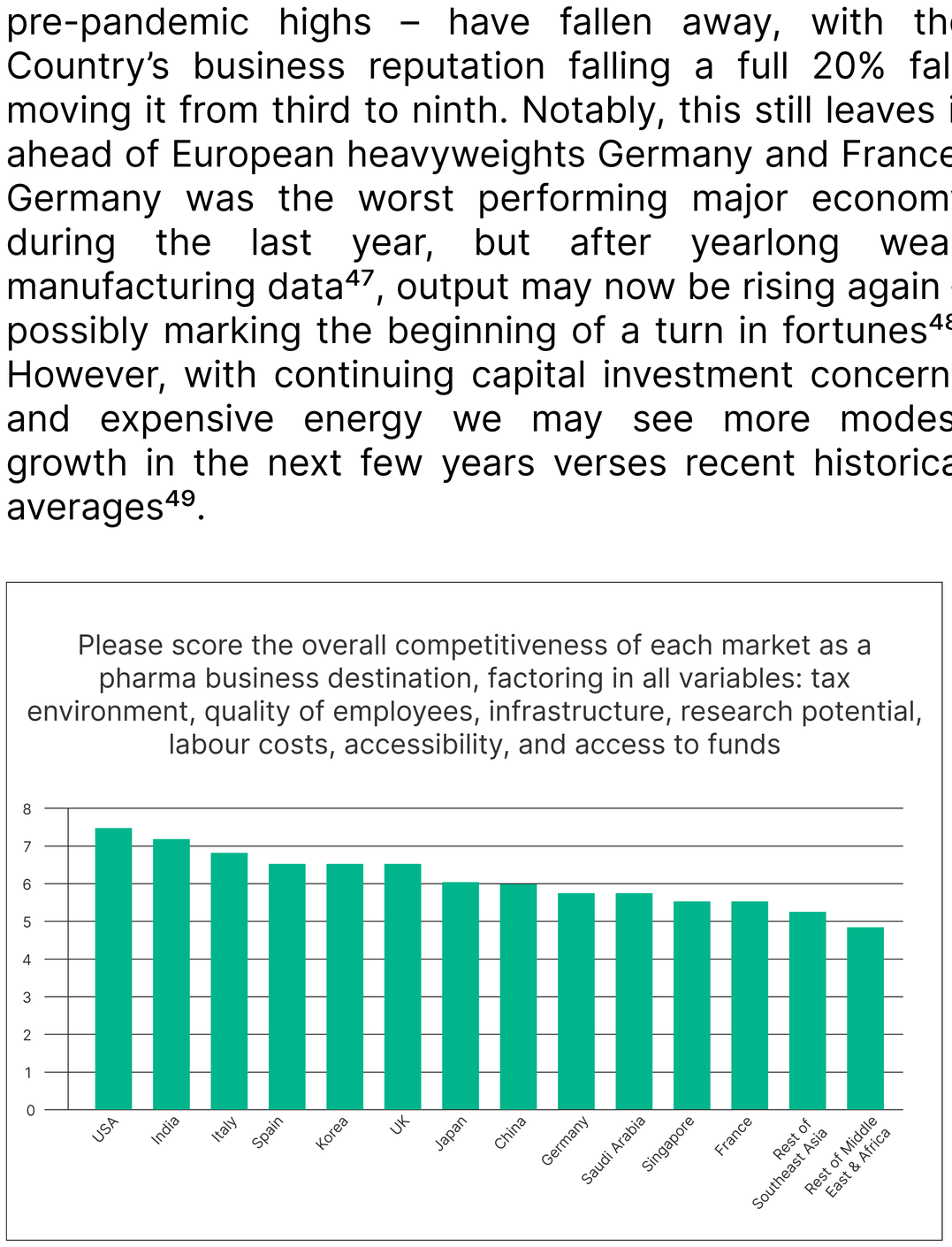
Encouraging Dr. Iain Moore – a senior advisor at EXCiPACT [and former Croda Global QA] – is however, a little more positive suggesting the rise of mRNA will necessitate newer excipients. He added, *"I think this is a conservative view, and there will be a burst of mRNA and related therapies, and these will require customised nanoparticle lipids. So it's here we could well see more novel excipients and the existing ones adjusted to the new products. Especially as there are now very exciting developments in curing what has been incurable in the past, and this will create a pull on the market to overcome any hurdles in the approval of novel excipients."*

Overall competitiveness by region

This category is typically the best overall reputational gauge – i.e. how a country's pharma market is perceived and the strength of its pharma industry – has been topped by the United Sates every year since the survey inception [around 7 years now]. So it is of little surprise to the USA [7.3] again lead the way. However, mirroring last year's results, it remains only narrowly ahead of India [7.1].

In fact, since the first ever survey we have seen notable shift and the USA's overall dominance is gradually reducing and the European nations are aligning with similar scores. In 2024, scores have remained consistent with just a few big year-on-year moves. Notably Spain has backed up its strong performance in 2023 to rise to 4th place in the tables, and Italy has emerged as the European winners for the first time. Both France and Germany have displayed weakening reputation – finishing 10th and 13th respectively – with Korea [6.3] again scoring strongly.

The obvious trend reversal is that the post-covid gains China saw last year – when it had nearly achieved its pre-pandemic highs – have fallen away, with the Country's business reputation falling a full 20% fall, moving it from third to ninth. Notably, this still leaves it ahead of European heavyweights Germany and France. Germany was the worst performing major economy during the last year, but after yearlong weak manufacturing data[47], output may now be rising again – possibly marking the beginning of a turn in fortunes[48]. However, with continuing capital investment concerns and expensive energy we may see more modest growth in the next few years verses recent historical averages[49].

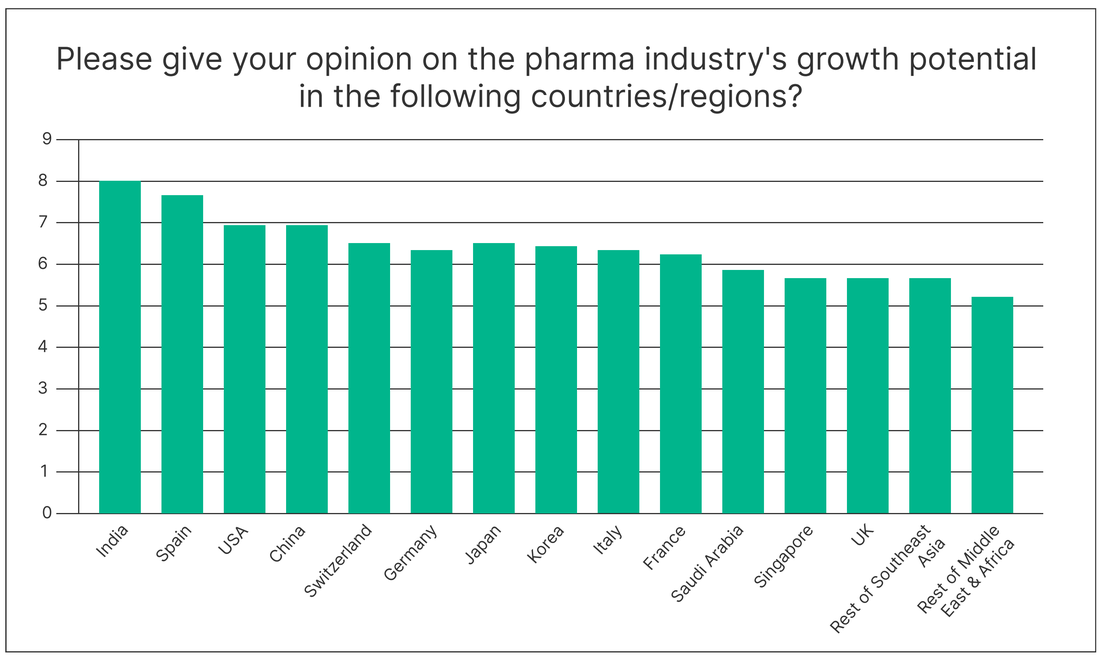


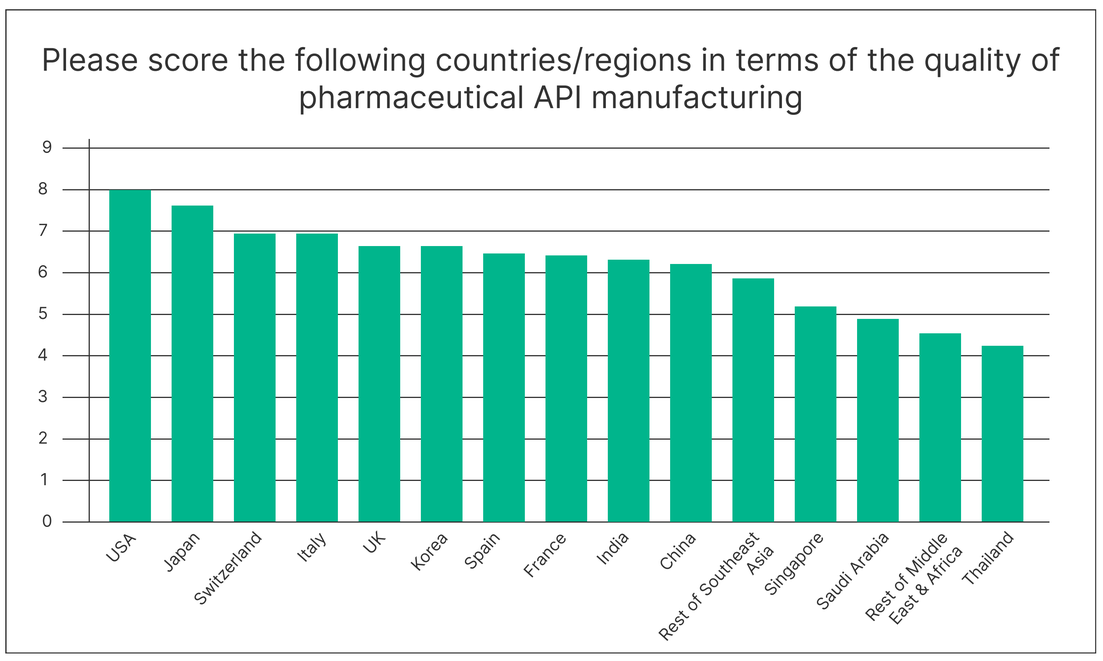
Growth Potential

In one of the more surprising findings of this year's survey, Spain has continued its surge up the rankings – last year it went from 12th to 6th – and has overtaken the United States in second place. The reasons for this are not completely clear, however, Spain has been on the rise for over 18-months with its burdening biotech sector now helping stimulate growth in adjacent parts of the industry. For example, recent data shows the country is now the leading nation for clinical research, with 40%[50] of clinical trials authorised by the EU via the Clinical Trials Information System conducted in centres across the country[51]. Further adding to the positive conditions, in a depressed investment year [2023] Spanish biotech R&D hit record levels – according to Farmaindustria reaching 1.5bn – with this now increasingly passing through to a growing manufacturing base[52].

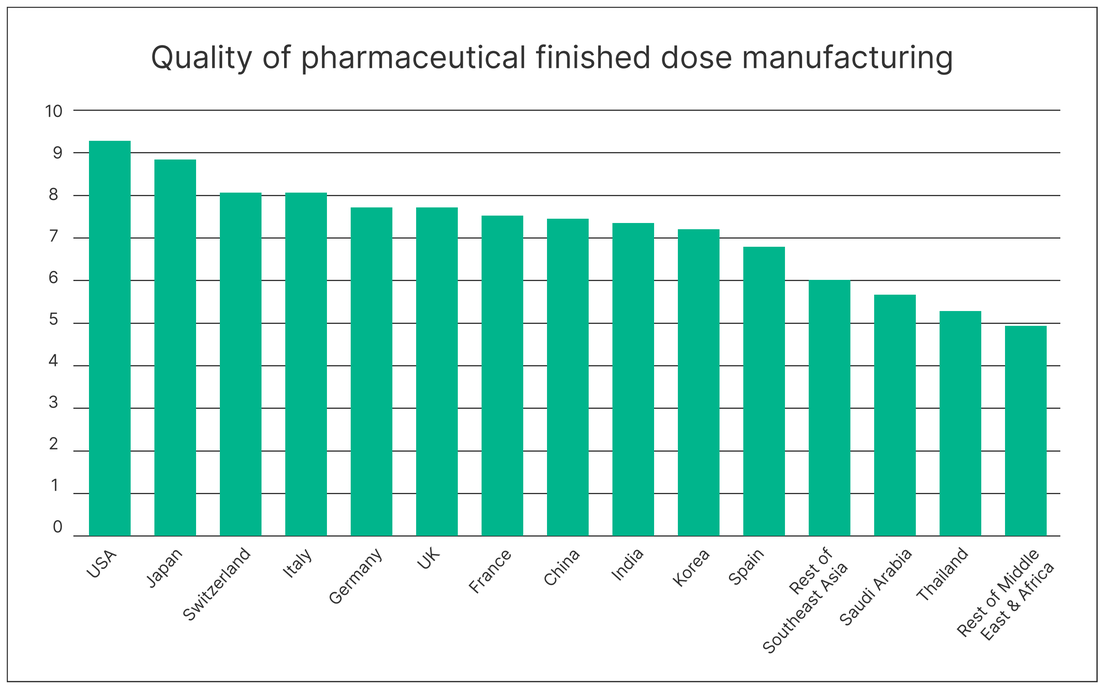
India has retained its position at the head of the table and unsurprisingly has further improved its score [8.1] in a year of positive sentiments. The country, buoyed by a wave of positive stories, growth in the CDMO sector, and an expected medium-term surge of CRO services – accelerated by BIOSECURE

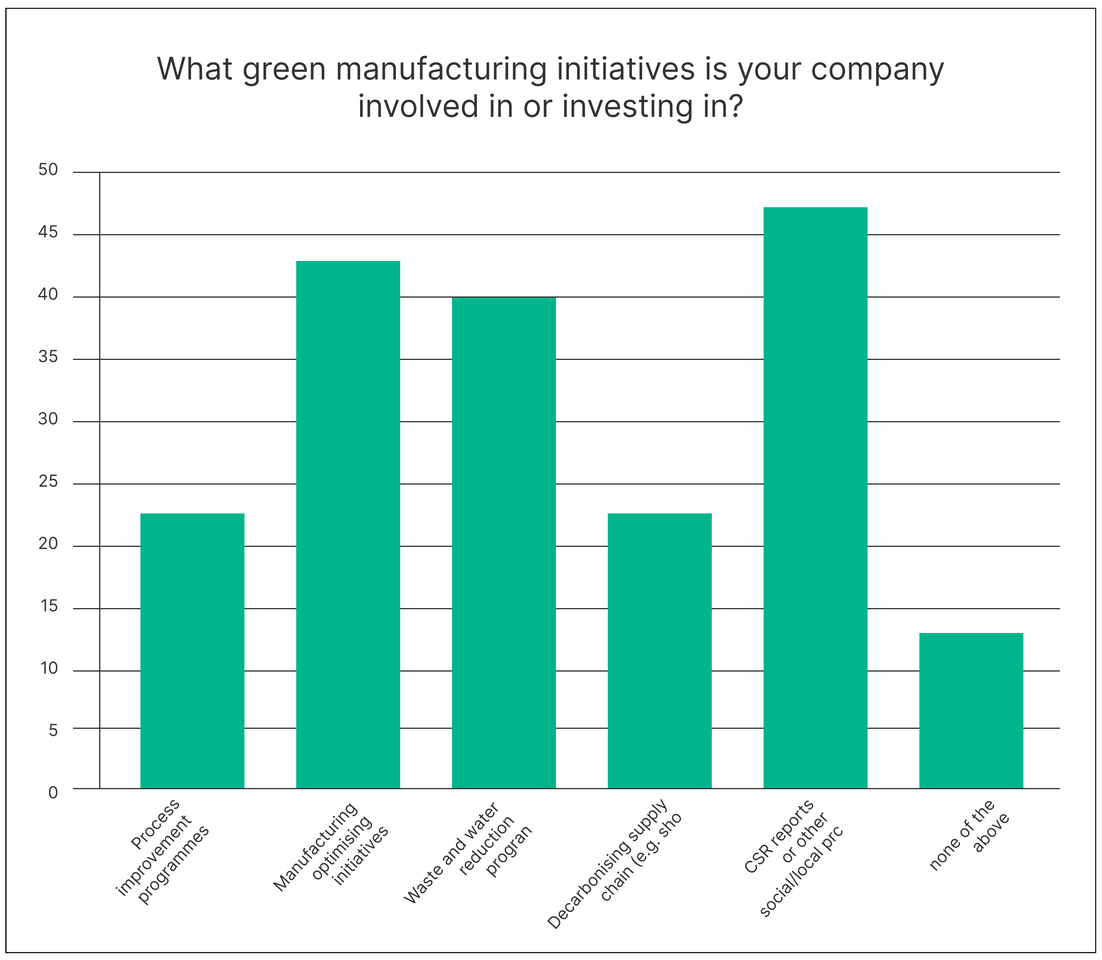
France having plummeted down the rankings last year has clawed back some ground – improving to 11th from last place – but is still performing weakly compared with its historical averages. China despite the ongoing uncertainty with macro tensions with the United States is performing steadily – largely retaining its year-on-year score [at circa 7].

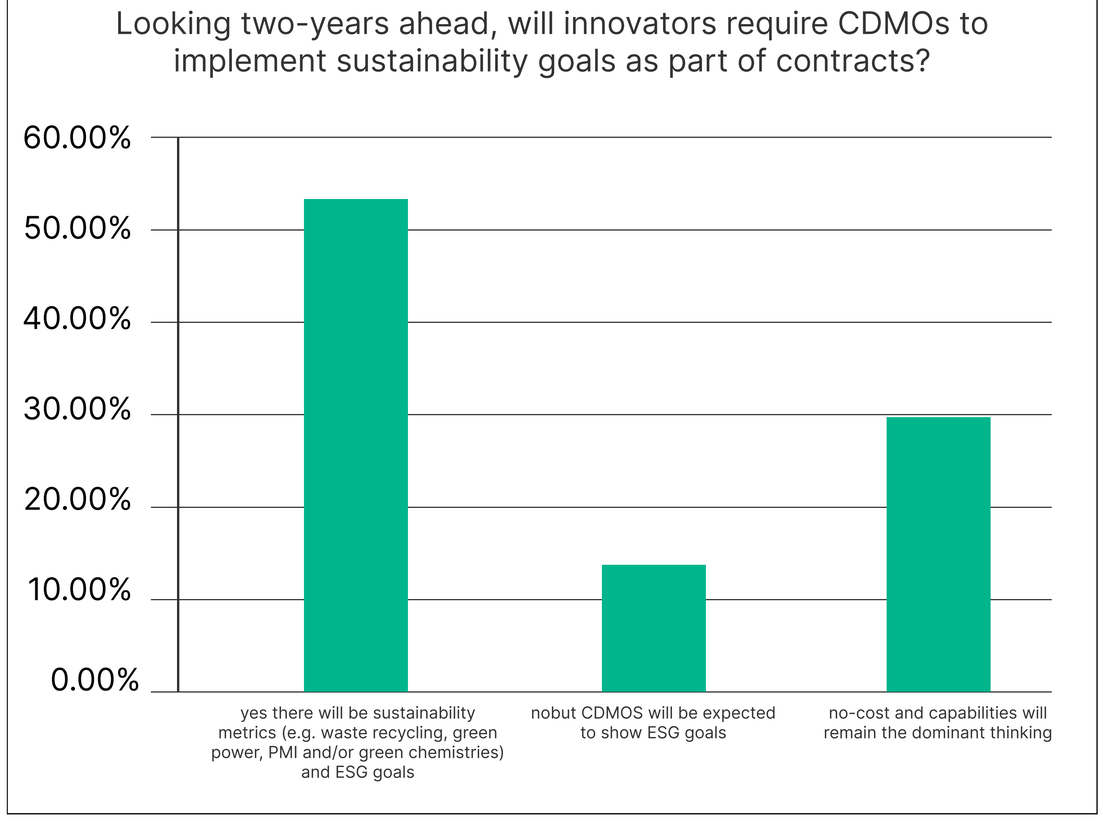


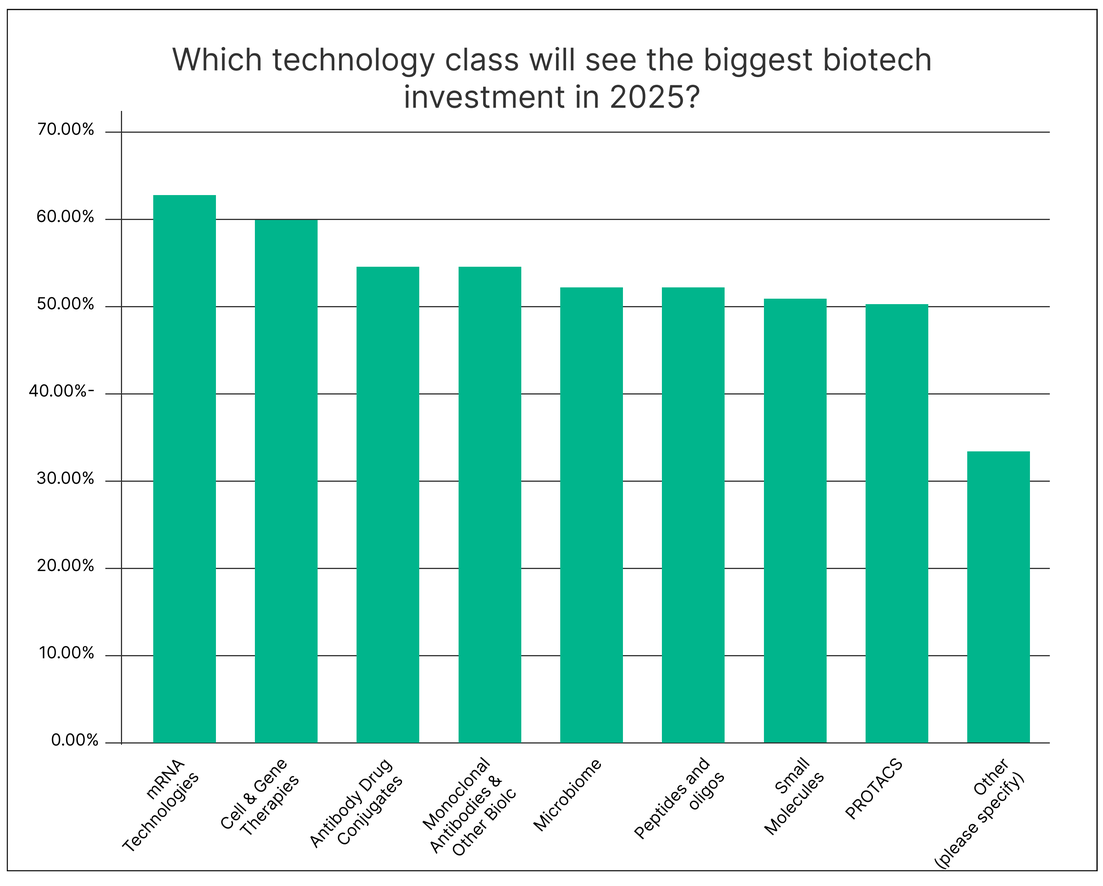


47. https://www.ft.com/content/46ab3c55-21c1-4941-ad0d-0cd27a7c593c
48. https://www.reuters.com/markets/europe/german-industrial-orders-rise-39-june-2024-08-06/
49. https://www.telegraph.co.uk/business/2024/08/25/germanys-economic-woes-much-more-deeply-rooted-britain/
50. https://www.farmaindustria.es/web/otra-noticia/espana-es-el-pais-de-europa-con-una-mayor-participacion-en-ensayos-clinicos-de-nuevos-medicamentos/
51. https://ionanalytics.com/insights/mergermarket/coming-to-the-boil-spanish-pharma-ma-simmers-as-country-tops-clinical-trials-leaderboard-dealspeak-emea/
52. https://www.investinspain.org/en/news/2024/farmaindustria









Report conclusions

The 2024 CPHI Annual Report paints, despite some short-term concerns, a compelling growth narrative for the medium term of the pharma, biotech and associated outsourcing sectors. For example, while investment (both VC and PE) has been slow to recover and filter through into outsourcing, over two thirds of novel therapies – particular complex drugs – are now discovered by biotechs, which are much more reliant on CDMO services meaning a faster growth as capital is released[53]. Significantly, there are also now more targets than at any point in history [20,000+][54] and attrition rates are improving with potentially step-change improvements in manufacturing costs and timelines ahead, so medium term prospects through to 2030 look robust.

The stock market – AI hype and September crash aside[55] – has also shown impressive resilience, signalling strong investor confidence in the sector's long-term potential. In fact, most biotech and leading CDMO stocks a have recovered from a difficult 2023 and are now once gain above pre-pandemic valuations.

A key factor driving this optimism is the anticipated surge in capital deployment. Private equity (PE) firms are expected to make significant acquisitions in 2025, while VC funding, which has been on hold, is almost certain to flow again soon. It should be noted this report anticipated a faster return of funding last year, but this does not negate this prediction being accurate today and moving into 2025.

In fact, this capital influx means, once deployed, that 2025-27 will likely be some of pharma's best ever years for growth and therapy approval rates – with CDMO capacity once again potentially strained. The other advantage for accelerating innovation is that CMO capacity is growing and will reach 60% of total capacity available in largest [top ten] companies by 2028 [or 52% of all available capacity when grouped together with hybrid companies – see Dawn Ecker's article in this report for more details]. Why is this significant? Because in the United States there are currently over 1,800 biopharmaceutical products in some stage of clinical development and the majority (~88%), are produced in mammalian cell culture systems. These biotech companies in most cases do not have commercial facilities, so this improved access will help supercharge the next era of MAb approvals – as even smaller biotechs will be able to access appropriate capacity quickly.

53. https://www.norstella.com/small-biopharma-end-to-end-cdmo-partnerships-accelerate-development/
54. https://www.statista.com/statistics/791288/r-and-d-pipeline-drugs-worldwide-by-phase-development/
55. https://www.ft.com/content/eb21baea-6050-42b2-a17a-c1122e9ae8b4

In small molecule manufacturing, our first ever European Manufacturing [hub] index identified Lombardy as Europe's preeminent region for API and small molecule production. However, the area is also now building a stellar reputation as location for the switch to advanced manufacturing and biologics. Similarly, the European Biotech [Hub] Ranking reflects a landscape that is becoming increasingly competitive. London and the Golden Triangle remain dominant, but regions like Basel are catching up, while Barcelona has slipped slightly on last year's impressive second place. Despite this, the overall trend suggests a narrowing gap between major biotech hubs, indicating that regional centres are becoming more attractive for biotech innovation and investment is becoming more dynamic – with Europe as a collective beginning to rival the output of the nine major US centres[56]. This increased competitiveness, combined with innovation happening across the continent, sets a strong foundation for the future.

In terms of contract services, the outlook is similarly positive. The cooling seen in early 2024 has given way to renewed growth, with only 7% of the industry reporting a negative outlook for the next 18-months. The demand for contract development and manufacturing organizations (CDMOs) and contract research organizations (CROs) is likely to grow, and with uncertainty at both WuXi and Catalent – demand could outstrip supply for the most qualified CDMOs. In fact, this shift in prospects has seen CDMOs and CROs surpass biotech and AI companies [which dominated the investment landscape last year] as the most appealing investment options.

However, this report also emphasizes the need for evolution within these sectors. The long-term projection is that both CROs and CDMOs will need to evolve more quickly than in the past to meet the demands of next-generation medicines. Biologics, peptides, and advanced therapies are expected to increasingly dominate growth in the coming years, requiring CDMOs to adapt their capabilities to handle these complex modalities. For instance, biologics have seen a steady rise in FDA approvals, with 17 new approvals in 2023, and this trend is expected to continue. Additionally, the rapid rise of Tides drugs, which blur the line between small molecules and biologics, presents both a challenge and an opportunity for CDMOs. Focus has mostly centred on the 'fill finish' component for injectables, with big pharma investing billions in plants, yet very few CDMOs specialise in peptide actives – and even fewer have the capabilities to take these from discovery though to commercial supply. If R&D rates and consumer demand are sustained, both types of CDMO facilities will need to be expanded.

Similarly, the innovation happening in next generation biologics and advanced therapies is not only driving demand, but also creating new opportunities for profitability. With improved linker technologies and broader payload options, antibody-drug conjugates (ADCs), after a quite 2024, will likely see at least three approvals in 2025. MAbs will potentially see approvals in the teens, while in 2023 the industry saw a record five cell and gene therapy approvals – suggesting we will now see consistent and rising approvals numbers [after many years of promise yet slow approval rates][59].

Meanwhile, PROTAC drugs are a significant medium- and long-term opportunity, and it's very possible that once we gain a first approval, we will see a similar cascade in activity not dissimilar to peptides – albeit without the 'supercharged' demand of weight loss drugs. What is interesting is that very few CRDMOs are active in this area and, those that invest now, will likely see tremendous demand in 2-3 years' time assuming the technology further matures. Put this together and we forecast that a new approval record will be secured in the next few years, with FDA approvals rates routinely above 40 and possibly 50 in most years.

Geographically, India is expected to be the biggest medium-term beneficiary for CRDMO services, driven by its strength in chemistry and biology. However, the United States also stands to gain, particularly as domestic production [CMO] becomes a priority for supply chain security. But much further investment is needed if the big goals are to be achieved, with rhetoric alone not sufficient to transform a multi trillion-dollar industrial base. However, the creation of US domestic starting martials – if it ever happens – is at least a decade or more away. The other nagging uncertainty that will likely reach a crescendo by the end of 2024 is BIOSECURE and the likelihood is a version will pass [70%[60]] – probably encased within a bigger act and the National Defense Authorization Act [NDAA] has been muted as one option – but what the specifics of this are, and its timelines, are well beyond this report's powers of prediction.

The conclusion is that despite a more difficult 18-months – with smaller CDMOs known to be struggling – the industry is in a strong position to build from 2025 through to 2030, with the promise of significant growth and profitability on the horizon. The capital is there, the innovation is there, and the market demand is there. So the industry's key players need to react to the future growth, rather than base the next 18-months on what happened in the preceding 18 – to seize the moment and shape the future of pharma, with regions like Lombardy at the forefront of the ongoing manufacturing transformation in Europe. If investment can be made and commitments sustained beyond the next election, the US is also poised further grow its manufacturing base – particularly for innovative medicine – while India increasingly, if gradually, is replacing China as the world's research powerhouse, bridging the translational gap in discovery and commercial supply with CRDMO services. These two trends are likely to sustain over the medium term and will profoundly shape discovery and supply networks built in the next 5-years. What we will see in five years, is greater CRO research options, but also, a more competitive manufacturing space – where decisions about clinical and commercial supply are made based on security, robustness and access to technology [gone are the days where outsourcing is a simple cost/gram, API or tablet unit measure].

56. https://www.biospace.com/hotbeds
57. https://www.reuters.com/business/healthcare-pharmaceuticals/weight-loss-drugs-fuel-boom-firms-that-fill-syringes-2023-10-09/
58. https://www.bioprocessintl.com/facilities-capacity/eli-lilly-novo-nordisk-expand-operations-amid-glp-1-drug-boom
59. https://www.nature.com/articles/s41587-024-02166-7
60. https://www.bloomberg.com/news/articles/2024-09-09/after-tiktok-china-biotech-next-to-face-wrath-of-us-congress

Part 01

Biologics and Advanced Therapies

Mammalian Biomanufacturing Trends – An Overview of the 2000-2028 Mammalian Biomanufacturing Supply

Dawn M. Ecker

Managing Director of bioTRAK Database Services,
BioProcess Technology Group, BDO USA, P.C.

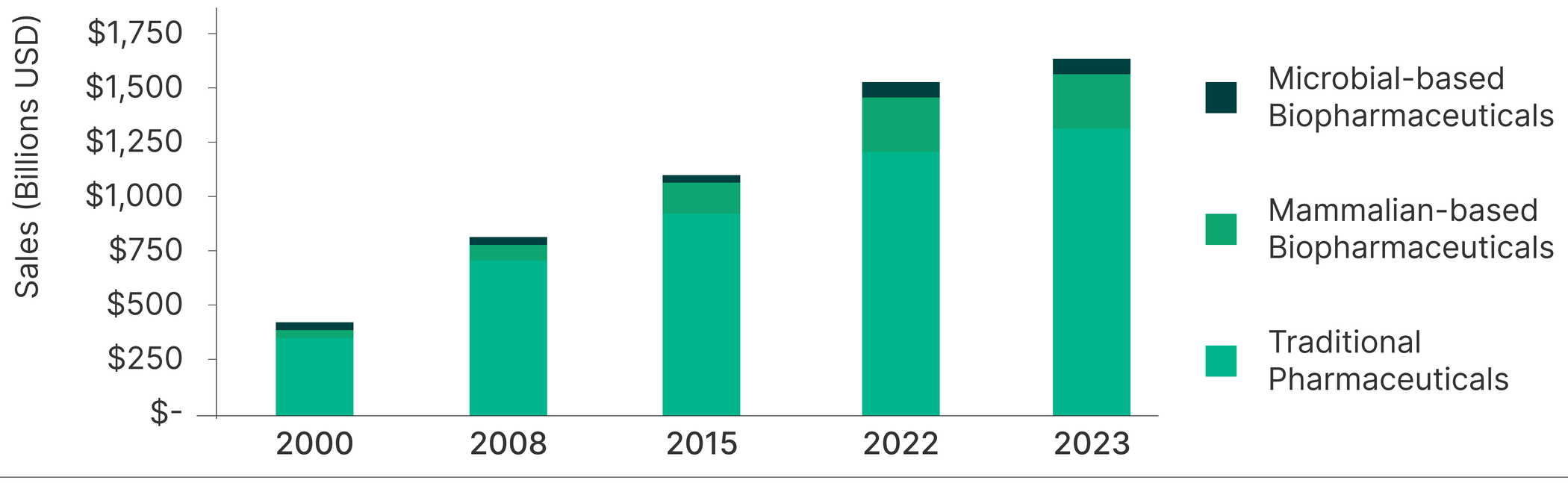
Trends Overview 2000-2028

- Biopharmaceuticals, more specifically mammalian-based products have grown steadily since their emergence in the global pharmaceutical market, with a marked shift in the overall product profile when compared against historical product profiles.
    - This product profile shift is not surprising given the advances in antibody discovery, development, and manufacture over the last two decades.
- To ensure patient access to biopharmaceuticals, companies with biologics manufacturing capacity have increased their capacity significantly over the last two decades from nearly 600kL in 2000 to just over 6,700kL today and capacity is projected to increase to nearly 9,000 kL by 2028.
    - Although Product companies have traditionally held the most capacity, CMOs are projected to increase their control of capacity so that by 2028, CMOs will hold nearly 40% of all capacity and will represent four of the top five capacity holders in 2028.
    - While Europe has and will hold the largest amount of manufacturing capacity, within the CMO sector, Asia has a larger proportion of capacity than Europe or North America.

Since the approval of the first recombinant therapeutic (Humulin) in 1982 and the first monoclonal antibody (MAb) OKT3 (muromonab-CD3) approval in 1986, the biopharmaceutical industry has evolved significantly. Product profiles of marketed products and the preceding development pipeline have progressed from a mix of antibody-based products and non-antibody products to a nearly homogenous antibody-based product profile. Similarly, just as the industry's product profile has evolved, so has the mammalian-based manufacturing landscape – with significant changes in capacity volumes, capacity type and control, as well as scale and type of reactors. This article provides a high-level overview of the past, present and future of the manufacturing supply of mammalian-based biopharmaceuticals with a special focus on contract manufacturing organizations (CMOs).

As a part of the global pharmaceutical product landscape, biologics, more specifically recombinant biopharmaceutical products have emerged as a thriving sector within the industry since the 1982 approval of Humulin. Representing just over 5% of all sales in 2000, biopharmaceuticals sales have increased to represent over 20% of all pharmaceutical sales in 2023. The growth of this sector, as displayed in Figure 1, is being driven by mammalian-based products which first entered the market with the 1986 approval of OKT3. Mammalian-based biopharmaceutical sales have yielded a 2000-2023 annual growth rate of 14.5%, nearly 2.5 times the growth rate of traditional pharmaceuticals (5.8%) during the same period.

Figure 1: Sales Growth of the Overall Pharmaceutical Market

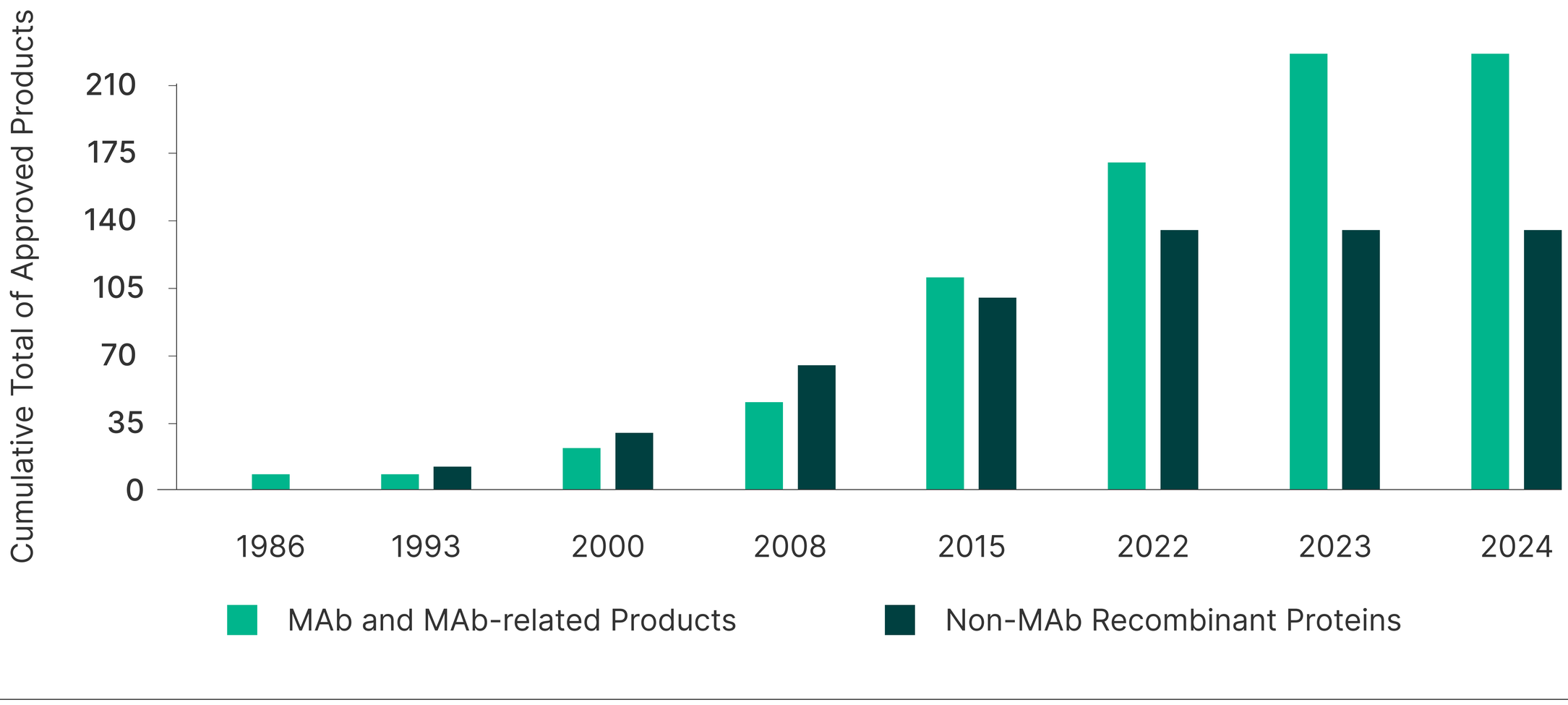


1. BDO considers the product group of "antibodies and antibody-based products" to include naked monoclonal antibodies, antibody fragments, bispecific antibodies as well as conjugates of any antibody or antibody fragment, and also includes Fc-fusion proteins and other antibody related products.
2. BDO considers "non-antibody products" as a product group which includes recombinant blood proteins, cytokines, enzymes, hormones, non-antibody fusion proteins as well as other recombinant proteins.

In 2000, the top five selling recombinant proteins generated nearly $8B in sales and included two mammalian hormones (Procrit and Epogen) and three microbial-based products, two cytokines (Neupogen and PEGIntron) and a single insulin, Humulin. In contrast, the top five products in 2023 generated over $80B in sales, with four of the five products classified as antibody-based products (Keytruda, Humira, Dupixent, Stelara) with sales totaling nearly $62B. The fifth product, Ozempic/Wegovy, posted just over $18B in sales and is a microbially-expressed glucagon-like peptide-1 (GLP-1) receptor agonist.

Focusing on mammalian-based products, this product profile shift is evident in the overall profile of products approved for the United States and European markets - transitioning from a majority of non-antibody recombinant proteins (67% in 1993), to a slight majority of non-antibody recombinant proteins (56%, 2000) to a majority of antibody and antibody-related products (70%, 2024) as displayed in Figure 2.

Figure 2: Approved Mammalian-based Biopharmaceuticals, by Product Type

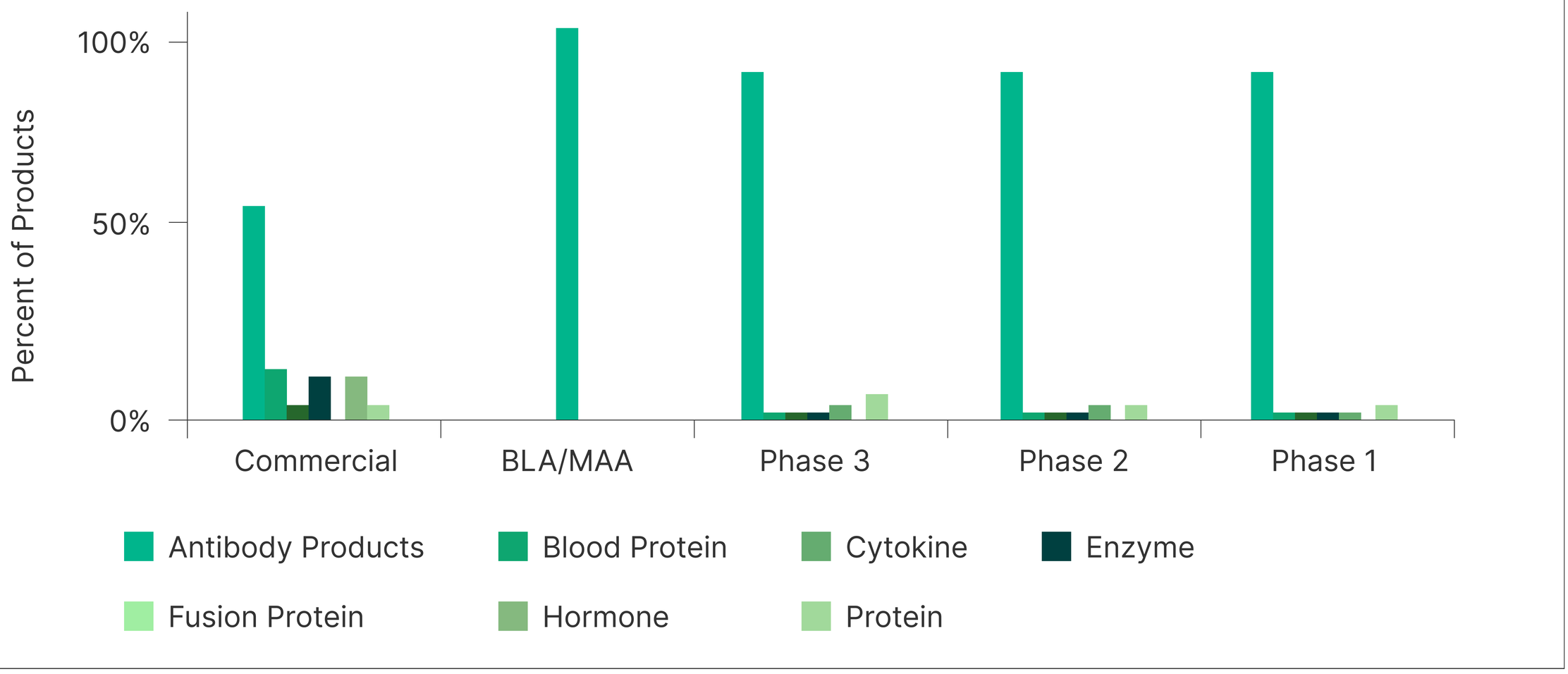


To provide additional context around this segment of the pharmaceutical market, BDO's proprietary bioTRAK® database of biopharmaceutical products and manufacturing capacity estimates that as of June 1, 2024, there are currently over 1,800 biopharmaceutical products in some stage of clinical development in the United States or Europe. The majority (~88%), are produced in mammalian cell culture systems. We evaluated the current distribution of mammalian products by product type and phase of development to further refine the biopharmaceutical manufacturing market. Figure 3 shows the current distribution of product types, including antibody products, blood proteins, cytokines, enzymes, fusion proteins, hormones, and other recombinant proteins, by phase of development. Antibody products are the dominant commercially-marketed product type at 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.

[3] Adapted from: IQVIA Institute for Human Data Science. Global Use of Medicines 2024. Outlook to 2028 [Internet]. 2024 Jan [cited 2024 Sep 1]. 60 p. Available from:

[4] https://www.iqvia.com/-/media/iqvia/pdfs/institutereports/the-global-use-of-medicines-2024-outlook-to-2028/iqvia-institute-global-use-of-medicines-2024-forweb.pdf

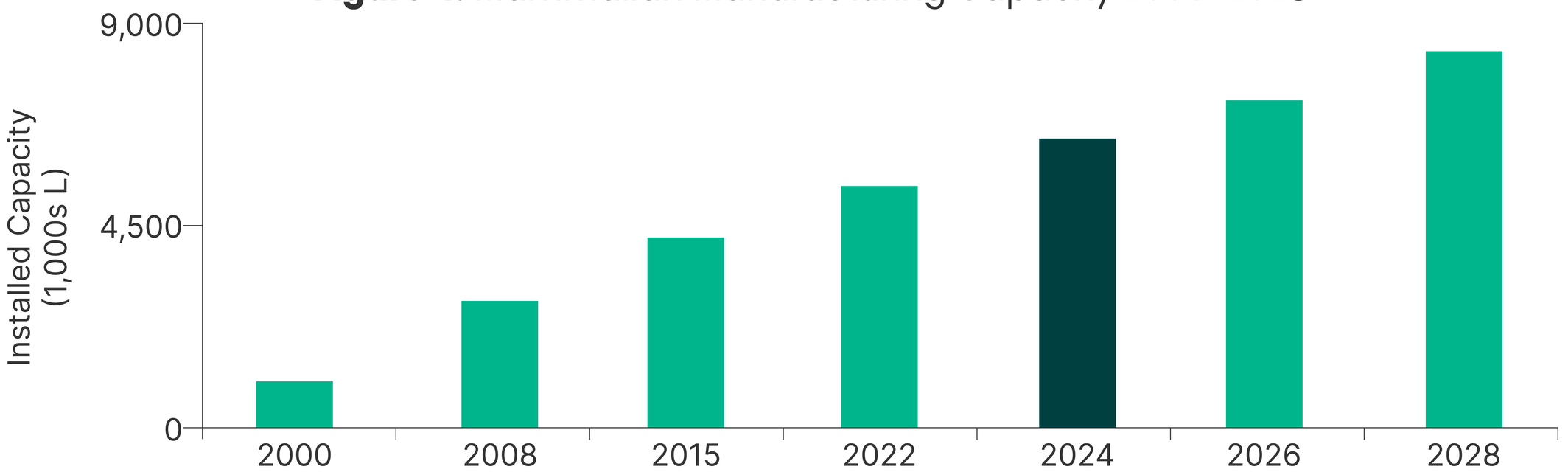
Figure 3: Current Distribution of Mammalian Products by Product Type and Phase of Development



The product profile shift from all recombinant proteins to a majority of antibody-based products is not unexpected. Antibody discovery, development and manufacture were initially enabled by in vivo methods of antibody generation. By the 1990's, the use of yeast and phage display technology began to accelerate the industry's interest in discovery of antibodies leading to a product profile favoring antibody products. Over the last few years, antibody discovery and development are being further accelerated and expanded by in silico modeling leveraging today's computing capacity to predict epitope binding, enabling the rational design of antibodies and sequence optimization to ensure developability. We predict that these technological advances in conjunction with harnessing "big data" and artificial intelligence will allow the industry to discover even more targets and develop more antibodies which will continue to fuel the development pipeline and will likely continue to shift the mammalian-based biopharmaceutical profile towards an even higher proportion of antibody-based products.

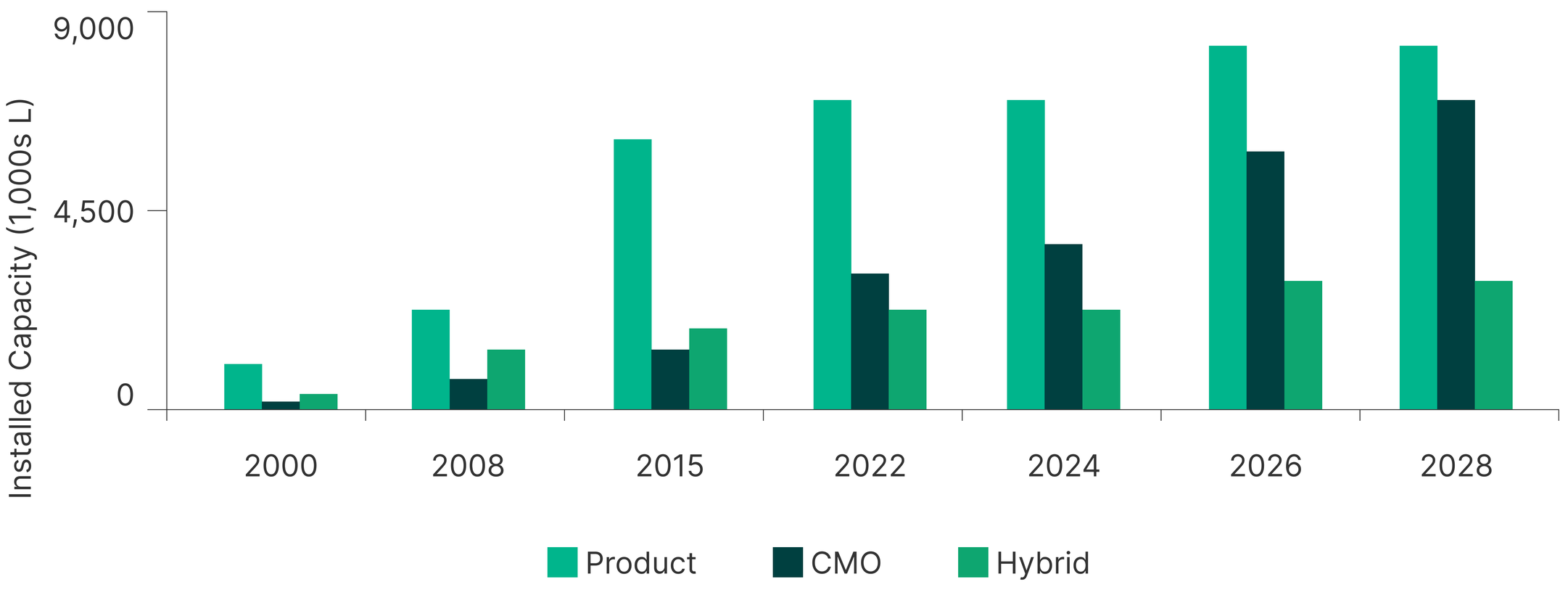
Whether commercially approved or in development, the manufacture of each of these products requires access to mammalian production capacity and like the changes seen in the product profile over the last two decades, mammalian manufacturing capacity has also undergone changes and has increased its manufacturing capacity significantly. From nearly 600kL in 2000, to approximately 6,750kL as of Jun 4, 2024, and we predict growth to continue to nearly 9,000kL by 2028, an estimated 15-fold increase from 2000 and a 1.3-fold increase from 2024 as shown in Figure 4.

Figure 4: Mammalian Manufacturing Capacity 2000-2028



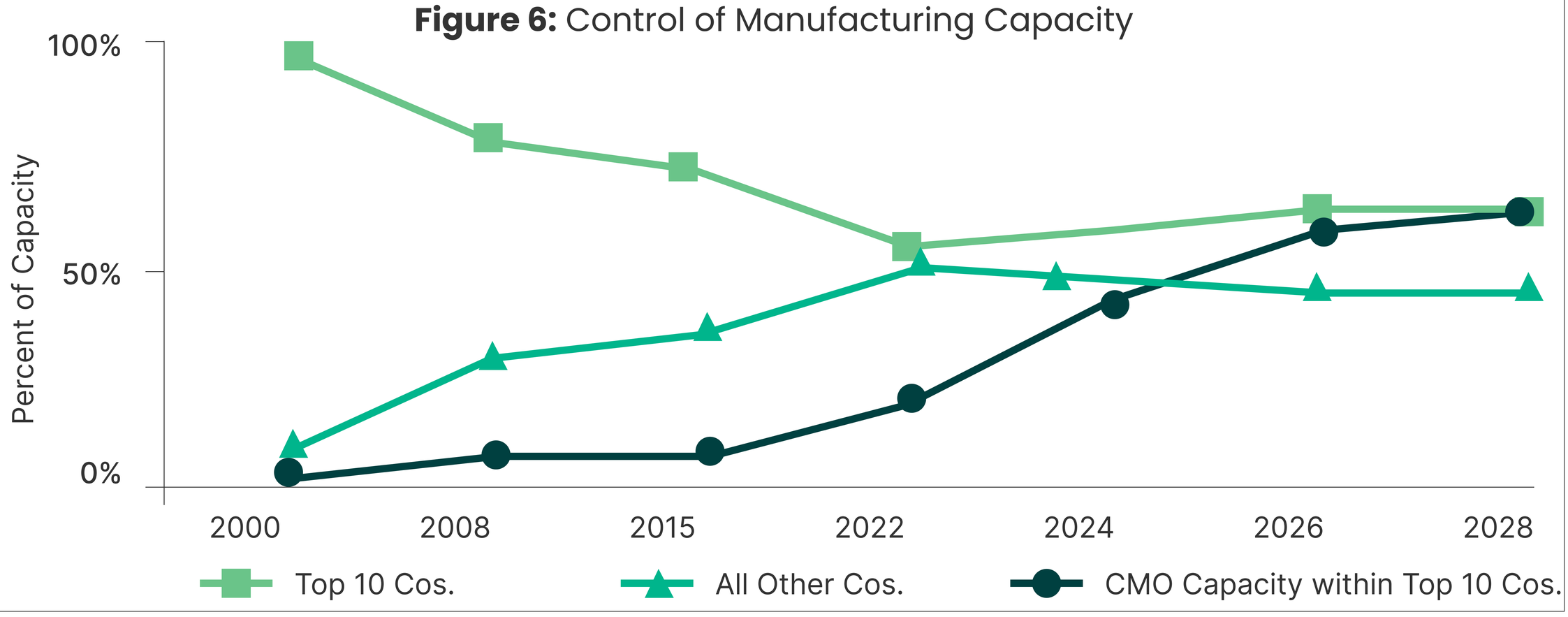
Despite the increases in aggregate capacity, not all capacity is equally available throughout the industry. As of 2024, product companies, defined as companies focused solely on product development, control nearly 60% of the installed mammalian cell culture capacity. CMOs (strict fee for service manufacturers) 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 (28%, 15% respectively) as displayed in Figure 5. This distribution of capacity changes in 2028, with Product companies controlling just half of the installed capacity, while CMO capacity increases nearly 40%, with Hybrid companies decreasing slightly to 14%. These proportions are significantly different than those in 2000, where Product companies possessed nearly 70% of all capacity, Hybrid companies holding nearly 25% and CMOs holding just over 7.5%.

Figure 5: Distribution of Mammalian Capacity by Company Type



While Product companies have maintained control over the majority of cell culture capacity over the last two decades, the distribution of this capacity continues to be concentrated (>50%) within ten companies, as shown in Figure 6. In 2000, the top ten companies controlled over 90% of the available capacity, this top ten proportion has shifted to 55% today and is predicted to shift slightly to 58% in 2028. When CMO capacity within the top ten capacity holders was analyzed, CMOs held very little (<5%) of the top ten capacity in 2000, however within the top ten, CMOs have increased their current share to 42% and, by 2028, they are projected to hold nearly 60% of the capacity within the top ten capacity holders.

Figure 6: Control of Manufacturing Capacity



To provide additional details on the top ten capacity holders, **Table 1** displays the top ten companies for several timepoints in the 2000-2028 timeframe and includes company type, rank, and proportion of capacity (top five only). As emphasized in **Figure 6**, the capacity possessed by CMOs in 2000 was limited, but has expanded significantly with CMOs constituting four of the top five capacity holders.

Table 1: Control of Manufacturing Capacity

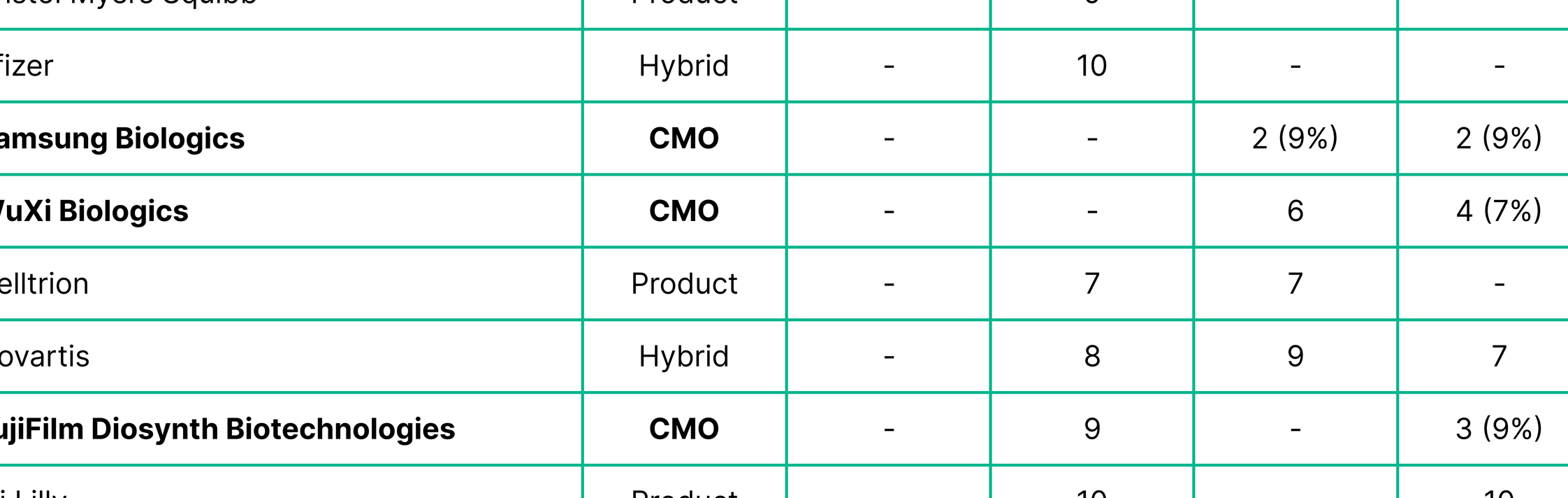
While the bioTRAK database tracks capacity able to manufacture to US and EU manufacturing standards, we are agnostic to the location of a manufacturing facility. Figure 7 illustrates the geographic distribution of the manufacturing facilities and chronicles the globalization of biopharmaceutical manufacturing. In 2000, mammalian manufacturing was primarily based in North America (>75%) with some capacity in Europe and no capacity located in Asia. Fifteen years later, Asia and Europe have built significant capacity, while in 2022, nearly 40% of all

mammalian capacity is in North America, followed by Europe (37%) and Asia (14%). Currently with minimal capacity growth in North America and healthy growth in both Europe and Asia, Europe now hosts the majority of mammalian capacity, which is expected to continue into 2028. The projected annual growth rates (2024-2028) for Asia (8.2%) and Europe (8.1%) exceed that of North America (5.2%), with Europe responsible for the largest proportion of new capacity installed by 2028 (910kL, 43%).

4 **Bold** denotes CMO based capacity.

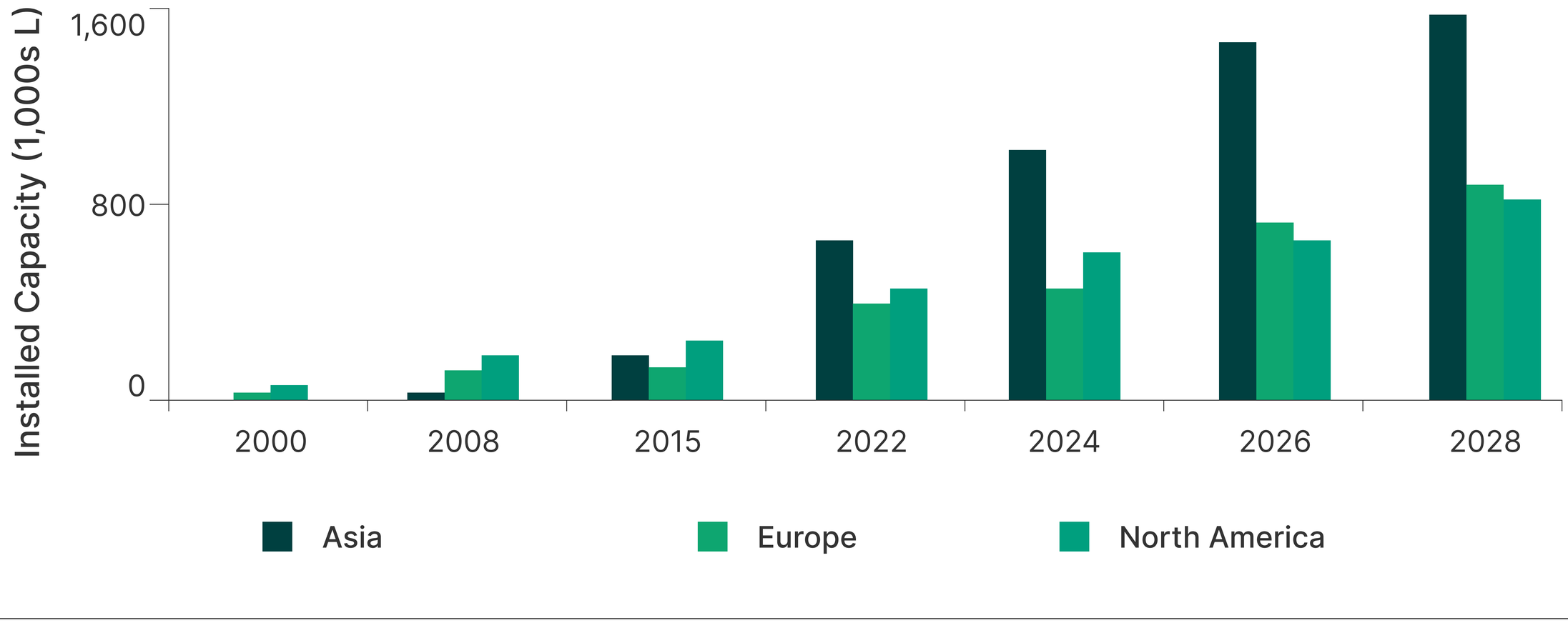
Company	Company Type	Rank (% of Capacity) 2000	2015	2028	2000
Genentech (acq. by Roche in 2019)	Product	1 (32%)	-	-	-
Boehringer Ingelheim	Hybrid	2 (21%)	2 (6%)	4 (6%)	6
American Home Products (became Wyeth in 2002, acq. by Pfizer 2009)	Product	3 (11%)	-	-	-
Genzyme (acq. by Sanofi in 2011)	Product	4 (9%)	-	-	-
Amgen	Product	5 (7%)	5 (5%)	8	8
Lonza 4	**CMO**	**6**	**4 (6%)**	**1 (10%)**	**1 (9%)**
Collaborative Corp.	Product	7	-	-	-
ICOS Biologics (acq. by Eli Lilly in 2007)	Product	8	-	-	-
Biogen	Product	9	6	10	-
Schering AG	Product	10	-	-	-
F. Hoffmann-La Roche	Product	-	1 (22%)	3 (7%)	5 (6%)
Johnson & Johnson	Product	-	3 (6%)	5 (4%)	9
Sanofi (acq. Genzyme in 2011)	Product	-	7	-	-
Merck KgAa	Product	-	8	-	-
Bristol Myers Squibb	Product	-	9	-	-
Pfizer	Hybrid	-	10	-	-
Samsung Biologics	**CMO**	-	-	2 (9%)	2 (9%)
WuXi Biologics	**CMO**	-	-	6	4 (7%)
Celltrion	Product	-	7	7	-
Novartis	Hybrid	-	8	9	7
FujiFilm Diosynth Biotechnologies	**CMO**	-	9	-	3 (9%)
Eli Lilly	Product	-	10	-	10

Figure 7: Geographic Distribution of Capacity



With the significant capacity CMOs currently possess and are predicted to install by 2028 coupled with the extensive growth in capacity in Asia and Europe, we determined the geographic distribution of CMO capacity as depicted in Figure 8.

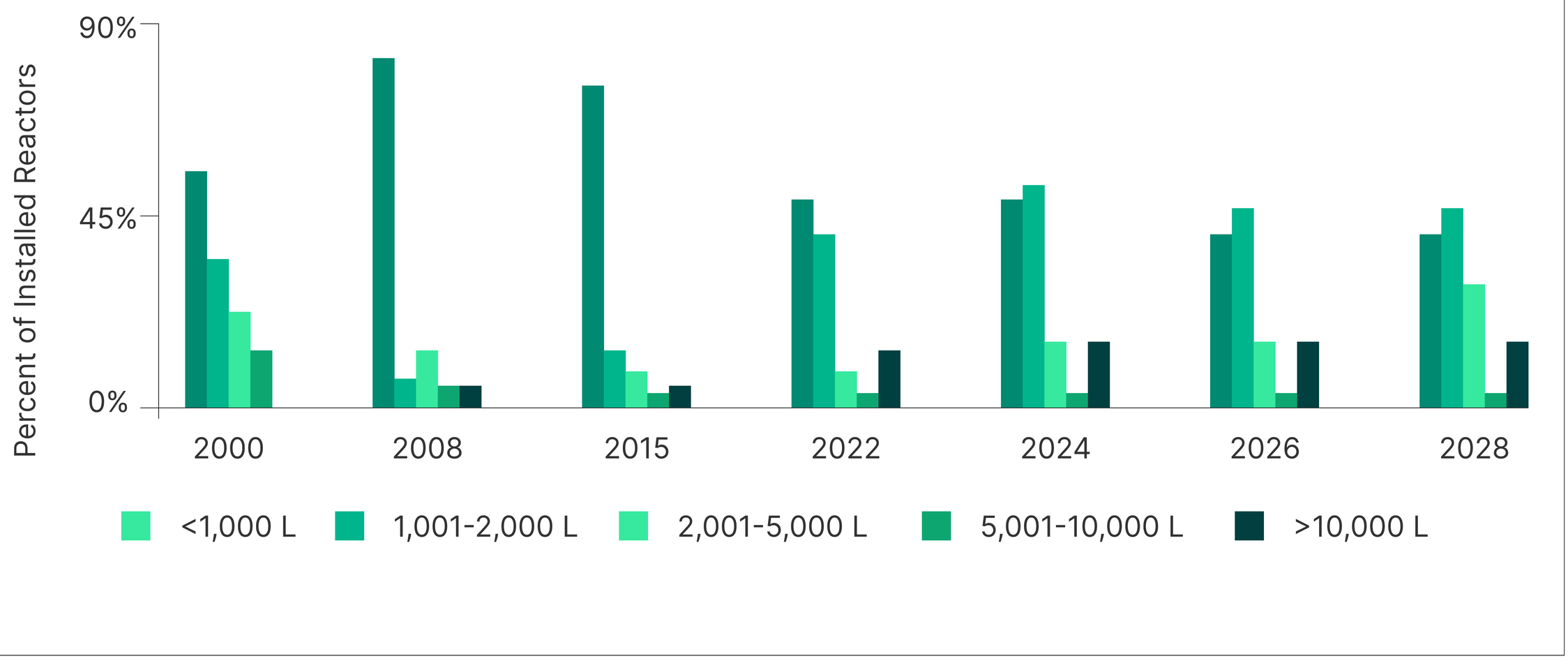
Figure 8: Geographic Distribution of CMO Capacity



While Asia may currently not possess largest proportion of capacity installed (in aggregate), it does have the largest quantity of CMO owned capacity. Beginning in 2022, just over 45% of all CMO capacity was located in Asia – which is predicted to continue through 2028. During this time, Europe and North America remain consistent, each possessing just over 25% of all CMO capacity.

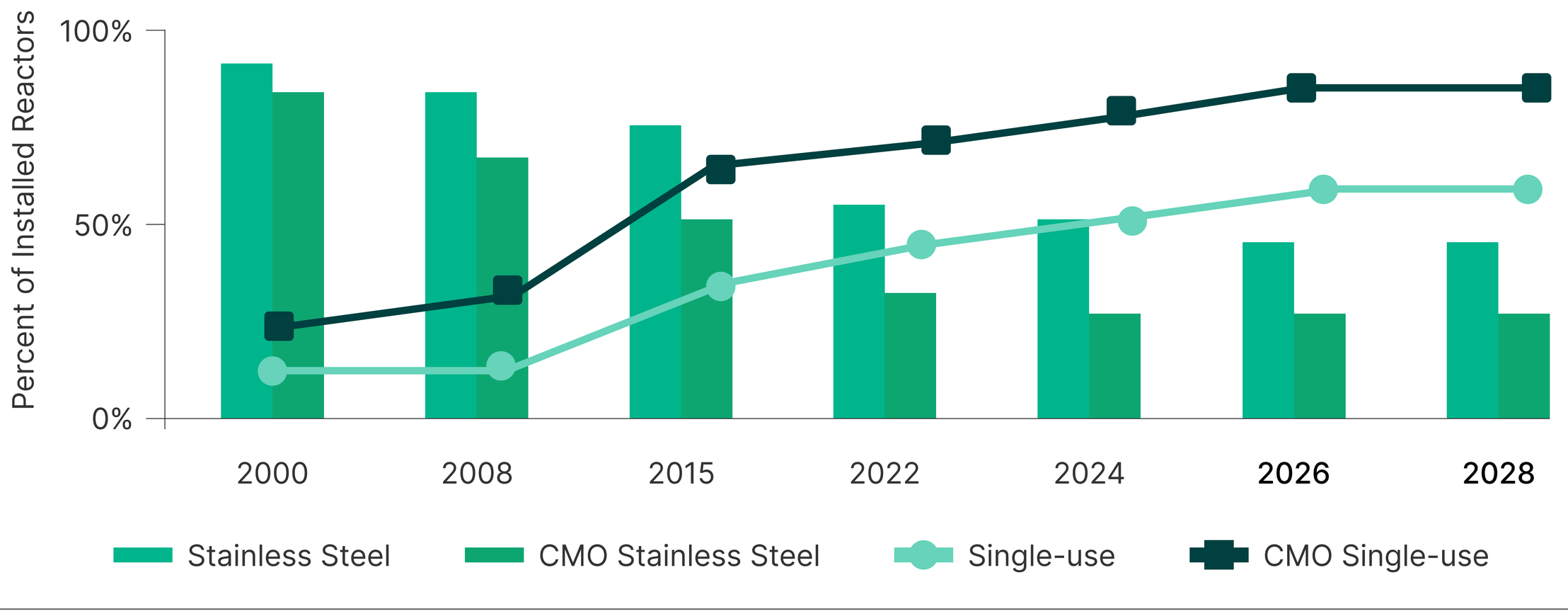
If we analyze the number and scale of bioreactors online and projected to be online between 2000 and 2028 owned by CMOs (Figure 9), it is evident that during this time span, the majority of bioreactors owned (or projected to be owned) by CMOs are in the sub-2,000L scale. Interestingly, beginning in 2008, there is a noticeable decrease in the proportion of <1,000L scale bioreactors while there is a noticeable increase in the 1,001-2,000L scale of bioreactors, interestingly, single-use bioreactors are highly available at this scale.

Figure 9: Percentage and Scale CMO-Owned Bioreactors



Since the launch of the first single-use bioreactor, the rocking WAVE Bioreactor, in 1996 and the first stirred-tank reactor by Hyclone in 2004, use of these single-use systems was limited within the industry, with stainless steel bioreactors being the mainstay. Uptake has increased since industry-wide since 2008, achieving near parity in 2024 with the proportion of single-use bioreactors slightly greater than stainless steel beginning in 2026 (56%, 44% respectively) as displayed in Figure 10. Along with the industry's historic implementation of single-use and stainless-steel bioreactors, CMOs adoption of single-use bioreactors is also present. CMOs have adopted single-use technology more readily than the general industry, beginning in 2008 and steadily installing single-use bioreactors so that by 2024, over 70% of the bioreactors controlled by CMOs are single-use. This high utilization (over 70%) of single-use bioreactors is projected to continue through 2028.

Figure 11: CMO Adoption of Single-Use Bioreactors



Just as advances in antibody discovery and development were essential to the significant increase of antibody products in the pipeline, single-use bioreactors have enabled manufacturers, more specifically CMOs to create flexible, more nimble facilities with higher throughput, reduced cleaning and lowered utility costs all resulting in improved facility efficiencies.

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. Capacity is expanding to meet the manufacturing demand for these products, but control and location of capacity can affect accessibility. While the majority of capacity is (and has been) product-based, rather than CMO-based, contract manufacturers have (and 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. 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 adopting new technologies which will enable them to rise to the challenge of meeting the current and future 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.

The Waiting Game:
A Bottom Is Imminent For Bioprocessing In China With A Return To Growth Two Years Away

Vicky Qing Xia

Analyst at BioPlan Associates

The difficult times of today should be seen in the wider context of resetting an oversupply in the market – bursting an economic bubble if you will – so that the industry has strong fundamentals to grow from in 1-2 years' time, when consolidation has occurred, prices have reset, and talent is better allocated.

Introduction

Though a relatively young business with history less than one decade, the number and size of bioprocessing contract developing & manufacturing organizations (CDMOs) in China have been expanding robustly for several years. During 2017-2021, total market size of China bioprocessing CDMO has increased from RMB 2.93 billion to 15.9 billion with a CAGR of 52.7%, and it is projected that the market will reach RMB 49.4 billion in 2025 with a CAGR of 32.7%[1]. However, since the end of the pandemic, China's contract bioprocessing industry has entered a bitter winter. According to Wind, among the 35 publicly listed CXO companies which have published half year financial reports of 2024, 14 show decreased revenue and 23 show negative growth of net profit[2]. The situation for multinational bioprocessing CDMOs in China is even more challenging. On Jan, 2024, Lonza closed its bioprocessing facility in Guangzhou due to lack of business[3]. Other MNC bioprocessing CDMOs, including Thermo Fisher, Merck and Celltrion, have made strategic choices to downsize or sell their China operation as domestic peers grab more market share with cost competitiveness[4]. The slow-down of the industry has also impacted the bioprocessing vendors as quite a few bioprocessing CDMO put a hold on their capacity expansion. An industry insider in bioreactor business has pointed that the whole contract bioprocessing industry is losing its value to vendors since 2023[5].

Reasons leading to the current cooling down of the industry

1. Investment in Biotech/biopharma plummets

A main driver for CDMO growth in China is the biopharmaceuticals from domestic developers entering clinical pipeline and reaching commercial scale, which relies heavily on investment into the sector. Investment peaked in 2021 with over USD 20 billion, but drops to ~ USD 6 billion in 2023(Figure 1)[6]. Exit via IPO is also becoming more difficult. The number of IPOs in biopharma sector has plummeted from eight deals totaling RMB 18 billion in first half year of 2021 to just three deals totaling RMB 1.32 billion in first half year of 2024 (Figure 2)[7].

Figure 1: 2019-2023 Investment in China's Biopharma Industry (in hundred of millions of USD)

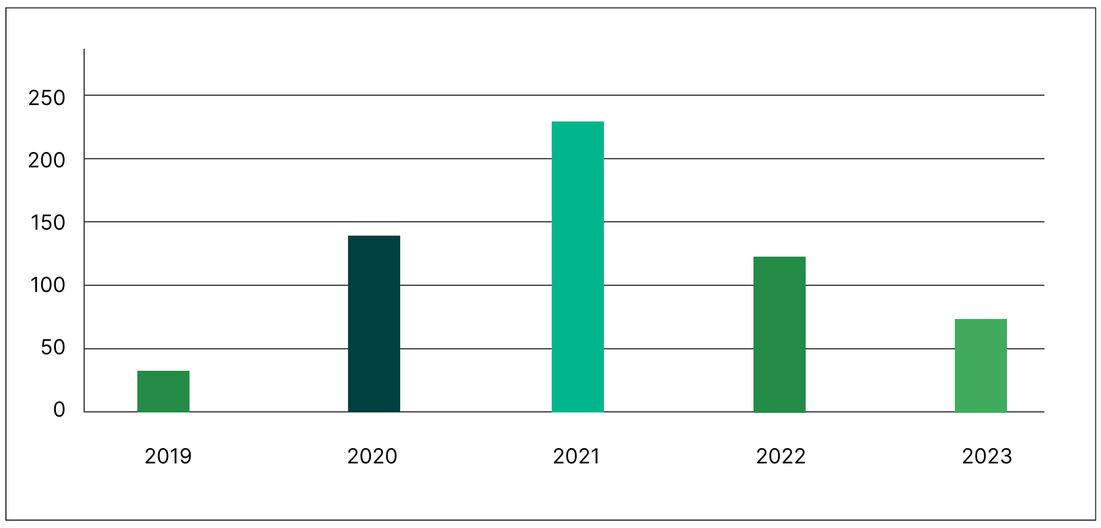
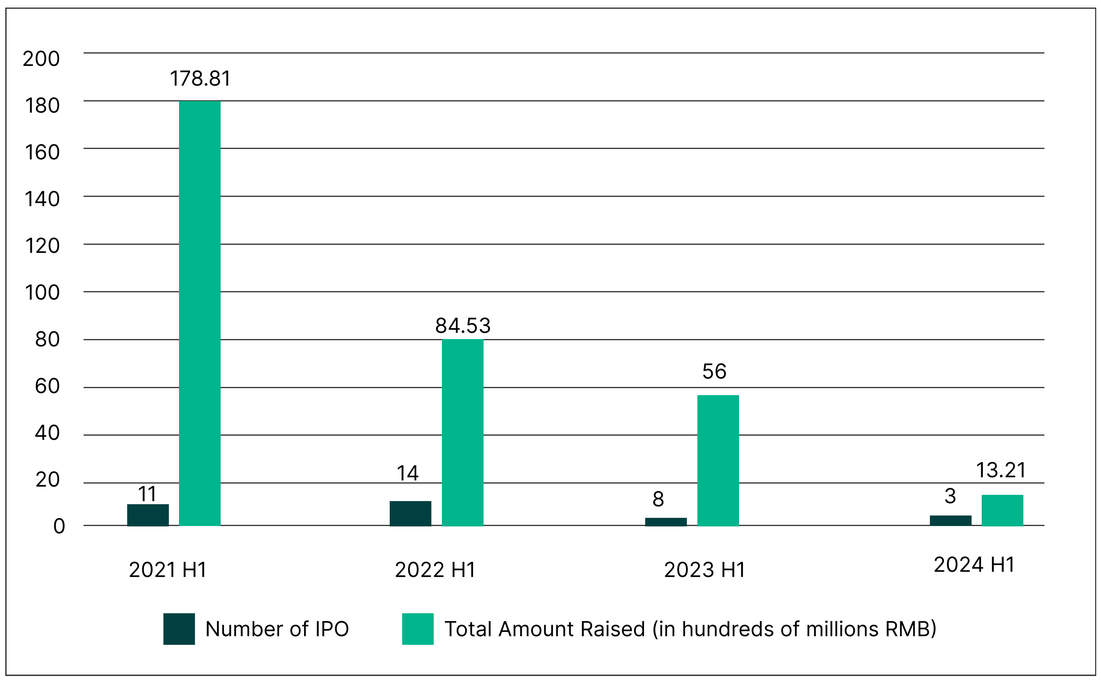


Figure 2: 2021-2024 First Half Year IPO



The cooling down of investors' enthusiasm is obvious in many industries, including real estate, luxuries, retail, etc. as China's whole economy slows down. Biopharma has been hit especially hard, as investors are beginning to realize that the domestic market for innovative biopharmaceutics may be less than what they expect it to be due to policy moves aimed at controlling drug prices. In 2022, China's national healthcare insurance spends RMB 48.18 billion on innovative drugs, which is only 1.96% of the total national healthcare spending while the same year 80% of the USD 580 billion US drug market is composed of innovative drugs[8]. 'Investors are getting much more cautious in biotech companies; it used to be the case that start-ups with IND in hand can easily raise money, now you have to have clinical pipelines to attract investment', as one industry insider puts it[9].

2. Worsening geopolitical tension also becomes an issue

On 7 March 2024, the US Senate Homeland Security and Governmental Affairs Committee advanced a bill, dubbed the BIOSECURE ACT, by 11-1 to the full Senate floor, which would limit US pharma companies from using certain Chinese manufacturing and trial service providers including WuXi AppTec, WuXi Biologics (Jiangsu, China), BGI Genomics (Shenzhen, China), etc, for security reasons. The BIOSECURE Act, which proposes banning certain "foreign adversary biotech companies of U.S. national security concern" from accessing federal funding, which means U.S. and other drugmakers would need to cut ties with the Chinese contractors by 2032 to retain their spots on Medicare and Medicaid. On 13 March, the Biotechnology Innovation Organization (BIO) announced it was parting company with WuXi after the company proactively ended its membership. Stock price of WuXi Biologics plummeted to multi-year lows after the news. According to WuXi Biologics' financial statement, in 2024 H1 total revenue dropped by 8.64% and net profit dropped by 20.20% due to the impact of the BIOSECURE Act. Though the Act only mentions a few Chinese names, the whole China's CDMO industry is deeply concerned that US clients may be reluctant to work with Chinese vendors due to supply chain security issues.

WuXi's predicament may be good news for its competitor in South Korea, Samsung Biologics. The company has been expanding its capacity rapidly in recent years. In June and July 2023, Samsung signed contract bioprocessing deals with Pfizer totaling over USD1.3 billion; it also renewed contract which is worth over USD 213 million with Roche to the end of 20274. It is widely believed that geopolitical tensions would benefit South Korean CDMOs targeting the US market.

3. Over-competition in China-based biologic CDMO

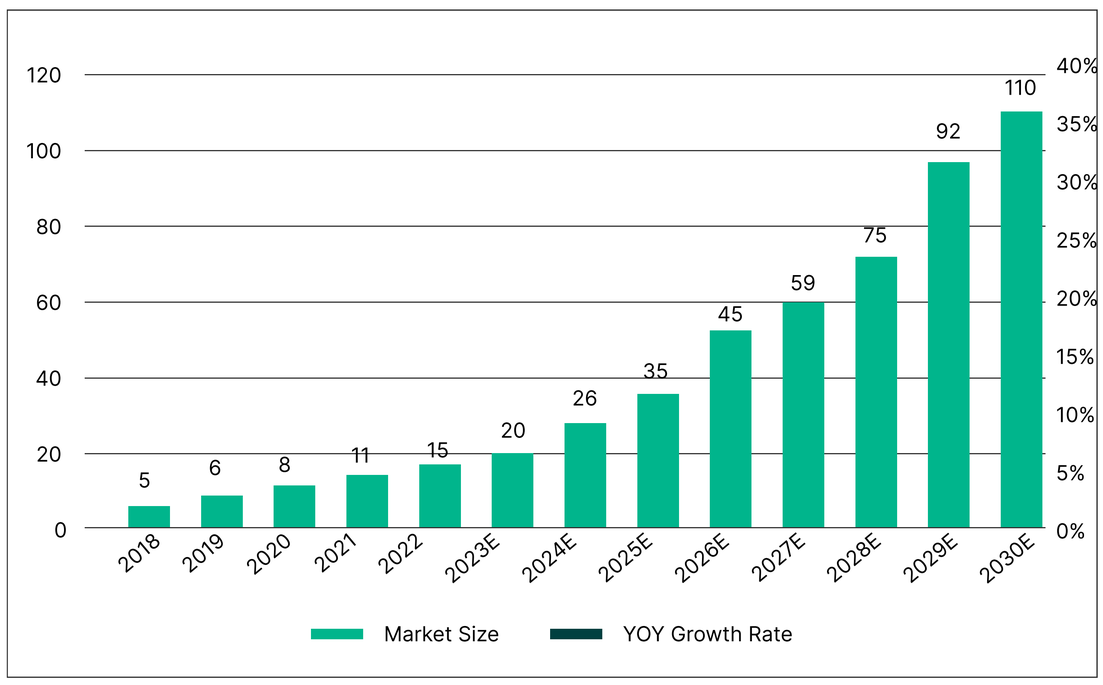
The past decade is a witness of a wave of opportunities for contract bioprocessing in China. China is now home to over 70 biologics CDMO9, with WuXi Biologics the clear leader. The second tier includes Pharmaron, Genescript, Chime Biologics, MabPlex, etc. However, we also now some biopharma companies taking part in the contract bioprocessing business, utilizing their idle capacity, among which are Antonbio (subsidiary of Henlius), Altruist Bio (subsidiary of Innovent Bio), Foster Bio (subsidiary of Mab-works), and Sigo Bio (subsidiary of 3S Guojian) among others. This had resulted in one unintended consequence as we effectively see too greater competition and the dispersing of bioprocessing talents across too many companies, which is negatively impacting the ability of players to build strong and experienced teams with good track records on delivery. Additionally, bioprocessing in China – WuXi aside – remains a nescient industry still building its global reputation. The smaller players are therefore caught in 'catch 22' situation unable to buy in experienced resources and unable to build them easily as global partners what experienced teams before considering sending projects to China.

Major Reactions of the Industry

1. **Cutting Price.** Chinese companies are known for using price cutting as a major strategy in competition, which is certainly true for contract bioprocessing business as well. The typical price of an IND project has dropped from over RMB 20 million to ~ RMB 10 million; and one biotech usually will see 6 or 7 CDMOs bidding for a contract bioprocessing deal. Even WuXi Biologics, the leader of the industry, has recently cut its price by ~ 40%[9, 5]. Industry insiders believe this wave of price cutting will certainly drive the smaller and weaker CDMOs targeting domestic market out of business.
2. **Focus on niche markets.** There are some positives, and niche markets in contract bioprocessing are seeing strong growth, the biggest being ADC bioprocessing. Quite a few domestic bioprocessing CDMOs have grabbed this opportunity, including WuXi XDC, MabPlex, ToT BioPharm, Altruist Bio, Porton Pharma, Asymchem etc. WuXi XDC, the leader in this niche market and the first IPO in ADC CDMO, realized RMB 2.1 billion in revenue and net profit of RMB 412 million in 2023. Since the start of its operation, the company has signed 427 deals in ADC bioprocessing, with ~60% of revenue coming from overseas. The company is expected to grow robustly as more early-stage projects

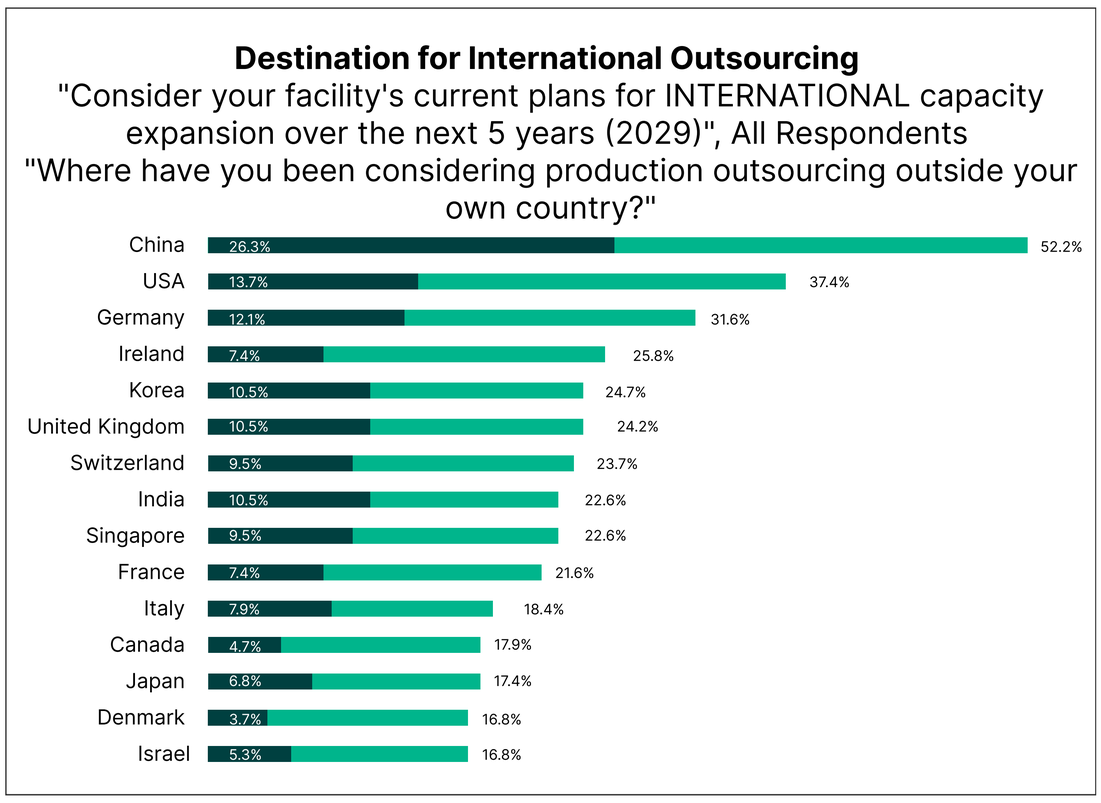
mature into clinical pipeline. ToT BioPharma, which is a biotech & CDMO, posted RMB 141 million revenue for contract bioprocessing of ADC in 2023, which is 94% growth over that of 2022. The company is developing 3rd generation ADC based site-specific conjugation technology platform, and has annual capacity of ADC stock solution of 960kg3. Porton Pharma, which put its ADC R&D center in Shanghai into operation in Sep, 2023, has invested another RMB 1.01 billion to build up a commercial scale facility for ADC bioprocessing and this is expected to have an annual capacity of 46,080 kg of ADC3.

Figure 3: Global ADC Contract Bioprocessing Market (in hundreds of millions of USD)[10]



3. Starting overseas operation. Though geopolitical tensions are wielding negative impact on the industry, China-based CDMO still have strong cost competitiveness that is attractive to global clients, especially the smaller biotech companies. BioPlan's Annual Survey shows that China is the 2nd most attractive destination for international outsourcing of bioprocessing, outperformed only by United States11. Another survey from BioCentury in March 2024 shows that among the 141 interviewees, 75% admitted that they have worked with China-based bioprocessing CDMOs and 53% agree shifting to other CDMOs would be difficult, and 64% think if they have to shift to other CDMOs the process would definitely slow down pipeline development[12]. Global business is important for China-based CDMOs, especially the leading companies. In 2023, WuXi, Proton Pharma, Pharmaron, all have revenue from overseas composing ~80% of their total revenue[12]. To counter the impact of BIOSECURE Act, some Chinese CDMOs are building facilities overseas, especially in Singapore and Europe. For example, in 2023, Pharmaron made a joint investment of USD 30 million in Singapore-based Rxilient Biohub Pte.Ltd. Whereas WuXi plans to build up capacity of 45,000L in Europe, 30,000L in US, and 120,000L in Singapore.

Figure 4: Destination for International Outsourcing[11]



In fact, many China based industry insiders hope that the launch of biopharmaceuticals originated from Chinese developers in regulated market will gradually improve the image of bioprocessing in China, which in turn will help domestic bioprocessing CDMO to gain commercial scale bioprocessing deals from global companies.

Other strategies include end-to-end service, differentiation via proprietary tech platforms, etc. WuXi Biologics is famous for its end-to-end capability, and Proton Pharma also announced that it has end-to-end service solution for bioprocessing. Smaller CDMOs who do not have the resources to build end-to-end capability are attempting to leverage partnerships to complement each other[9]. Another potential solution championed by industry analysts is to differentiate via IP-protected tech platforms[13], as WuXi Biologics and ToT Biopharma have done. However, other analysts forewarn that it may result in less flexibility for clients and doubt its effectiveness as a strategy[14].

When will the market rebound?

Th million or billion dollar question and bioprocessing CDMOs are waiting for a gradual reduction in tensions and a 'warming' of the macro-economic conditions. For example, in the first half of 2024, investment in US biopharma sector shows positive signs with 107 financing

deals totaling USD 7.6 billion[15]. Dr. Chen Zhisheng, CEO of WuXi Biologics stated that global biotech financing has bounced back from the last quarter of 2023, and the trend continues in first quarter of 2024. He believes that the domestic investment in biotech would certainly follow16. Orient Securities states that there are 1143 IND projects for innovative drugs in 2023, and in the first five months of 2024 the number is 442, which shows that the biopharma industry is still poised to grow in the years that follow17.

There are also improved policy signs on the horizon. The 2024 Government Work Report from China states that the government will support innovative drug industry, the first of its kind in such reports. For example, the National Medical Products Administration (NMPA) drafted an announcement (in consultation stage) in April 2024, which states that for any MNC pharma which decides to move manufacturing of its pipeline to China, the pipeline will be granted priority review status4. It is widely believed that this may bring opportunities for domestic bioprocessing CDMOs.

Industry insiders are also quietly waiting for a round of M&A to reduce the number of players in this industry. With the price war going on, some smaller bioprocessing CDMO will certainly go out of business in the foreseeable future, empowering the stronger ones with greater access to talent and clients. This story has happened in many industries in China before and we expect the bioprocessing CDMO to be no exception. However, the painful process will likely take another 1-2 years for the market to bottom, reset and rebound from stronger foundations9,13, or even longer if China goes into a long economic recession14.

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Navigating New Paradigms: The Impact Of Cell And Gene Therapy Approvals On Manufacturing Capabilities

Irena Maragkou

Senior Healthcare Researcher at GlobalData Plc

SF: Trends in gene therapy approvals in recent years are rapidly shaping the future of manufacturing capabilities in the pharmaceutical industry.

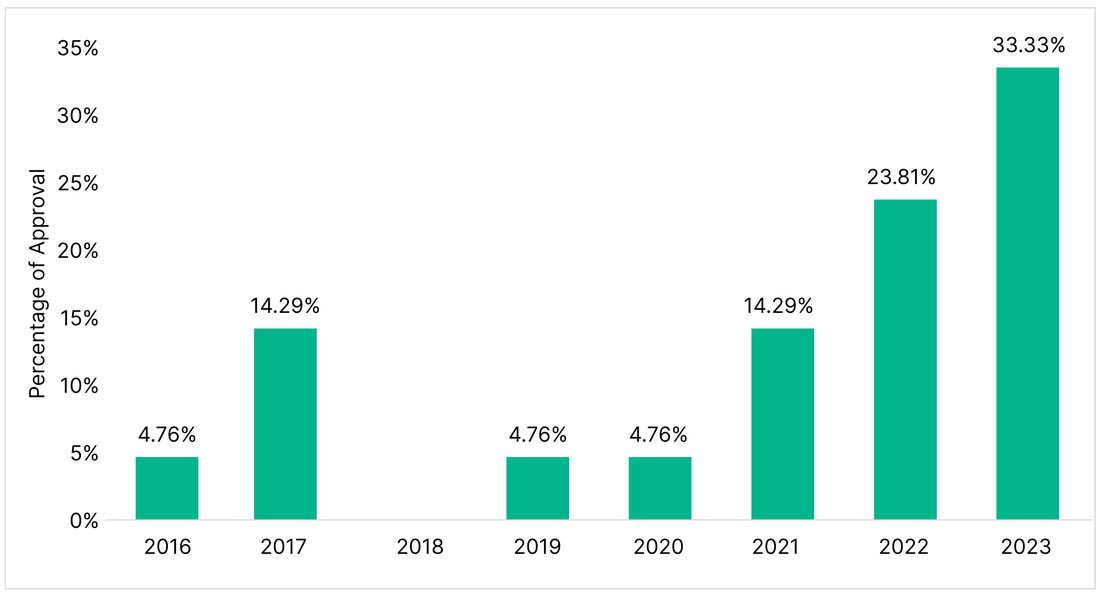
Innovative cell and gene therapies (CGTs) have significantly disrupted the treatment landscape for several genetic diseases. In recent years, the number of CGT approvals has been on an upward trajectory, with there being ten global approvals announced just last year.

According to a survey completed by GlobalData in November 2023, CGT was scored as the industry trend to have the greatest impact on the pharmaceutical industry in 2024, followed by personalized/precision medicine1.

Currently, there are 69 marketed CGTs worldwide, approved by regulatory bodies such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and others. In 2023, a total of seven novel CGTs received FDA approval including notable treatments like Sarepta Therapeutics' Elevidys (delandistrogene moxeparvovec-rokl), and bluebird bio's Lyfgenia (lovotibeglogene autotemcel) **(Figure 1)**. The acceleration in approvals in recent years not only highlights the staggering potential of these therapies but also the growing demand for specialized and expanded manufacturing capabilities.

While CGTs are anticipated to become well-established treatment approaches, maintaining rigorous safety and efficacy standards has proven difficult while trying to meet the growing global demand for this therapy class.

Figure 1: CGT approvals in the US in recent years



Source: GlobalData, Pharma Intelligence Center Drugs database (Accessed September 19, 2024) © GlobalData

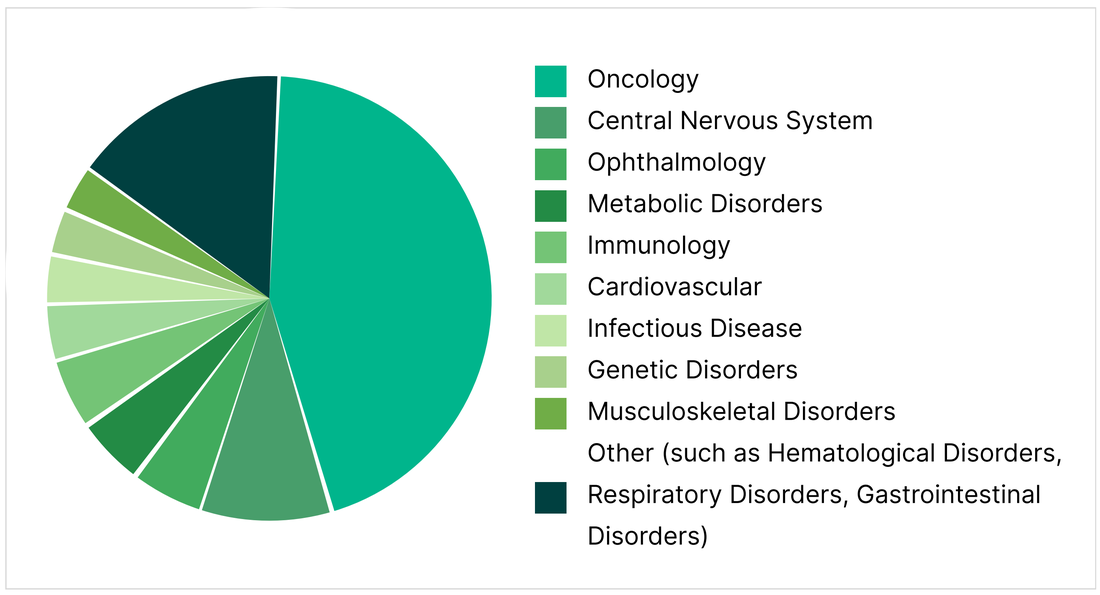
Note: *The chart displays the share of CGT approvals each year among the total number of CGT approvals as per their first approval date. The percentage of CGTs is applicable for marketed drugs only and approval dates are based on publicly available information.*

Oncology at the forefront of CGTs

According to GlobalData, the CGT market was valued at $6 billion last year and is projected to grow to $80 billion by 2030 at a compound annual growth rate (CAGR) of 45%. The surge in CGT approvals is largely driven by advancements in technology and genetic engineering tools such as CRISPR gene editing and novel viral vector delivery systems, enabling more precise and personalized therapies that address and target the genetic cause of a condition. Thus, CGTs have emerged as innovative approaches for the treatment of previously "incurable" genetic conditions, offering solutions beyond merely managing symptoms.

Based on a global analysis of the marketed and investigational CGTs, oncology remains the leading therapeutic area for CGTs, the market for which is set to reach approximately $37bn by 2030, as per GlobalData. Almost 45% of all pipeline and marketed CGTs are developed for oncology indications **(Figure 2)**. However, CGTs may also offer new treatment options for central nervous system disorders, metabolic disorders, immunological conditions, and various rare diseases. The dominance of oncology in the CGT pipeline is expected to persist in the future[1].

Figure 2: Marketed and pipeline CGTs according to therapy area



Source: GlobalData, Pharma Intelligence Center Drugs database (Accessed September 18, 2024) © GlobalData

Note: *The chart displays the percentage of pipeline and marketed CGTs by therapy area based on publicly available information.*

TILs are anticipated to have the greatest impact among CGTs in the solid tumor space2. This year, the first tumor-infiltrating lymphocyte (TIL) therapy, Iovance Biotherapeutics' Amtagvi (lifileucel) gained FDA approval for the treatment of unresectable or metastatic melanoma, a type of solid tumor. CGT sales are expected to be

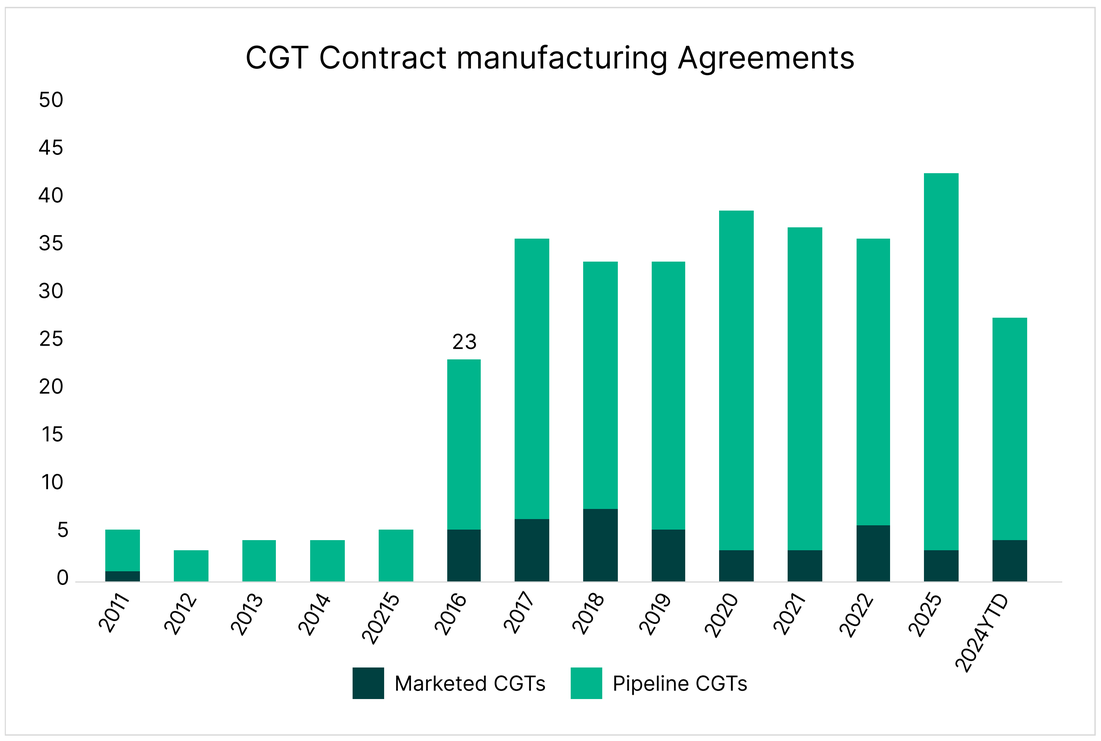
fueled by expanding into earlier treatment lines for conditions like non-Hodgkin lymphoma and multiple myeloma[2].

While efforts are underway to extend the success of cell therapies in oncology to other therapy areas most of these trials remain in early development stages, with limited suitable targets and ongoing assessment of CGT efficacy and safety1. In the gene therapy field, chimeric antigen receptor (CAR)-T cell therapies stand out as a leading treatment, drawing significant investment1. Trends in CGT approvals are crucial, as they will strongly influence the manufacturing practices and the future scalability, cost, and accessibility of these regenerative therapies.

Outsourcing vs in-house manufacturing

The number of contract manufacturing agreements for CGTs has been increasing in recent years, in line with increasing approvals and R&D in the CGT space. Up until now, there are more contracts for CGTs in development in comparison to commercial contracts for contract manufacturing organizations (CMOs) (Figure 3). However, this is likely to change as the surge in CGT approvals continues3. Nonetheless, even if there are fewer commercial contracts for approved CGTs, those strategic partnerships are critical due to their high value[3].

Figure 3: Contract manufacturing agreements for CGTs per year

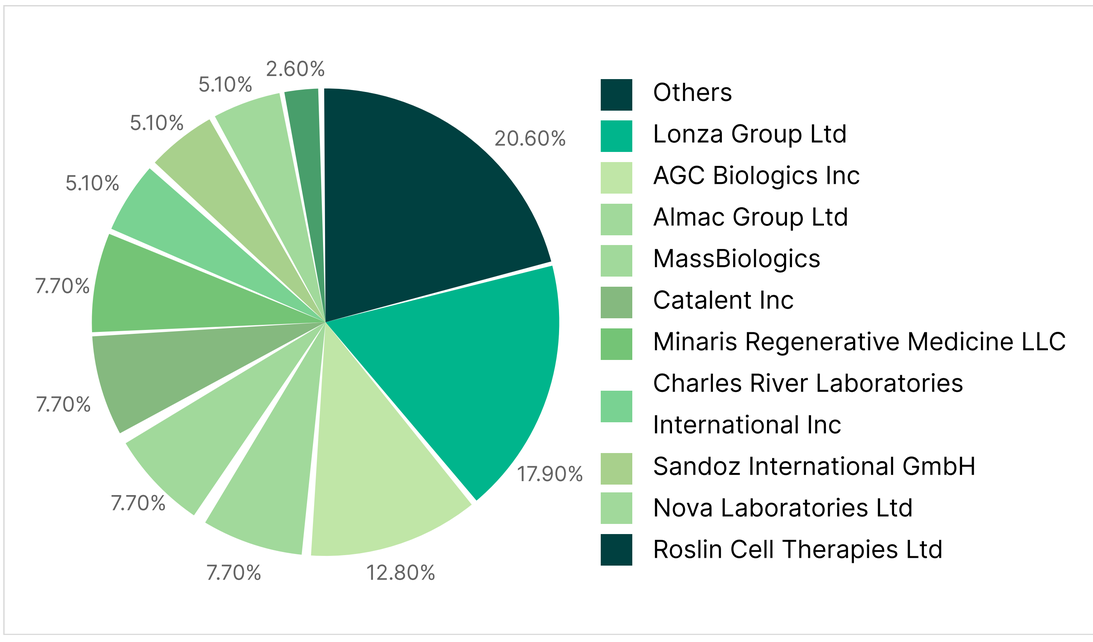


Source: GlobalData, Pharma Intelligence Center Deals database (Accessed September 18, 2024) © GlobalData

Note: *The chart displays the number of contract manufacturing agreements for CGTs by year based on publicly available information.*

Lonza Group is the leading CMO for contracts of marketed CGTs, owning 17.9% of CMO contracts, based on publicly available information recorded by PharmSource, a GlobalData product (Figure 4). AGC Biologics in the next leading CMO (12.80%), while Almac Group, MassBiologics, Minaris Regenerative Medicine and Catalent all possess about 7.7% of the publicly known CGT manufacturing contracts for marketed CGTs **(Figure 4)**.

Figure 4: Contract manufacturing agreements for marketed CGTs

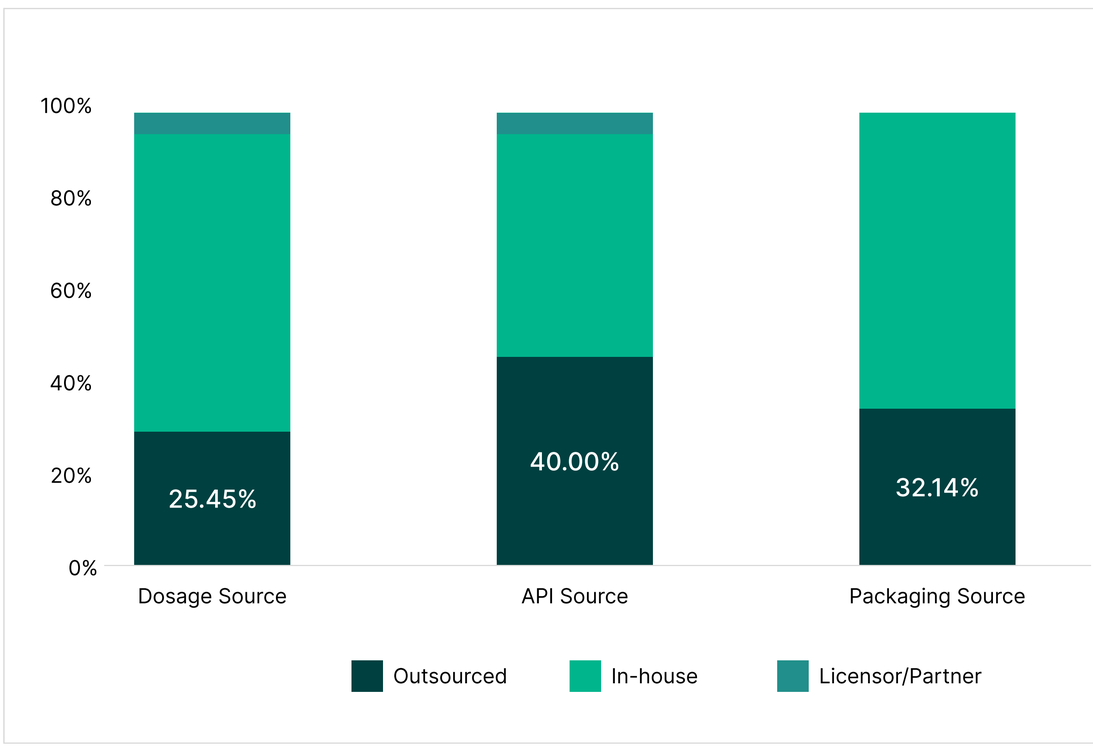


Source: PharmSource, a GlobalData product. (Accessed September 18, 2024) © GlobalData

Note: *This analysis only includes biosimilar and innovator drugs approved in the US, UK, and/or EU, specifically through the EMA's centralized authorization procedure.*

Regarding marketed CGTs in the US, UK and EU, the active pharmaceutical ingredients (APIs) of around 40% of marketed CGTs are outsourced to CDMO facilities **(Figure 5)**. The highest percentage of in-house activities is observed in dosage production, as only 25% of marketed CGT dosages are outsourced to CMO sites **(Figure 5)**. A similar trend is observed in the packaging of marketed CGTs, where approximately 32% of them are outsourced **(Figure 5)**.

Figure 5: Outsourcing vs in-house manufacturing of marketed CGTs



Source: PharmSource, a GlobalData product. (Accessed September 18, 2024) © GlobalData

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A key point to consider is that dual or multiple sourcing takes place in the CGT sector[3]. Due to complexity, some parts of production are completed in one facility and then shipped out to other facilities. As supply chains can be fragile, redundancies are built into supply chains on purpose. In general, smaller companies—those with a market cap lower than $2bn, tend to outsource their manufacturing as they lack the required facilities and in-house capabilities[3].

Scalability, staffing and supply chain hurdles

The manufacturing process for CGTs is highly intricate and requires complicated logistics involving cell expansion and manipulation, and viral vector engineering, which leads to high production costs compared to the manufacturing of small molecules and other biologics. According to a study published in June 2023, the cost of developing a new CGT was estimated to be around $1.94 billion, factoring in the research and development attrition rate[4]. Disruptive therapies such as CGTs also require skilled personnel and specialized facilities for production that add to the high R&D costs.

Currently, a shortage of skilled workforce and a small number of specialized facilities with limited capacity pose a strain on CGT manufacturing processes[3,5]. CGT manufacturing involves strict regulatory requirements and good manufacturing practices (GMP) stipulations, which may include sterile processing, waste decontamination, and stringent quality control measures—which pose a barrier to scaling up.

CGT manufacturing also has time and temperature sensitivity limitations. The short shelf lives require ultra-cold storage, adding to the manufacturing complexity as they are commonly sourced from many different facilities and involve a multifaceted supply chain.

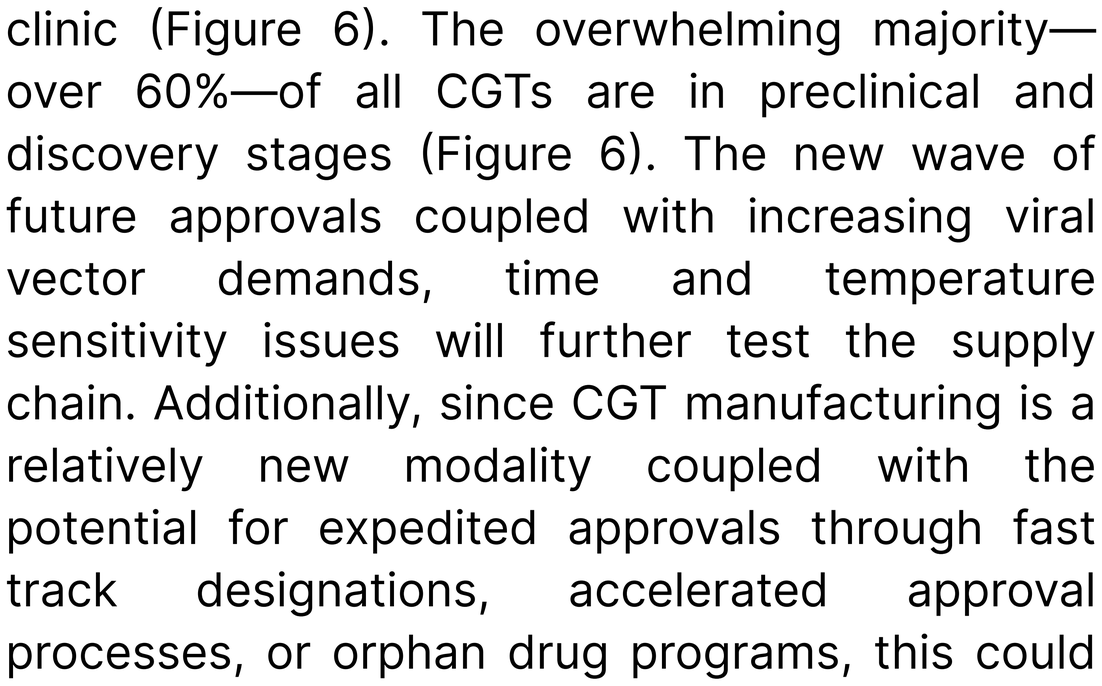
Improvements in the manufacturing processes to increase yield while lowering production costs are key to increasing patient access and affordability. This has led to major pharmaceutical companies and CMOs prioritizing capacity expansion and investing in specialized facilities and technologies.

Impact of CGT approvals on manufacturing procedures

The wave of CGT approvals is leading CMOs to acquire new capabilities, as sponsors already are and will become increasingly dependent on these production services. In the case of CAR-T therapies, the industry was rapidly developing new therapies while struggling to keep up with their advancement and had to adapt manufacturing processes to make such therapies widely accessible6. As a result, while in the past, it took ten to twelve years for biologic products to gain commercial approval, recent advances have significantly shortened the commercialization timelines[6].

The shortage of skilled workforce and specialized facilities combined with limited capacity is already a major stressor on manufacturing processes. CGT approvals are forecasted to be on a growth trajectory, with over 5,000 CGTs in early development stages and over 2,000 therapies already in clinical trials. Based on an analysis of pipeline and marketed CGTs worldwide, less than 1% of total CGTs are currently marketed while over 28% are in the clinic (Figure 6). The overwhelming majority—over 60%—of all CGTs are in preclinical and discovery stages (Figure 6). The new wave of future approvals coupled with increasing viral vector demands, time and temperature sensitivity issues will further test the supply chain. Additionally, since CGT manufacturing is a relatively new modality coupled with the potential for expedited approvals through fast track designations, accelerated approval processes, or orphan drug programs, this could place a further strain on manufacturing capacities.

Figure 6: The percentage of marketed and pipeline CGTs, according to development stage



Source: GlobalData, Pharma Intelligence Center Drugs database (Accessed September 18, 2024) © GlobalData

Automation and standardization as possible solutions

Automation and standardization will be crucial to advancing manufacturing processes7. Implementing some level of standardization in the manufacturing process, such as expedited facility switchovers or streamlined regulatory procedures, could be beneficial.

Adeno-associated viral (AAV) vectors are most used for CGTs, however, the adoption of new viral vectors could help solve the industry's demands for gene therapies and other types of products such as vaccines[7].

Equipment and analytical technology advancements have already helped integrate analysis into manufacturing for better efficiency and consistency in CGT products[6]. Process analytical technology systems (PAT) may hold promise in controlling CGT products. Efficient data gathering and integration of artificial intelligence in manufacturing processes hold promise for the future.

Lastly, advanced tracking systems have been set in place to ensure biological material identification for autologous cell transplants across the entire supply chain.

As the CGT space matures, the acceleration of the CGT approvals and growing demand for them is pushing for transformational change within the pharmaceutical industry. In the midst of this change, pharma companies and CDMOs are poised to display adaptability and responsiveness to unmet clinical needs, regulatory requirements, and patient-focused strategies while simultaneously keeping up with manufacturing demands.

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Additional Q&A on implications

Do you think weak funding for advanced therapies in the last 18 months might slow timelines? (We hear money is reluctant to go to 'riskier' advanced therapy biotechs)?

"Last year, the pharmaceutical and biotech sectors experienced a limited number of initial public offerings, along with a more challenging financing environment, as biotech companies opted to wait for more favorable market conditions[7]. In 2023, market uncertainty, driven by factors like the Inflation Reduction Act, resulted in a slower deal-making environment and coupled with other external factors such as geopolitical instability has contributed to prolonged negotiations and the use of contingent pricing in deals to de-risk valuations[7]. Acquisitions and IPOs have reached record lows, putting many private companies at risk of closure, allowing large pharmaceutical companies to acquire valuable assets or intellectual property at undervalued prices[8]. The higher development and production costs associated with cell and gene therapies, compared to small molecule trials, add further strain—cell therapy trials cost 15% more and gene therapy trials 20% more than small molecule trials[8]. The investment size needed to develop an asset is directly linked to the size of the molecule[8]. However, deals in oncology and rare diseases did increase last year, and according to E&Y's calculations, the oncology deal size reached an average of $2.2 billion per deal in 2023, which is an increase of 75% per year[7]. Pharma executives also predict that personalized medicine will be a key focus for investment this year, with chimeric antigen receptor T-cell (CAR-T) therapies standing out as the most appealing area for investors alongside antibody-drug conjugate (ADC) deals[7]"

In which regions will CDMOs benefit most (Europe, USA or Asia) from CGT approvals?

"There are 255 contract development and manufacturing organizations (CDMOs) that produce cell and gene therapy active pharmaceutical ingredients (APIs). These CDMOs operate 361 sites that produce CGT APIs. CGT API production is mostly concentrated in the US, Europe and China so these areas are likely to benefit more from future CGT approvals. Looking at specific countries, the US currently has 162 CGT API production sites, followed by China with 34 facilities and the United Kingdom, with 33 sites. The US's already advanced manufacturing capabilities and capacity make it a key player in the CGT landscape while trends indicate a geographic expansion, particularly into emerging markets like Asia, where the growth rate for CGT CDMOs is expected to outpace other regions[9]. Countries such as Ireland could see advantages from the BIOSECURE Act, as Chinese companies facing scrutiny may look to invest in other nations[10]. Additionally, India is well-positioned to become a key destination for pharmaceutical manufacturing, offering cost-effective services and a highly skilled workforce, making it an attractive alternative for companies seeking to diversify their supply chains away from China[11]"

If Wuxi advanced therapies is effectively removed as an option (BIOSECURE), could access to qualified CDMOs be an issue that majorly slows development timeline?

"The potential impact of the BIOSECURE Act on Chinese contractors remains uncertain. The US pharma industry relies heavily on Chinese CDMOs and such collaborations with these companies are attractive due to the low costs associated with producing and sourcing active pharmaceutical ingredients (APIs) abroad[11]. WuXi Biologics, a prominent Chinese company mentioned in the bill as a concern for the US, reported strong performance in early 2024, securing 61 new projects,

with half coming from US clients despite legislative uncertainties11. Some companies, like Novartis, are reassessing their partnerships with Chinese firms in light of the bill, while others, such as Sound Pharmaceuticals, plan to maintain their relationship with WuXi despite the ongoing discussions around the BIOSECURE Act[11]. However, biopharma companies with suppliers based in China are flagging the BIOSECURE Act as a significant upcoming risk, according to GlobalData's review of corporate filings and disclosures[11]. Shifting manufacturing operations out of China is expected to raise costs and create material shortages, particularly affecting smaller biopharma companies and start-ups than larger pharmaceutical companies. These smaller organizations are less equipped to handle the additional financial burdens, supply chain disruptions, and complexities of changing suppliers compared to larger companies leading to a higher risk of operational strain and potentially slower development timelines[11]."

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Great Majority of Biomanufacturers to Outsource More Production Over the Next Five Years

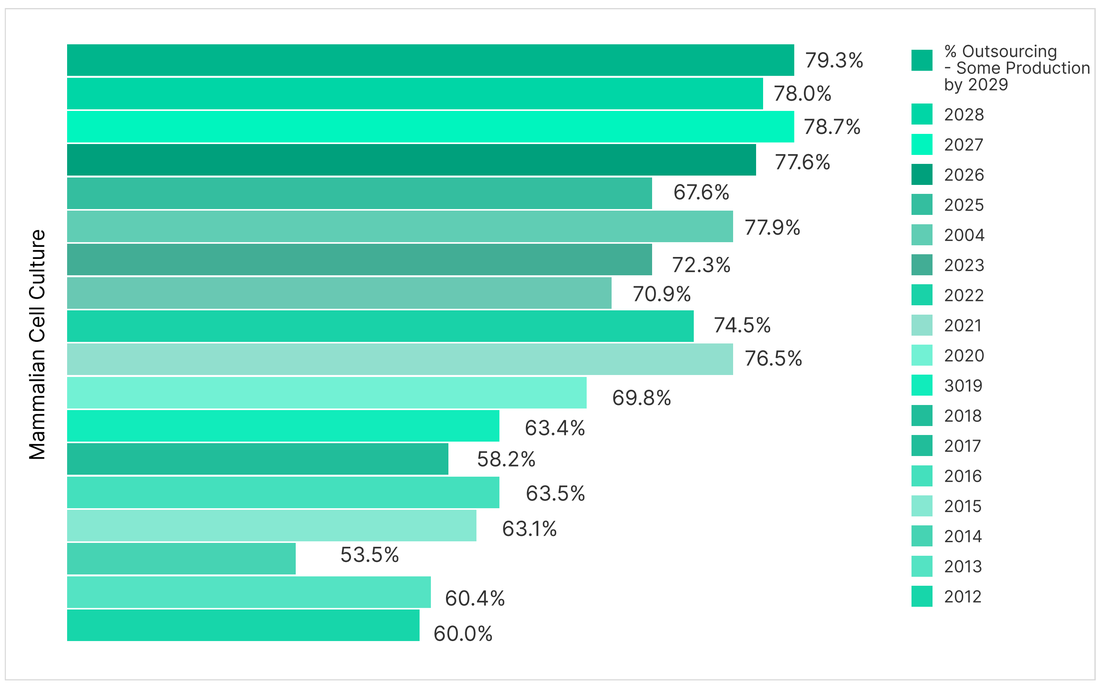
Ioanna Deni

Market Analyst for BioPlan Associates

80% of manufacturers using mammalian cell culture expected to be outsourcing at least some bioproduction; up from 60% in 2007

There has been consistent growth in outsourced biomanufacturing. Over the span of 15 years, BioPlan Associates' 21st Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production1 has seen an increase in the reliance to external capacity and expertise for all platforms (mammalian cell culture, gene and cell therapies, plant and insect cells, microbial fermentation and yeast). In five years, by 2029, 79.3% of industry biomanufacturers surveyed indicated they expected to be outsourcing at least some of their production (Figure 1).

Figure 1: Percentages of Biotherapeutic Manufacturers Projected to be Outsourcing at Least a Portion of their production – 5 Year Projections



Source: 21st Annual Report and Survey of Biopharmaceutical Manufacturing Capacity, 2024, BioPlan Associates, Inc. Rockville, MD)

For the layout: % Outsourcing Some Production by 2029	2028	2027	2026	2025	2024	2023	2022	2021	2020	2019	2018	2017	2016
0.0%	78.0%	78.7%	77.6%	67.6%	77.9%	72.3%	70.9%	74.5%	76.5%	69.8%	63.4%	58.2%	63.5%

Smaller platforms have experienced even more pronounced growth in outsourcing expectations. Yeast, plant, and insect-based systems have also seen substantial increases. Notably, insect cell culture facilities reported a surge in outsourcing expectations from 25% in 2009 to 87.1% in 20241. Cell therapy outsourcing has remained consistently high, maintaining levels in the mid-70% range over the past six years1. These trends toward higher production outsourcing indicate that decision-makers now view Contract Development and Manufacturing Organizations (CDMOs) as essential components of their future manufacturing strategies.

Back in 2006 when we began measuring key outsourcing trends the majority of biologics innovators did all their manufacturing in-house. However, since then, the percentage doing it all in-house has decreased steadily at around 5% annually. Since 2006, the percent with zero outsourced production has dropped from 57.6% to 26.9% today.

On the other hand, some, especially in innovative areas such as cell therapy, have no internal bioproduction, and no alternatives but to outsource. Access to capacity is one challenge, but access to skilled bioprocessing expertise can be even more of a problem for complex platforms.

There are several compelling reasons driving the increased outsourcing of biomanufacturing processes, each reflecting the evolving needs and priorities of the industry. For instance, CDMOs offer:

- **Capacity Flexibility and Scalability:** One of the foremost reasons for outsourcing is the ability to scale production efficiently without the need for significant capital investment in infrastructure. This flexibility is particularly critical for companies managing multiple product pipelines or those with products at varying stages of development.
- **Access to Specialized Expertise:** Outsourcing provides biomanufacturers with access to highly specialized technical expertise that may not be available in-house. This is especially true for newer platforms like gene and cell therapies, where the complexity of the manufacturing process requires not only cutting-edge technology but also niche knowledge in regulatory requirements, process development, and manufacturing scale-up. CDMOs offer advanced capabilities and insights that can help biomanufacturers navigate these complexities effectively.
- **Cost Efficiency:** Outsourcing can significantly reduce operational costs by avoiding expenditures associated with building and maintaining manufacturing facilities. Instead, biomanufacturers can focus their internal resources on R&D while utilizing CDMOs for production. This cost model is particularly attractive for smaller biopharma companies or startups that are capital-constrained and need to prioritize R&D over manufacturing investments.

- **Risk Mitigation:** Outsourcing allows biomanufacturers to mitigate risks associated with capacity constraints, supply chain disruptions, and regulatory compliance. CDMOs often have multiple sites and established quality systems that enable redundancy and ensure continuity in production, even in the face of global challenges. Additionally, external partners are often more adept at navigating the regulatory landscape, ensuring that biomanufacturers remain compliant with evolving standards.

The combination of enhanced flexibility, cost efficiency, and speed to market provided by CDMOs gives innovators greater options and reduces their risks in getting their products to market. We anticipate that outsourcing relations will remain a key aspect of the biomanufacturing industry as it becomes an essential driver of growth, innovation, and competitive advantage for biopharmaceutical innovators.

Biomanufacturing Industry Wants More CMO Options for Cell and Gene Therapy

Outsourcing of gene and cell therapy production has always been a critical bioprocess strategy for these modalities. This year, our study is showing is a growing need for improvements across systems, platforms, and infrastructure for cell and gene therapy products. A range of proposed enhancements, include better virus/ vector analytical tests. Notably, 25.9% of biomanufacturers working exclusively on gene and cell therapies have expressed a desire for more outsourcing options for commercial production, while 23.8% are looking for more outsourcing options for clinical production. These gaps in available expertise and infrastructure are significant, considering the rapid growth in gene and cell therapy markets.

Nearly 40% of cell therapy manufacturers report facing challenges with sub-optimal process control and automation in their cell/gene therapy processes. This creates an opportunity for biomanufacturers to leverage the expertise and equipment available through outsourcing and CMOs. By partnering with CMOs that specialize in these sectors, companies can address their production challenges and ultimately gain a competitive edge in the market.

Analytical Testing and Toxicology Testing in Highest Demand

There is a significant trend in biomanufacturing outsourcing of specialized testing services. Since 2013, the outsourcing of analytical and toxicity testing has exceeded 70%, underscoring the shift towards leveraging external expertise in these areas1. In 2024, analytical testing for bioassays leads as the most outsourced activity, with 83.2% of respondents reporting reliance on external partners. Toxicity testing follows, with 77.7% outsourcing this function, and validation services are outsourced by 72.6% of respondents (Figure 2).

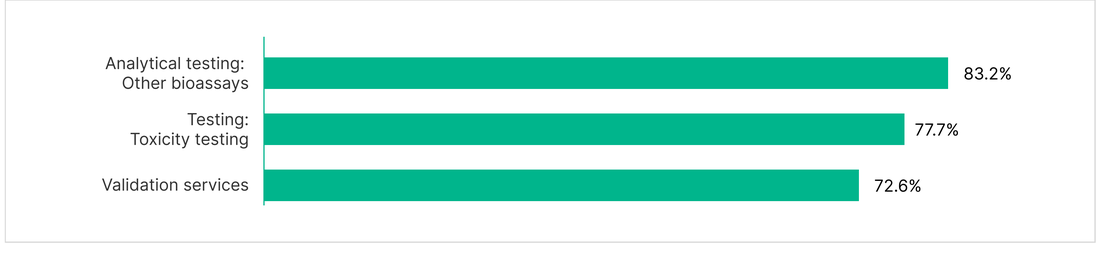
At the bottom of the list were activities like QbD Services, Upstream Process Development, and Project Management Services. While these activities have seen increased outsourcing over the years, project management remain an area where biomanufacturers prefer to retain control. Project management services were outsourced only by 53.8% of facilities showing that companies are opting to train and develop their own staff for these functions. This approach allows companies to cultivate a skilled workforce, intimately familiar with their production pipelines, and maintain tighter control over critical aspects like timelines and operational efficiency.

In-house project management also enables firms to build valuable institutional knowledge, ensuring agility and responsiveness to internal and market demands. By keeping these functions within the organization, biomanufacturers safeguard their long-term vision while maintaining flexibility to adapt to challenges unique to their operations.

This rise in outsourcing testing and similar services is likely driven by the increasing complexity of drug development and more stringent regulatory requirements. Many biomanufacturers struggle to keep up with rapid advancements in testing technologies and methodologies, making outsourcing a strategic necessity. Contract Research Organizations (CROs) have emerged as key players, offering specialized, compliant testing services that meet evolving regulatory demands. By distributing the costs of expensive equipment and highly trained personnel across multiple clients, CROs provide a

cost-effective alternative to in-house testing. Furthermore, the fast-paced technological advancements in analytical and toxicity testing have allowed CROs to stay at the forefront of innovation, providing biomanufacturers access to cutting-edge methodologies and tools.

Figure 2: Percentages of Biomanufacturers Outsourcing at Least Some Activity Today



Source: 21st Annual Report and Survey of Biopharmaceutical Manufacturing Capacity, 2024, BioPlan Associates, Inc. Rockville, MD

For the layout:	percentages
Analytical testing: Other Bioassays	83.2%
Testing: Toxicity testing	77.7%
Validation services	72.6%

US is a Top Outsourcing Destination

Despite initial concerns during the COVID-19 pandemic about reshoring production and reducing reliance on 'off-shoring' or overseas outsourcing, this trend has not materialized. Instead, the global outsourcing landscape continues to expand, with biomanufacturers increasingly seeking cost-effective, specialized capabilities wherever they are, including international markets. According to the Survey, 53.2% of biomanufacturing facilities indicated potentially outsourcing internationally to the U.S.1 This marks a steady rise in preference over time, positioning the U.S. as a key hub for expanding bioprocessing capacity. This also creates substantial opportunities for U.S.-based CMOs to attract business from international clients.

China followed as the second most popular destination, with 37.4% of biomanufacturing facilities considering it for outsourcing. We note, however, that these data were collected in early 2024, prior to the BIOSECURE Act. The act passed the US House of Representatives in September of this year and will likely become law unless vetoed by the President. The Act prohibits federal agencies or companies receiving federal funding from obtaining biotechnology equipment or service provided by a "biotechnology company of concern". This includes Chinese CDMOs and others. While there is a 5-year 'unwinding' period, this will likely affect China's role in biomanufacturing, and outsourcing.

In general, four of the top ten outsourcing locations are in Asia, highlighting the region's increasing prominence as a preferred outsourcing destination.

Europe is another major player, ranking as the third most preferred region for biomanufacturing outsourcing, offering highly experienced, competitive biomanufacturing capabilities across multiple countries. While the U.S. leads as the top single-country destination, the collective opportunities across Asia and Europe demonstrate the truly global nature of outsourcing in the biomanufacturing industry. Looking ahead, global outsourcing is expected to continue growing, further enhancing opportunities for CMOs across the world. This expansion will drive increased competition not only on pricing but also on the ability to build strong, long-term partnerships with biomanufacturers.

Future Of Outsourcing in Biomanufacturing

The sustained commitment to increasing outsourcing in biomanufacturing over the past nearly two decades underscores its strategic significance. Biopharmaceutical companies have recognized the vital role that CDMOs and CROs have in the global bioprocess landscape. They have integrating them deeply into their manufacturing strategies over time. The long-term trajectory points toward a continued and even heightened reliance on outsourcing. This will enable companies to navigate the complexities of drug development and production within an increasingly dynamic and competitive landscape. As the industry continues to advance, strategic partnerships between biopharmaceutical companies and CMOs will be crucial in driving progress and ensuring the timely delivery of innovative therapies to the market.

The adoption of novel technologies and the global expansion of CMOs, particularly in emerging markets, such as markets in Asia, are set to significantly reshape the biopharmaceutical manufacturing landscape.

They are enhancing the capacity and availability of CDMOs, providing biopharmaceutical companies with a wider array of options and more competitive pricing for commercial manufacturing.

While offshoring remains a key strategy for managing costs, there is an emerging trend toward a balanced approach that includes strategic on-shoring. This strategy aims to maintain control over critical aspects of biomanufacturing, such as project management roles, while still leveraging the cost efficiencies of outsourcing. The shift is driven by the need to balance operational control with economic advantages, ensuring both efficiency and resilience in the supply chain.

In conclusion, the future of biomanufacturing outsourcing is characterized by continued growth and deeper strategic integration of outsourcing across platforms. Companies that effectively leverage the expertise and capabilities of CMOs will be better positioned to adapt to industry changes, capitalize on emerging technologies, and meet the global demand for biopharmaceutical products. Outsourcing will remain a pivotal element in biomanufacturing strategies, fostering collaboration and innovation, and shaping the future trajectory of the industry.

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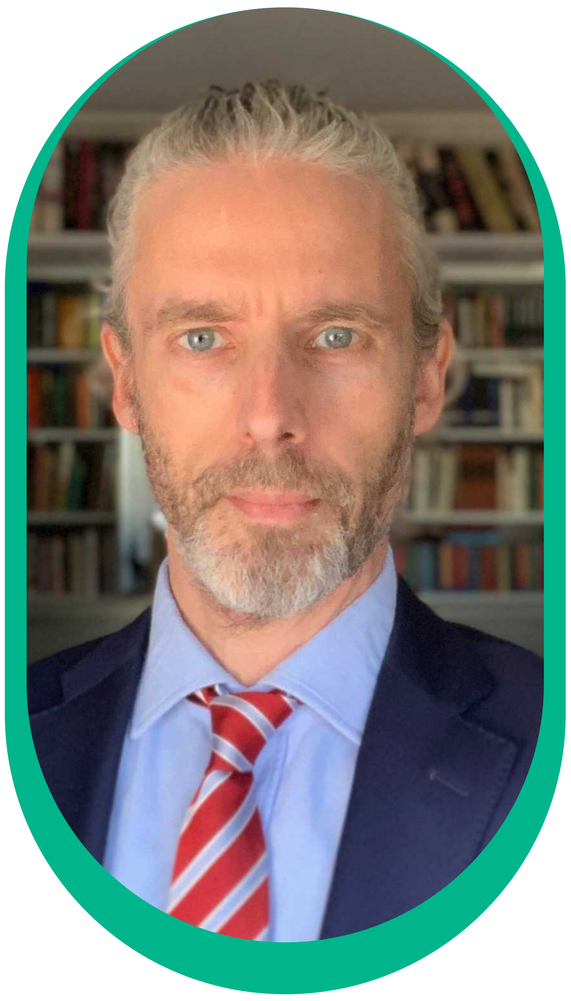
Part
02

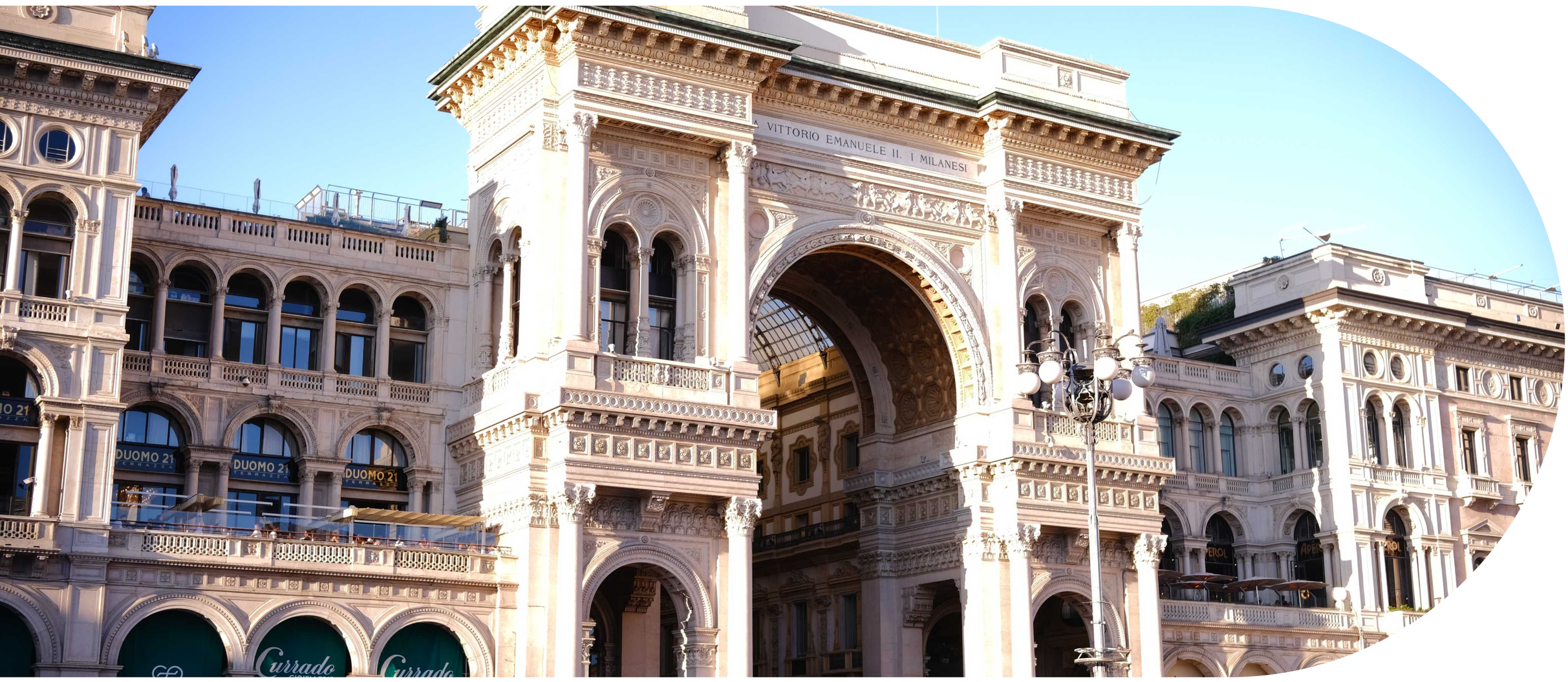
BIOSECURE

CDMOs: The Challenges & Opportunities In A Big Year Of Change For Two Of The ‘Big Boys’?



Gil Roth

Pharma & Biopharma Outsourcing Association



This fall marks 25 years (!) since I entered the CMO sector, before it even had a “D” and became CDMO. I helped launch Contract Pharma magazine as its Founding Editor in the fall of 1999, and almost 15 years later I left that role to launch the Pharma & Biopharma Outsourcing Association (PBOA) so I could help CMO/CDMOs work with regulators and legislators, and better understand their peers in the industry.

Some things have stayed the same for CDMOs over that quarter-century, like private equity pressures driving M&A, and deranged product forecasts from customers. But this year has brought some new wrinkles; whether they have staying power and signal long-term trends is the bazillion-dollar question.

Some of the issues I covered last year remain in effect for the CDMO space. R&D funding remains constrained. While reports indicate that dollars are flowing back to late-stage assets, there is little evidence that early-stage pipeline products are receiving funding. This means that the lifeblood of CDMOs — projects moving through the development pipeline and smaller customers sticking with key service providers — remains hobbled.

Also, supply chain transparency continues to be a key concern for FDA and other regulators and governmental bodies. FDA wants to increase its authority to compel reporting by API and finished dosage form manufacturers with the goal of better mapping the supply chain and understanding global and regional manufacturing capacities and flow.

At the same time, the US Administration for Strategic Preparedness and Response (ASPR) and Department of Commerce are engaged in an assessment of the US Public Health Industrial Base supply chain, an initiative that includes a survey focused on API and Key Starting Materials (KSM) suppliers of a number of FDA-designated essential medicines. In this case, the goal is to both gain supply chain transparency and promote onshoring of manufacturing, another key post-COVID trend I wrote abut last year. (More on that ahead.)

So what has 2024 wrought, and where do we go from here? Last year, I wrote, “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.”

Murky, it turns out, was an understatement. By early 2024, the US Congress was discussing the BIOSECURE Act, which would forbid certain key government contracts, grants and loans going to companies that do business with certain China-based companies, including WuXi AppTec and WuXi Bio.

In its current incarnation, the bill would give companies until January 1, 2032 to cease working with any of the named firms (as well as other companies that could get added to the list). At press time, BIOSECURE hasn’t been voted on in the House of Representatives, but could be on its way to becoming law by the the end of 2024, as part of a larger “must-pass” bill, like the National Defense Authorization Act.

In a conversation on Capitol Hill, a Congressional staffer asked me what I thought of the 2032 deadline — I should note that this was *after* BIOSECURE had adopted that provision, and that PBOA has played *NO* role in shaping or advocating for BIOSECURE — and I replied, “At first, I thought it was so far off as to be negligible, since a tech transfer should only take 2-4 years, at most. But then I thought, ‘A couple *HUNDRED* tech transfers happening *at the same time*, including clinical projects? Might take regulators and industry a while to work through that,’ and 2032 doesn’t sound so far off.”

The trajectory of BIOSECURE — from "not gonna happen" (my words, when I first heard about it in February 2024) to a rush of drug companies reaching out to alternative service providers to potentially shift work from the named companies — has been remarkable, and its impact could be far-reaching.

The uncertainty isn't just BIOSECURE itself, but what comes after, in terms of further US steps, potential Chinese response, and other regions' behavior. Will there be further disincentives or penalties proposed by US legislators? Will there be carrots to along with these sticks, incentivizing investment in manufacturing and services elsewhere? These and other responses will do much to shape the landscape for CDMOs and their customers.

One aspect of this that I will note is that, when BIOSECURE was first being floated, it was India-based CDMOs who drew my attention to it. And as I started outreach on it, CDMOs from that country seemed much better informed about the bill than their western counterparts. They only knew what was publicly available, but were *very* well versed in its particulars. That information-advantage dissipated over the spring trade show season, with more CDMOs telling me about increasing calls from potential customers, but I was intrigued by the notion that Indian CDMOs — and the manufacturing base overall in that country — may see BIOSECURE as an inflection point for their own position in the biopharma manufacturing ecosystem.

Of course, this ties back to my earlier comments around supply chains and onshoring. The US and other countries are realistic about how much manufacturing can be onshored, and how much local-only manufacturing may add fragility, not resilience, to supply chains. To that end, we may see multi-regional activity to bolster supply: friend-shoring.

In June, the US White House announced the formation of the Biopharma Coalition (Bio-5), including the US, EU, India, Japan, and South Korea. It's intended to strengthen biopharma supply chain resilience, and "will focus on building resilient supply chains for APIs currently sourced primarily from the People's Republic of China," per a White House statement, which went on to say, "The five countries will seek opportunities for their governments and the private sector to deepen coordination on policy, regulations, R&D capabilities, and other tools to enhance the resilience of this vital sector."

I can neither confirm nor deny being at the Bio-5's kickoff event, but the announced goal of building parallel API supply chains across regions could be a huge step.

BIOSECURE and geopolitics aren't the only major factor in the CDMO space this year. In last year's piece, I also alluded to "a potential $50 billion market for weight-loss drugs springing up virtually overnight", without expanding on the impact of GLP-1s on the CDMO space. Now I have to revise that to "maybe a $150 billion market," and "that has reshaped the CDMO sector."

The biggest direct CDMO story in 2024 was Novo Holdings' proposed $16.5 billion acquisition of Catalent, one of the world's largest pure-play CDMOs, in order to sell its three fill/finish sites to Novo Nordisk for $11.5 billion, presumably for use in internal manufacturing of Wegovy and/or Ozempic or their successors. The deal hasn't closed as of press time, but if it goes through as proposed, not only would it (presumably) remove three large fill/finish plants from the CDMO sector — Novo Nordisk said it would honor *existing* contracts at those sites, but my totally uninformed assumption is that they would not *renew* those contracts — it would also take the remaining Catalent business off the public equity market, as that becomes a piece of Novo Holdings.

(There's been plenty of speculation about Novo Holdings' plans for the remainder of Catalent if the deal goes through, but I'm not going to speculate on that, and you shouldn't listen to anyone who tells you definitively what's going to happen.)

That would mean no more quarterly financial reports from Catalent, resulting in less public information that can be gleaned — or misread or distorted, as is often the case — about the CDMO sector. And while I pride myself on the strength of my vibe-checks of the sector, this industry functions better when there's reliable data.

One of the questions that's arisen in the wake of this proposed acquisition is whether it will lead to other biopharma companies acquiring CDMOs to gain captive capacity.

While we've seen limited versions of this happen, especially with acquisition of CGT manufacturing capacity, I don't believe Novo-Catalent presages a wave of CDMO buyouts by biopharma. This move feels exceptional in terms of the specific capabilities and capacity Novo Nordisk needed, coupled with the truly mind-bending growth rate of the GLP-1 market.

Lilly has looked to build internal manufacturing to complement its current infrastructure and CDMO relationships, along with its purchase of Nexus Pharma, a non-CDMO asset, to advance its GLP-1 products, and — again, vibes — I suspect it's too late in the game to acquire another significant source of manufacturing capacity that could become a Monjauro/Zepbound dosage-form site. (Please don't prove me wrong before press time.)

Clearly, GLP-1s have been a net positive for the CDMO sector. At a conference I attended in August, the CEO of a new-ish CDMO that's very tech-driven admitted that his company's move into fill/finish and GLP-1 products "saved the company."

But CDMOs are benefiting from more than just GLP-1 volume. While some are manufacturing these products or their competitors, and others are providing packaging and distribution services, we're also seeing the growth in the market for products that are being displaced by GLP-1s.

Not every product needs massive scale and a prefilled syringe dosage form. In fact, Lilly recently made the move to market Zepbound in a single-dose vial through its direct-to-consumer platform, which should be easier to process than PFS doses. Fill/finish CDMOs in the vial space, as well as those that manufacture smaller volumes, may find themselves in high demand, especially if the customers in the Catalent facilities intended to transfer to Novo must find new CDMOs.

In the wake of the Catalent acquisition announcement, many CDMOs in the fill/finish space issued press releases about their new lines, expansion plans, and other services tied to their facilities, getting word out that the capacity exists (or will soon come on line) to absorb a lot of projects, even if that capacity isn't evenly distributed.

Uneven distribution has been a hallmark of this sector for the 25 years I've been around it. While BIOSECURE, GLP-1s, and the potential Catalent-Novo deal may create opportunities for some CDMOs, others may find themselves in rougher waters.

The economics of the US generic market continues to create pressures for commodity oral solid dosage products, while on the high-value end, advanced modalities like cell & gene therapies continue to face hurdles with clinical results, regulatory approval and market reimbursement, pressuring CDMOs who have invested in that area.

Even with the potential for governments to (co-)invest in shifting supply chains, the CDMOs most positioned to benefit will be the ones that focus on capability over capacity, and are able to meet their customers' needs without over-promising.

This year's CPHI global event promises to be a bellwether for the CDMO sector, helping the industry chart a path forward for customers and providers.

Additional Q&A

Key starting materials: many CDMOs are struggling to implement China independent supply chains – at client requests – so how realistic is it to expect this to be possible across all products? How do you predict an initiative like this (ASPR) progressing in the next 5 years?

"KSMs - that's a long-term issue, as in a decade-plus. The process, involving (re)building chemical infrastructure but also accepting changes in pricing for the most price-sensitive drugs. It's a long way off."

Indian and Korean CDMOs perceive themselves as the big winners from BIOSECURE – do you think this could prove to be a double-edged sword and that government(s) direction might harden further toward home or near-shored manufacturing as a preference?

"India/Korea - I think countries are looking at a mix of onshoring and friendshoring, recognizing that some things can't be made economically (or at all) in their home country. So yes such trade may strengthen bonds among 'friendly' regions."

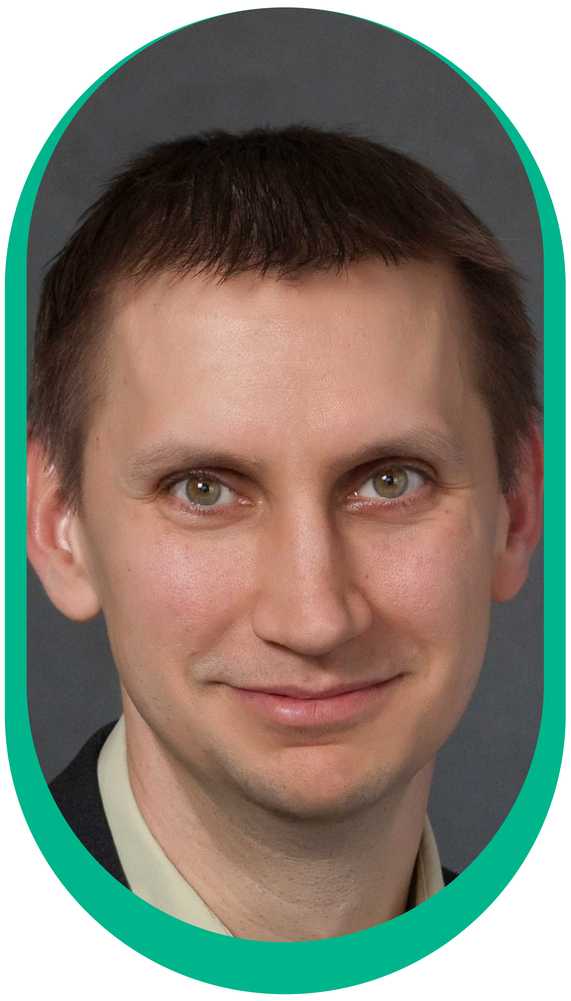
It's a big if, but if, BIOSECURE advances in its present form do you think this will slow development timelines – i.e. one by removing the single biggest CRDMO (WuXI) from the supply chain – but also as a knock-on effects of trying to have circa 60-80 commercial contracts tech transferred out… + many 100s of clinical contracts – surely this must further clog up what resources we have?

"BIOSECURE development fallout - no idea just yet; you'd have to talk to the applicant/license-holder side. However, shifting numerous projects both commercial and clinical — at the same time that there may be an attrition/migration from Catalent's fill/finish sites, if the Novo deal is completed as proposed — could create regulatory slowdowns as they review tech transfers, new sites, etc so that's another potential issue."

You have already mentioned that fill/finish will probably do well, but which modalities do we think have the best growth prospects ?

"In terms of other modalities than small molecule, ADCs? Bispecifics etc? mAbs are looking incredibly again strong, especially if more of the Alzheimer's treatments work out. However, for CGTs, they need room to grow, both clinically and in terms of reimbursement/cost."

BIOSECURing the Future: What an American Cold War with China Could Mean for the Pharma Industry



Nielsen Hobbs

interim Editor in Chief, the Pink Sheet

The pending US election brings much uncertainty for the biopharma industry, but one thing is certain: firms are still going to have to worry about the BIOSECURE Act even after the presidential contest is decided.

A nascent salvo in what some are calling an emerging cold war between the United States and China, the pending BIOSECURE bill would preclude US government contracting with firms that themselves rely on a “biotechnology company of concern” – defined in the legislation as five particular Chinese CDMOs as well as any others that that could be subsequently designated through a process created in the bill. The goal of legislation is to decouple the American pharmaceutical industry from “hostile foreign agents,” but its limited scope (sales to the Veteran’s Administration would be impacted, but not Medicare or Medicaid) – and the fact that the bill has yet to pass – means that biopharma firms are left wondering how to respond.

Adding to the uncertainty is the structure of the bill itself. The five firms that are named – WuXi AppTec, WuXi Biologics, BGI Genomics Co Ltd., MGI Tech and its subsidiary Complete Genomics Inc. – would be a banned from being involved with US government contracting starting in 2032. Firms that are subsequently added would have a five-year grace period.

The difference in approach to the two types of companies may open the legislation up to legal challenge if it does pass. Another similar piece of anti-China legislation that has been enacted, the law aimed at forcing the Chinese owners of TikTok to divest the video app, has already drawn a lawsuit arguing that TikTok is being denied the administrative and judicial protections that any other company eventually designated later would be afforded.

And while the BIOSECURE legislation enjoys large bipartisan support, the 306-81 vote in the House on Sept. 9 actually indicates more concern from lawmakers about the bill than has been previously voiced.

Given all that, firms that rely on contractors that might be impacted by the pending legislation are now faced with a dilemma. Do they assume that the legislation will pass and start finding alternative vendors now? Or do they wait and shift only once it has passed the Senate, been signed into law, and the legal challenges exhausted?

Acting now gives firms the most time and options, but might also end up being unnecessary; they would have deprived themselves of the cost-efficient creativity they have come to rely on from the Chinese contactors.

Waiting has its own risks: firms would have less time to find substitutes if they felt their business eventually needed to decouple to survive. What mix of revenue a company has from the affected government sales would also be a factor in how vital uncoupling would be.

The dilemma has caused no small degree of consternation in the industry, with the Biotechnology Innovation Organization actually changing its position and endorsing the legislation after new CEO John Crowley joined in March. The trade group also parted ways with WuXi AppTec as part of the switch.

Rivals of the CDMOs targeted in BIOSECURE would seem eager for the legislation and the increase in business that might result from it. But they themselves seem caught in the cloudiness around the prospects for the bill. Lonza’s outgoing chairman Albert Baehny told analysts earlier this year that “we are having very active discussions with customers as you can imagine, but with regard to the implication of that, it’s too early to tell.”

Indeed, a survey from L.E.K. Consulting released in July found that 11% of life sciences companies report “no impact” on their decisions from BIOSECURE, which the analyst attributed to the continuing uncertainty around the legislation. “Twenty-six percent of life sciences companies are looking to shift away from their current Chinese suppliers, though only 2% have taken actual unwinding steps,” the survey found.

“That said, companies are already taking some precautionary actions: 68% of life sciences companies are adjusting their activities, including

increasing legal and compliance requirements, planning to diversify suppliers and adding background checks for existing partners."

Perhaps most tellingly, a survey by CPHI of 280 pharma companies found "a majority of the industry is unsupportive of BIOSECURE's stated goals, with only 19% taking the view that China based-CDMOs 'are a threat and should be removed from Western supply chains'."

Of the survey respondents, 38% said that "BIOSECURE is a 'politically motivated issue that sets a concerning precedent for the industry'. The final 43% of the industry – and therefore the largest grouping – take a balanced view, which is both in support of 'WuXi's tremendous contribution to the industry', but also suggests that it is sensible for the industry to 'diversify supply partners'," CPHI said. Details of the survey are due to be released at CPHI Milan.

So industry seems to be mostly taking a "Wait and see but we'd rather not have to deal with this" attitude. And they won't have to – at least until after the election.

If Donald Trump returns to office, he will likely come in with Republican majorities in the House and Senate. That scenario could make enactment of BIOSECURE more likely, since nearly all of the votes against the bill in the House were from Democrats, and the current Democrat-controlled Senate has not shown much inclination to advance the bill.

The decoupling envisioned in the bill resonates with Trump's call for across-the-board tariffs on imports to the United States, but another proposal the former president could advance – international reference pricing – might actually bind US pharmaceutical policy closer to foreign governments.

Kamala Harris has not made confrontation with China a cornerstone of her campaign rhetoric in the same way that Trump has. Her stated goals in the Rx policy arena focus on expanding Medicare price negotiation, though implementation would require new legislation, and Democratic control of Congress seems unlikely next term.

Whether either the Harris or Trump pricing plans comes to pass is another piece of uncertainty for the industry.

The sponsors of BIOSECURE are already pushing for broader pharma decoupling from China even as the current legislation remain bottled up. A bipartisan group of House members has urged the US FDA to deny approval of drugs studied in medical centers affiliated with the People's Liberation Army.

Regardless of the fate of BIOSECURE, industry should not expect pressure like this to go away, and the congressmen's argument that FDA already has the legal authority to block applications relying on data from these Chinese firms means that an aggressive administration might at some point do just that.

Assuming BIOSECURE does eventually pass in a form that that survives a legal challenge, how it is implemented would also depend on the presidential administration. Firms could be added to the list of biotechnology companies of concern at a rapid pace or not at all.

In addition to how the legislation might be implemented if it does pass, there are multiple other policies that politicians could take and that industry will need to consider.

One possible path is to do nothing and wait to see the impact of BIOSECURE. Some biopharma leaders have predicted an expensive disruption, with shortages and higher prices resulting as firms are forced to uncouple. In contrast, the Congressional Budget Office predicts the legislation will have minimal impact, based on an estimate that firms will quickly be able to find replacements for the verboten contractors.

Another possible policy next step is additional legislation to further separate China from American Rx research and manufacturing. The letter targeting data from Chinese military hospitals is an example of what pressure might be coming next. Legislation seeking to extend the BIOSECURE restrictions to drugs used in Medicare and Medicaid could also be forthcoming.

A third possibility is one that the biopharma firms could actually be enthusiastic about: funding to

increase the domestic development and production capacity in the US. That kind of industrial policy has recently been enacted for computer chips, and the initial signs suggest the effort could be successful.

Doing the same for biotechnology would require mustering considerable Congressional enthusiasm, but BIO's CEO Crowley believes that's possible. "Maybe I'm biased, but I can't think of anything more important that we could do as a country together," he said earlier this year.

FDA Commissioner Robert Califf made a similar point in remarks to an industry group on Sept. 27. "Let me just be blunt about the supply chain," he said without mentioning BIOSECURE directly. "I don't think we have balance. I think we're in serious jeopardy right now with almost 100% of our key starting materials for pharmaceuticals coming from China, where, without going into great detail, I think everybody knows it's a significant adversarial relationship right now."

Striking a note of caution that many leaders have made about the escalating tensions, Califf noted, "At the same time, we've always counted on the fact that the Chinese economy and our economies are so intertwined that it would be not a wise move to create problems related to this dependence."

That interdependence is what makes the mechanics, and the politics, of BIOSECURE so difficult. Whichever path US policy ends up going down, the biopharma industry can at least plan on there being increasing political attention to its activities.

Part
03

Impact of Funding on the CRO and CDMO Sector

2024 – An Update on the Health of the CRO/CDMO Sector

An Improving Picture for Some, While Others Still Feeling The Pinch

Brian Scanlan

Operating Partner - Life Sciences, Edgewater Capital Partners

Introduction

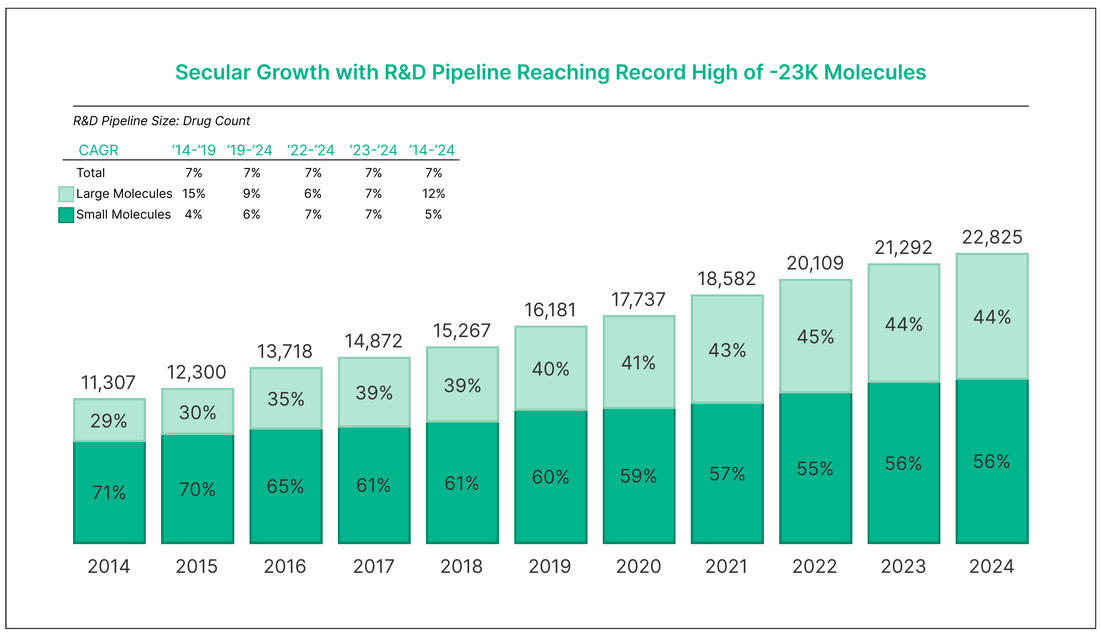
In last year's CPHI Annual Report, we discussed a period of re-alignment within the industry. While pandemic and geopolitical pressures were subsiding, inflation, higher interest rates, big pharma re-alignments, and the biotech funding supply/demand imbalance marshalled in a period of softening demand for services which was generally felt across the industry. Biotechs and emerging pharma companies generally migrated towards cash preservation mode, and while there were signs the funding environment had bottomed out, this needed to coincide with increasing pharma M&A and a more healthy IPO environment to get cash really flowing again. Our prediction was that CRO's and CDMO's would see a continued softening in demand (particularly from emerging pharma and in earlier phases of development) which we noted would likely extend well into 2024.

This year, we will take a look back at the past 12 months, and update our predictions on the health of the sector moving into 2025 and beyond. Generally speaking, we can say that our predictions from CPHI 2023 have generally lived up to expectations, and while demand remains somewhat soft in 2024, there are meaningful signs of a recovery in the sector. So what has happened since CPHI last year? Let's take a look.

Demand for Pharma Services and the Long-term Outlook:

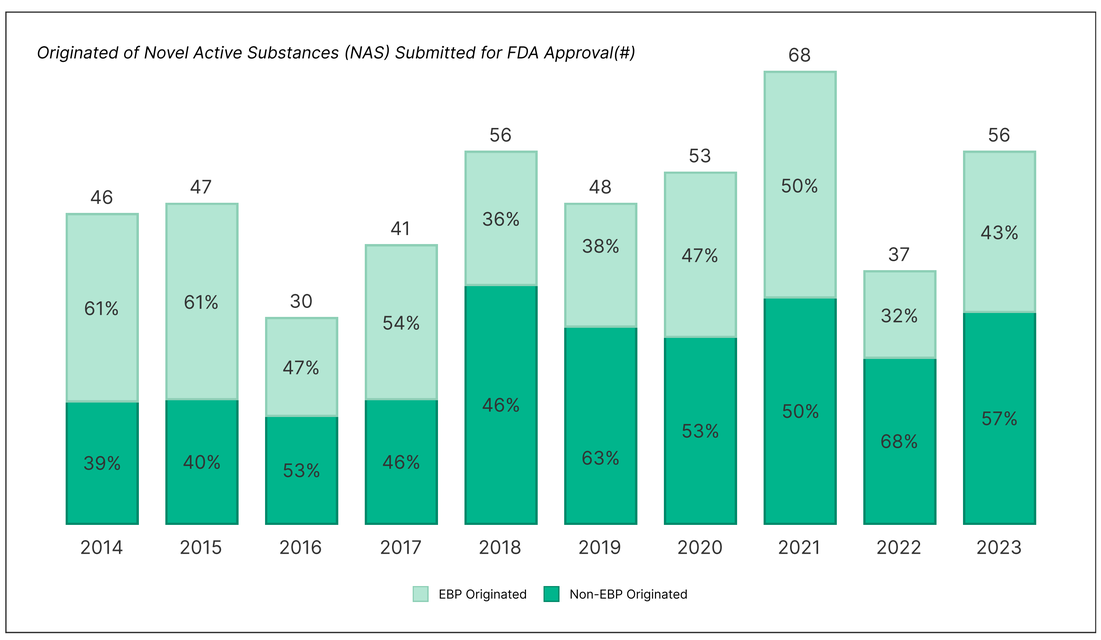
It is important to understand that the long-term growth drivers for the industry remain very strong, notwithstanding unforeseen geopolitical turmoil. A strong pharma services sector requires growth in the number of compounds in development to feed a healthy funnel of programs (Figure 1). Growth rates for small and large molecules are currently around 5% and 12% CAGR respectively, with slightly more than half of the compounds still favoring small molecule modalities. Over the next decade the split will likely favor large molecules, but a balance will settle in over time based on the relative risks and benefits of the various therapeutic modalities. The long-term outlook is strong for CRO/CDMO's across all therapeutic modalities.

Figure 1: Total Number of Compounds in Development Pipelines; Piper Sandler, Pharma Intelligence, Sept 2024



The industry's long term health also requires speed and innovation to bring the best therapies to market with an eye on managing development costs. Over the past 10+ years the number of Novel Active Substance (NAS) approvals has pivoted toward those developed by emerging pharma companies (Figure 2), and nearly two-thirds of drugs approved over the past six years have originated by emerging pharma where nimbleness, speed, and innovation enable faster progression of novel compounds into the clinic, and ultimately to launch.

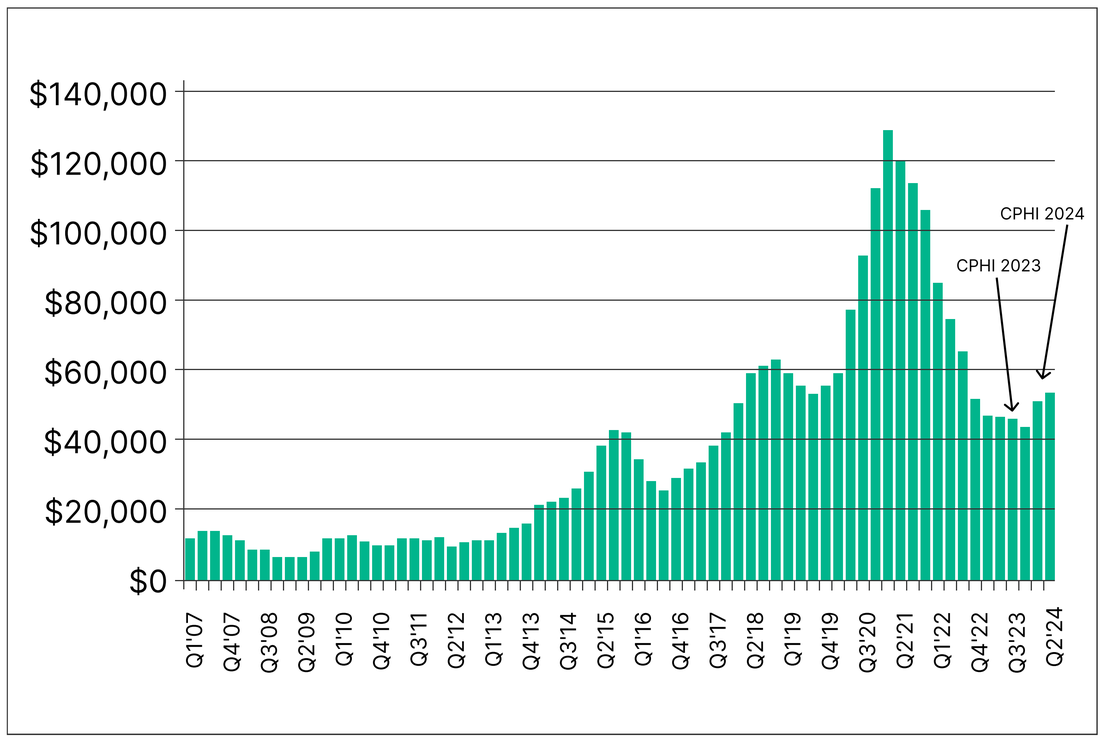
Figure 2: Origination of Novel Active Substances for FDA Approval; Pharma Intelligence, Piper Sandler Sept 2024



Update on Biopharma Funding – A Key Barometer for CRO/CDMO Health

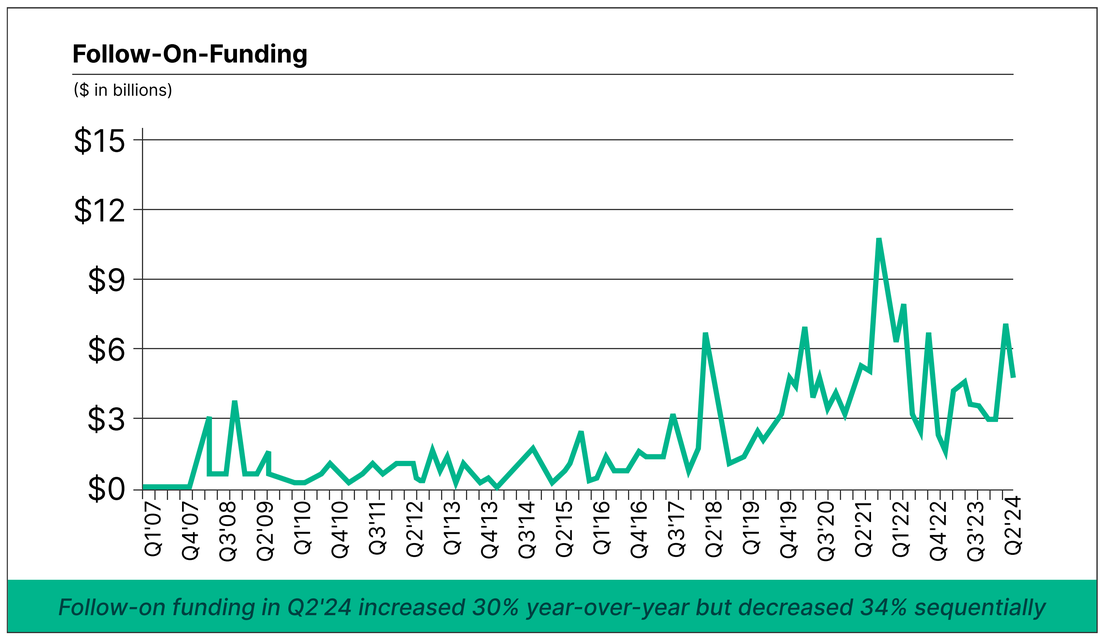
A proxy for determining the health of the CRO/CDMO sector is funding into the biotech (emerging pharma). As mentioned previously, nearly two-thirds of all drugs submitted for FDA approval originate from these companies. During last year's CPHI, total funding into the sector appeared to be bottoming out, and we asked "Is the worst behind us?". It is safe to say that through the first half of 2024, total funding into the sector is improving (Figure 3).

Figure 3: TTM Quarterly US Biotech Funding – All Sources. William Blair Equity Research, August 2024



Looking at the underlying sources of funding into the sector (Venture, Follow-Ons, IPO's) reveals a mixed bag. Venture and Follow-On funding (figures 4) have trended quite well, and there is room for optimism here.

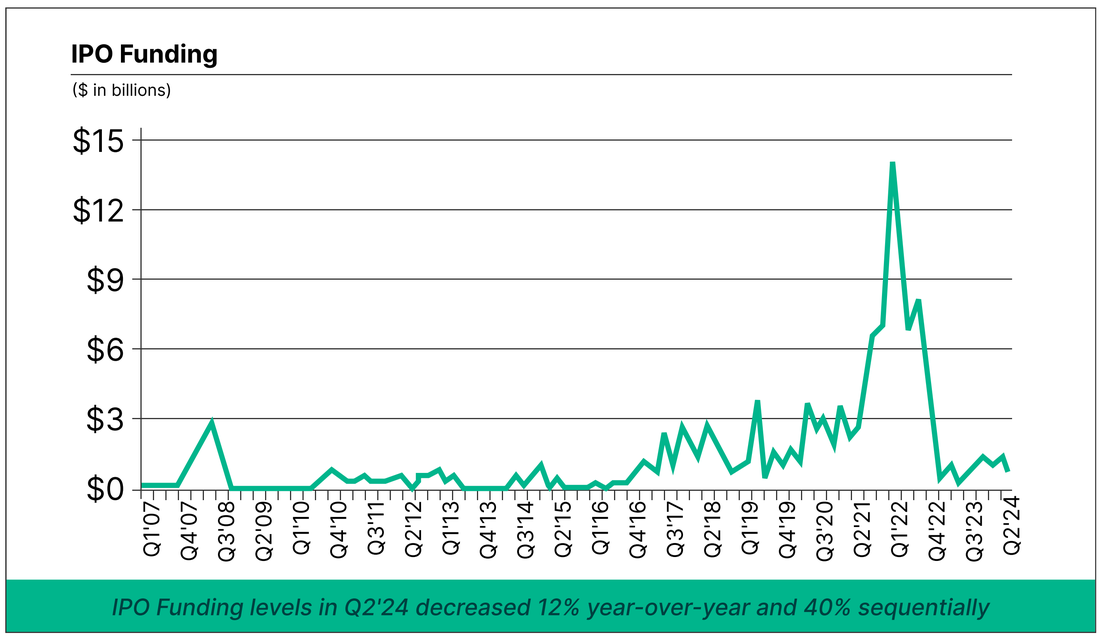
Figure 4: Quarterly US Biotech Follow-On and Venture Funding. William Blair Equity Research, August 2024



Follow on's have improved significantly from the low point in Q2 2022 with generally positive trends, while Venture Funding has exceeded pre-pandemic levels in Q2.

IPO's are showing some signs of life, but continue anemic versus both the pandemic and pre-pandemic levels (Figure 5).

Figure 5: Quarterly US Biopharma IPO Funding. William Blair Equity Research, August 2024.

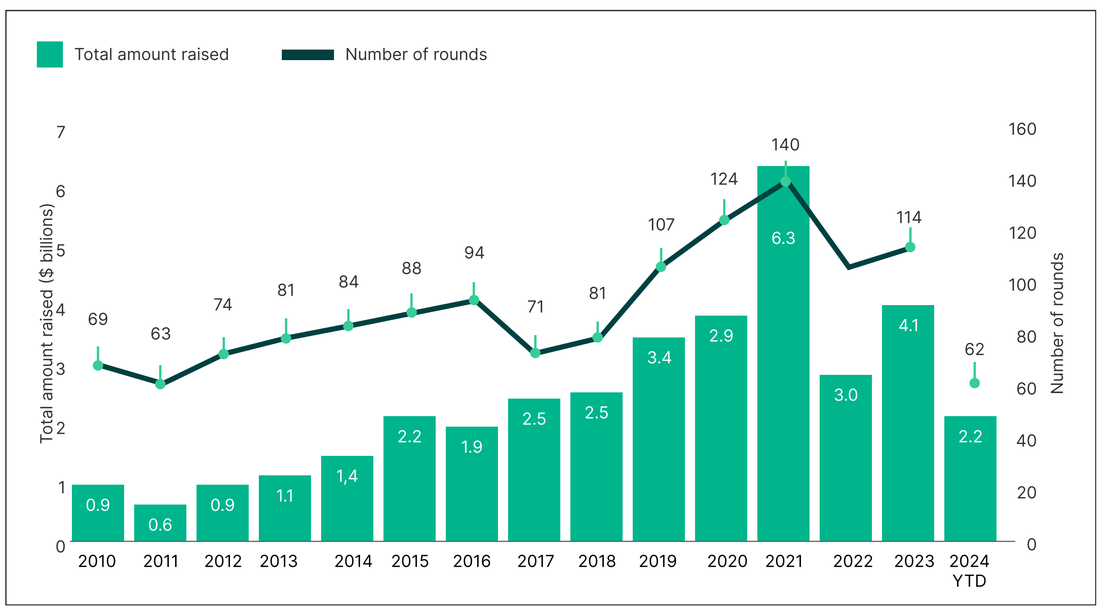


As of mid-September 2024, the US logged 18 biotech IPO's and just under $3Bn raised which is close to the totals for full year 2023. Q3 2024 saw over $900M of IPO activity. Very encouraging signs as we move into the final quarter of 2024. A recovering IPO market will fuel more investment across the sector including venture and follow on financings.

EU Biotech Venture Funding

Turning to Europe, venture funding has been quite strong in 2024 versus the prior two years, and is on pace to exceed every prior year except 2021 (Figure 6). Increasingly US investors have looked to Europe/UK for their emerging hubs of innovation.

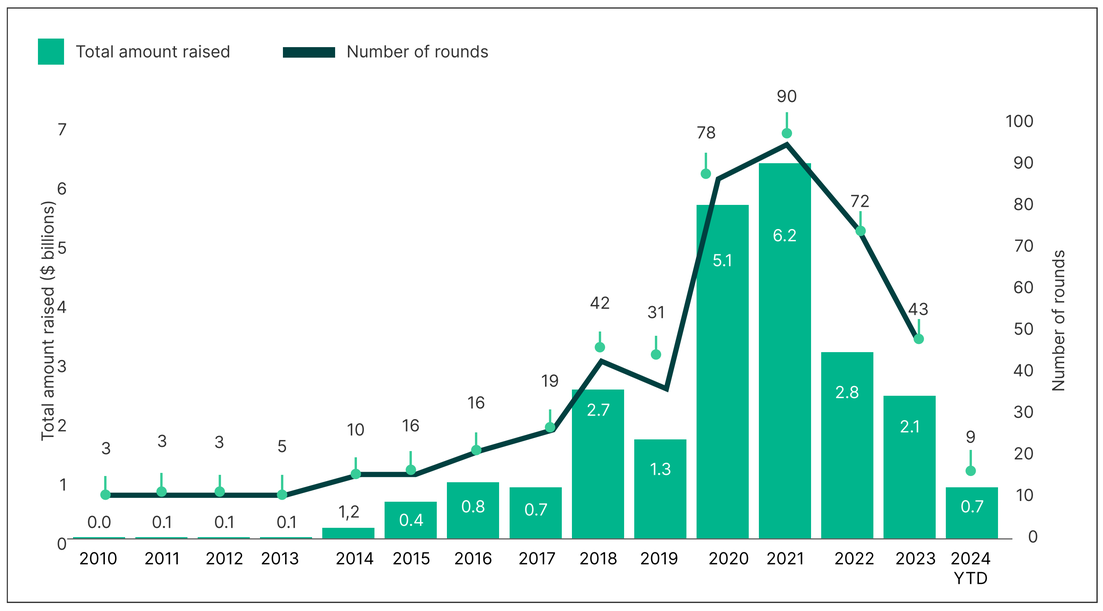
Figure 6: Total Venture Funding in Europe; Nature Biotechnology; DealForma Database



China Biotech Venture Funding

The Chinese venture market paints a different story, and continues a downward trajectory in 2024 which is on pace to end around 2019 levels, but well below 2022 and 2023 (Figure 7).

Figure 7: Total Venture Funding in China; Nature Biotechnology; DealForma Database

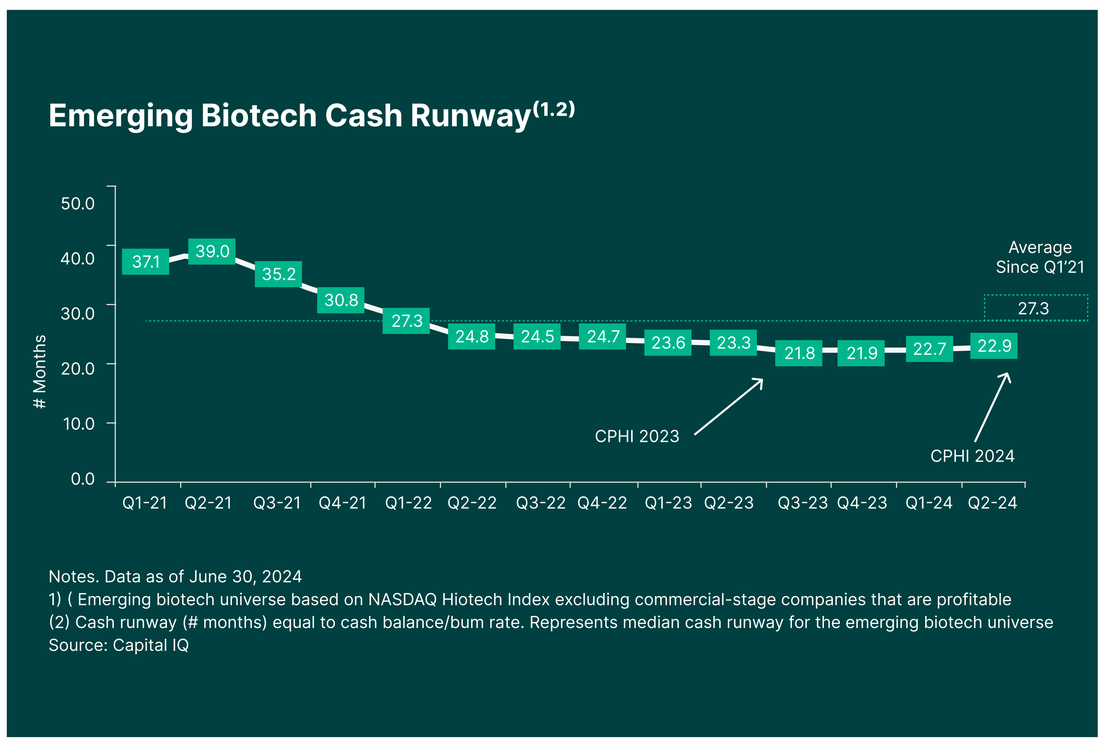


China is still trying to navigate geopolitical obstacles, fallout from the US BIOSECURE Act, and other economic issues which have affected venture investment.

Biotech Cash Runways Stabilizing:

Last year we looked at Biotech's cash runway given the lack of evidence of a sustained financial recovery. At that time, the cash runway was well under two years, and the trajectory was still declining (Figure 8). Biotechs were doubling down on cash preservation mode, and this rippled out into the CRO/CDMO sector.
This year, with generally more solid evidence that we are in the beginning of the recovery phase, the cash runway seems to have stabilized from a trough in Q3/Q4 2023, and has now started a slow recovery.

Figure 8: Capital IQ; KPMG Corporate Finance - US Biopharma Services Industry Update H1 2024



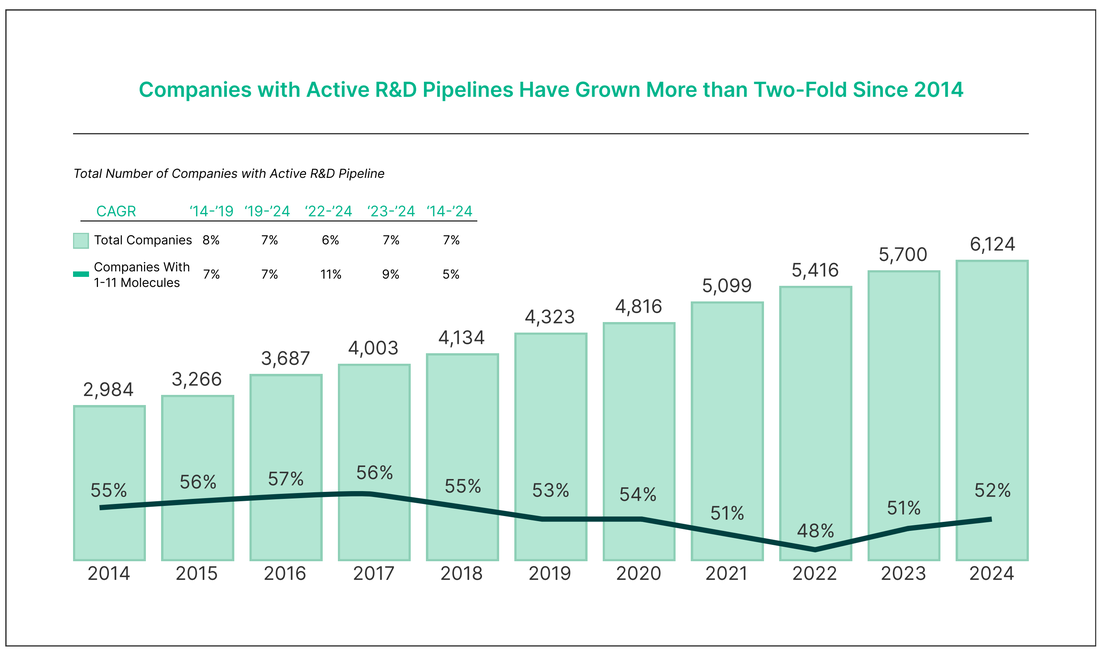
An improving cash runway, along with improving economic conditions and interest rate cuts, means biotech's should start moving back into more traditional spending patterns with CRO/CDMO's reflecting more confidence in the next 12+ months financial outlook. This will, however take time to start rippling over into the pharma services sector, and CRO/CDMO's should be monitoring closely average proposal value improvements, and time-to-close as leading indicators here.

Still Too Many Biotechs….Still Too Little Cash

In last year's CPHI annual report we discussed the capital supply/demand imbalance, and large number of biotech companies vying for too little capital which was putting pressure on valuations and distribution of capital across the sector.

In spite of some consolidations and rationalizations within the biotech sector, the total number of companies with active R&D pipelines has continued to grow through 2024 (figure 9). As of mid-year, there are now over 6000 pharma companies with active R&D pipelines, and over 50% of these companies have only 1-2 products in the pipeline.

Figure 9: Number of Biopharma Companies, Pharma Intelligence, Piper Sandler, Sept 2024



Source: Pharma Intelligence - Annual Review

More biotechs mean more fuel required to progress pipelines, and while funding into the sector is generally showing signs of life, there are more companies today (versus last year) vying for available capital. Investors have nearly infinite choices on where to invest in the sector, and with more biotechs, more compounds in development, and only slightly more capital flowing, investors have been even more discriminating around where they are investing.

So Where are Investors Placing Their Bets in 2024?

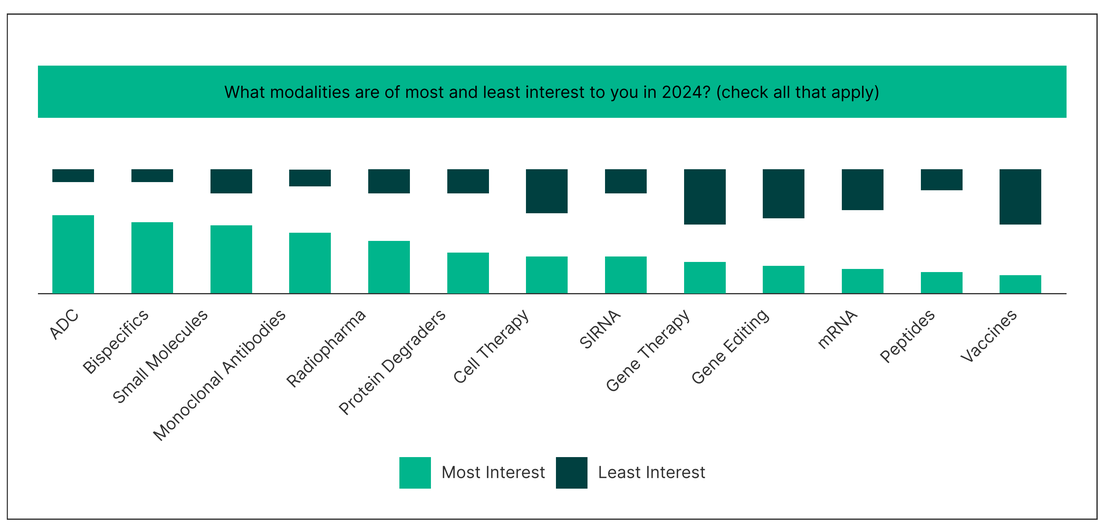
Generally speaking, in the current environment, investors have gotten more cautious and have

tended towards focusing on: 1) Therapeutic assets/modalities with more of a historical track record of success, and 2) Those therapeutic programs that are further advanced in the clinic. So where are investors placing their bets?

Biotech Investment By Therapeutic Modality

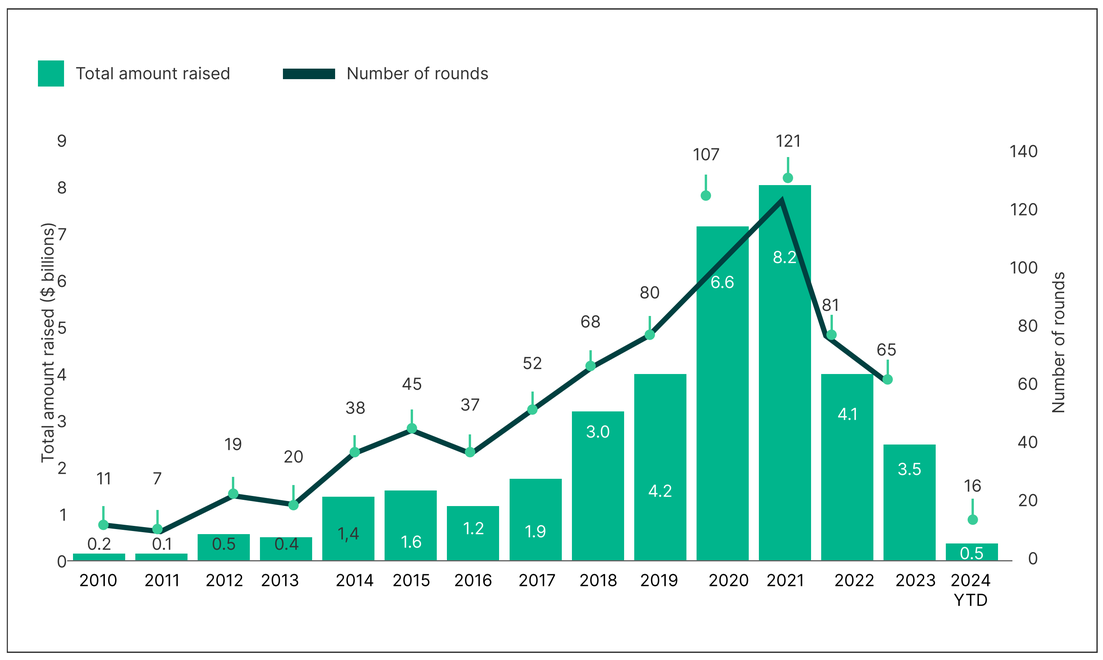
Highlighting current investor sentiment, Oppenheimer's 2024 proprietary survey pinpoints where investors view the best bets in the current biotech investing environment (Figure 10).

Figure 10: Oppenheimer 2024 Proprietary Investor Survey. Presented at Chemoutsourcing Sept 2024



According to the survey, ADC's, Bi-specifics, and Small Molecules top the list. Surprising is the lower interest noted in cell and gene categories, given the public funding into those companies has been strong in 2024. However looking at early stage venture funding into cell and gene reveals a deep trough in these modalities in 2024 (Figure 11).

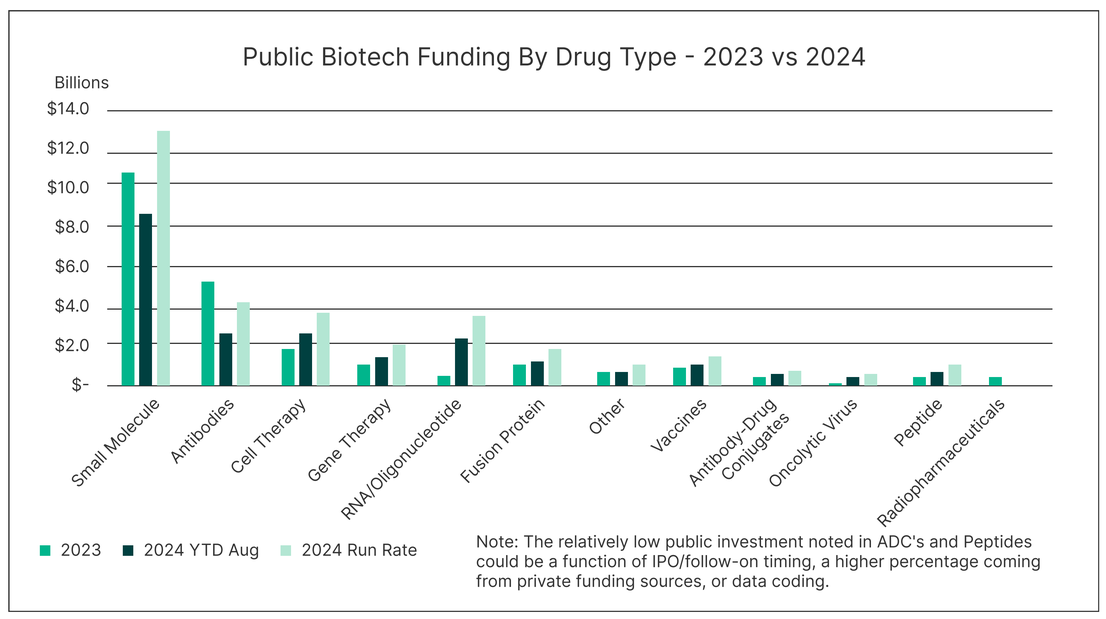
Figure 11: Venture Funding - Cell and Gene companies; Nature Biotech August 2024, Dealforma Database H1 2024



As of mid-year 2024, only 16 CGT companies received venture rounds totaling only $500M, compared with 65 companies receiving $3.5Bn in all of 2023. Investors have cited clinical, manufacturing, and commercial hurdles as reasons to be more cautious.

Turning to public funding by drug type (Figure 12), the data reveals the top 5 modalities receiving public investment thus far in 2024 is small molecules, followed by antibodies, cell therapies, oligonucleotides and gene therapies. The biggest public funding increases versus 2023 came in oligonucleotides and cell therapies.

Figure 12: Public Biotech Funding (IPO's and Follow-ons only). Source: Dealogic funding data for public markets



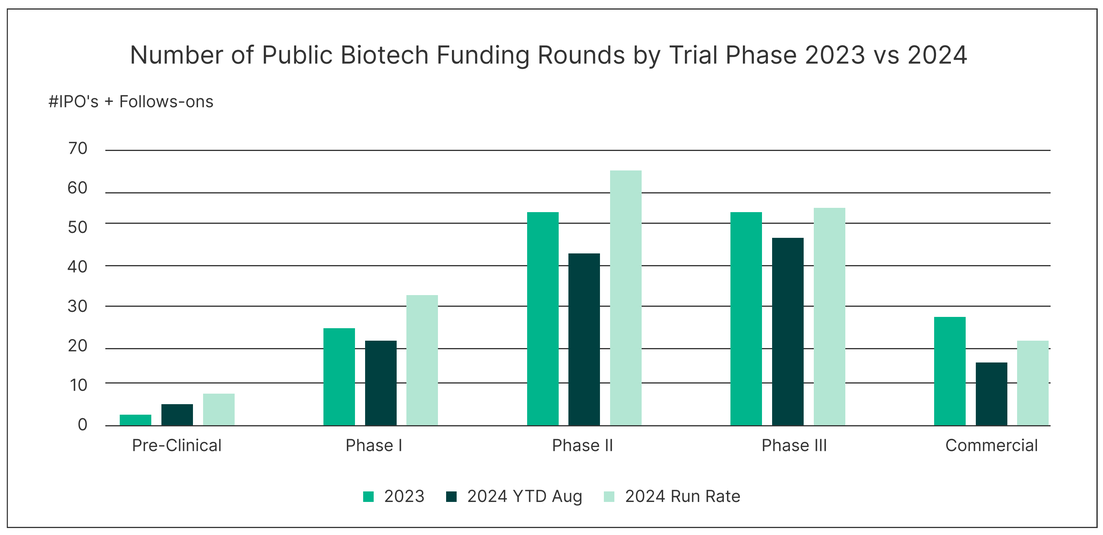
According to Biopharma Dive's US Biotech IPO tracker, as of September 2024, 18 IPO's launched thus far which is nearly the level of the number launched in all of 2023.

Biotech Investment By Stage of Development:

According to Pitchbook, through mid-year 2024, private venture investment into preclinical phase biotech was around 28% of the total (~$3.5Bn), while 62% (~$7.6Bn) went to support clinical stage companies. Overall the percentage is down from previous years. Notably, increasing investment in preclinical biotechs drove 2021 and 2022 to record funding levels.

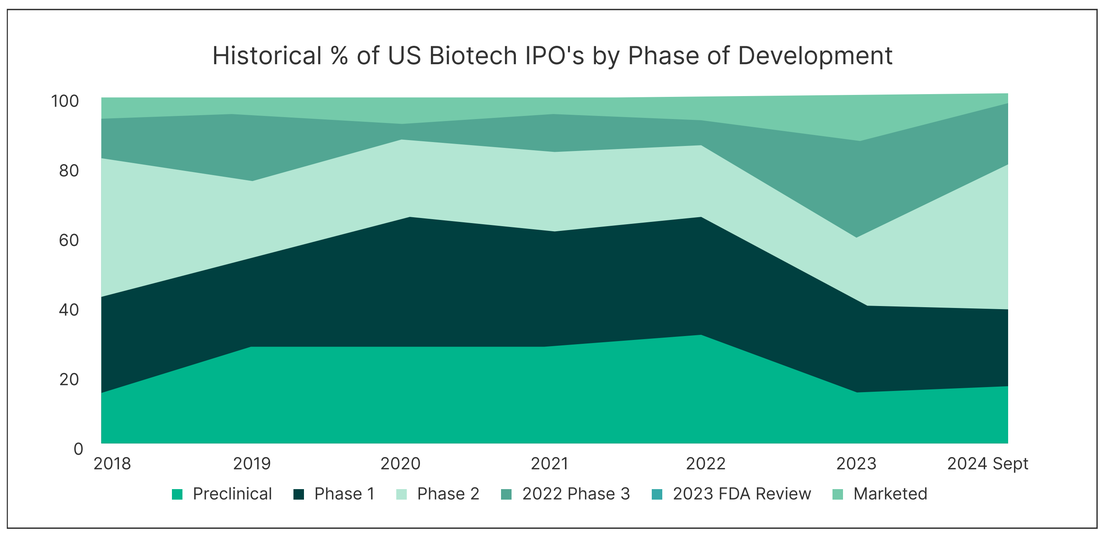
With less private funding going towards early-stage biotech, many have tried to turn to the public markets, however IPO's and public follow-ons are now heavily tilted towards clinical stage where more advanced ("de-risked") assets and more seasoned management teams are in place (Figure 13).

Figure 13: # of Biotech IPO's + Follow-ons by Lead Phase of Development; Dealogic funding data for public markets



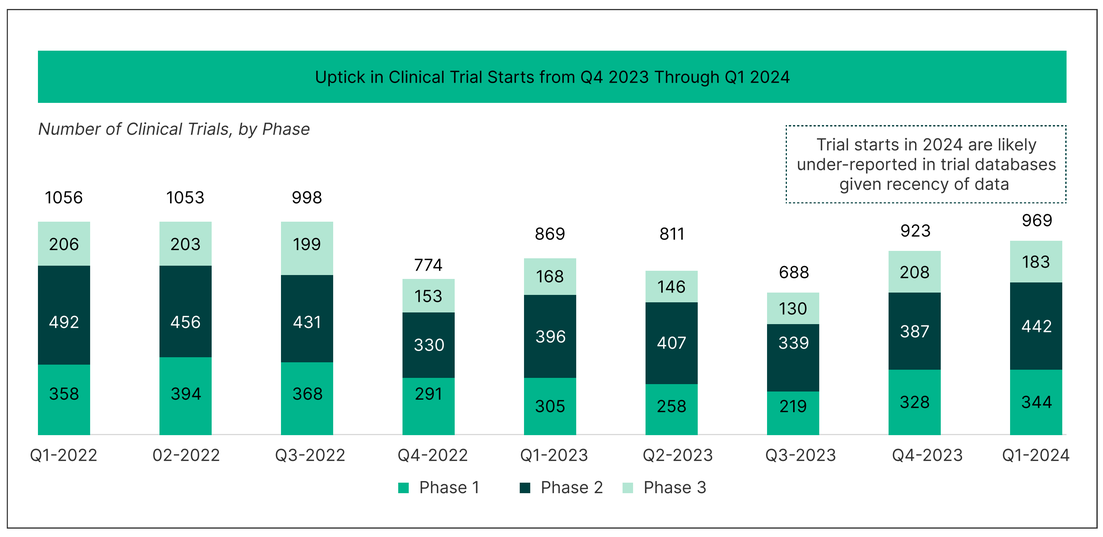
Also noteworthy is the percentage IPO's in preclinical companies is at about half the rate seen over the prior 4 years (Figure 14). With the overall share of public and private funding tipping towards clinical biotech, it is not surprising that the platform/preclinical stage biotechs have been feeling a significant funding pinch.

Figure 14: Percentage of US Biotech IPO's by Lead Phase of Development, Biopharma Dive.



Conversely, the jump in relative funding into clinical phase companies appears to be fueling an uptick in clinical trial activity. Starting in the fourth quarter of 2023 and continuing into 2024 there has been an increase in Phase 1 and Phase 2 clinical trial starts (Figure 15).

Figure 15: Clearview, Globaldata, Harris Williams Pharma Services Sector Brief Q2-2024

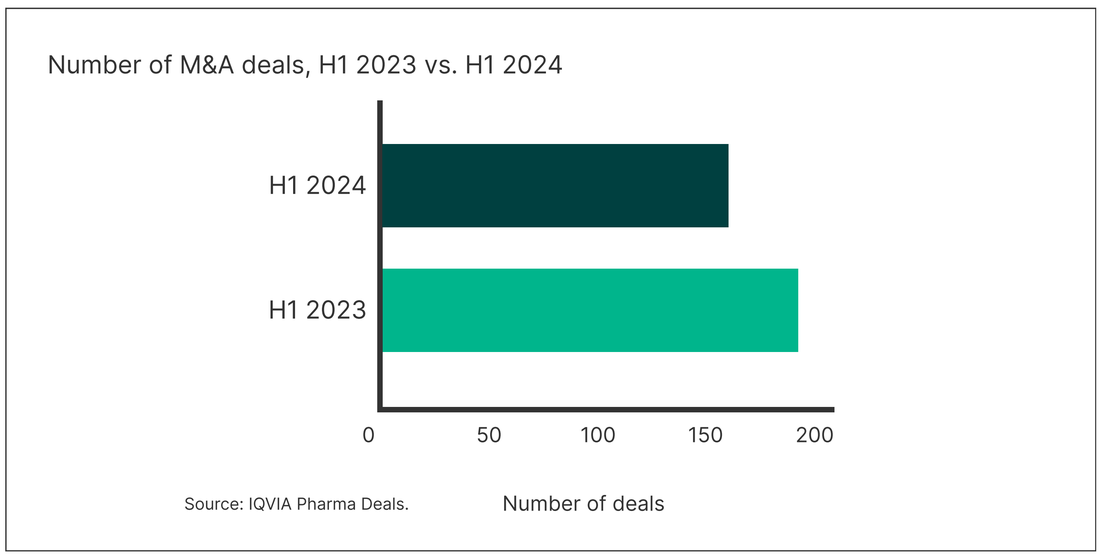


What's Going on at Big Pharma?

We can't overlook big pharma in this equation. In fact, big pharma is the life blood for many of the largest CRO's and CDMO's in world, as they have historically relied on the larger integrated pharma service providers for more strategic long-term relationships. Over the past year, big pharma has generally continued its pattern of cost reductions in light of lingering economic issues, impending patent cliffs, and certain aspects of the Inflation Reduction Act. Big pharma may also be pursuing fundamental pivot away from outsourcing discovery and early R&D. So, what's going on at big pharma, and how might it impact the CRO/CDMO sector?

Impending Patent Cliffs and the Need to Accelerate M&A: Big pharma has around $190 billion in patent exclusivity at risk between now and 2033. This is putting pressure on them to accelerate M&A, particularly given they are sitting on $150 billion in dry powder. The industry expectation in 2024 was for accelerated M&A growth at big pharma to address this. However, the first half of 2024 is about 20% behind the 2023 pace in terms of deal volume (Figure 16).

Figure 16: Iquvia Pharma Deals Half Year Review 2024



Iquvia cited continued macroeconomic pressures and regulatory scrutiny that kept deal activity muted in the first half of this year. Even despite the patent expiries, and the market's anticipation of more M&A, big pharma's M&A momentum appears slower than anticipated. Big pharma will need to pick up the pace of M&A over the next 12 months to address this.

Interestingly, similar to biotech investors, big pharma M&A activity in both 2023 and YTD 2024 has tended towards more de-risked assets. Iquvia noted that for all of 2023, preclinical M&A activity accounted for less than 5% of the total. In fact, big pharma M&A has favored acquiring more clinical phase companies and assets to help bolster the mid/later phase pipelines. Not

surprisingly, the lack of preclinical M&A, combined with the anemic venture funding in early development has led to some alarm bells at some of the early phase outsourced providers.

Pivoting Away From Outsourced Early R&D - Towards M&A? As part of big pharma's streamlining, it appears that a fundamental shift in its discovery and R&D outsourcing may be underway. Charles River Labs (CRL) recently cited a shift in the way big pharma handles outsourced discovery and early stage R&D activities. CRL has historically dominated this space with large, strategic programs from big pharma. CRL announced in August 2024 that it was significantly cutting its forecast due to a material and sustained pullback from big pharma in outsourced discovery and R&D services. CRL surmised big pharma would accelerate its M&A activities to effectively buy more advanced pipelines. A fundamental realignment of big pharma outsourcing behaviors here could cause shockwaves through the CRO world, particularly among those who currently rely on big pharma for early-stage outsourced business. CRL noted that this shift would mean that it would likely be getting more early-stage business from emerging pharma, however as pointed out earlier, in the near term, demand will remain muted here as funding into the early stage biotech sector has been anemic.

Shortly after the CRL announcement, Evotec announced a challenging first half 2024, down 7% driven by softness in its early-stage business in what it called "a slowdown in early-stage R&D spending". Note that Evotec mentioned they rely on both big pharma and biotech's across its business units.

Implications for CRO/CDMO's: If big pharma does pivot its outsourced discovery and R&D resources towards M&A, the early development falls back to the biotech companies, placing more emphasis on them as a key customer demographic for both big and small CRO/CDMO's in early development.

Layoffs Continue, But Signs of Stabilization: One significant initiative by big pharma has been to address cost reductions in order to further streamline their organizations for the future. A large component of this has been layoffs, and big pharma constitutes a large percentage of the layoffs industrywide. According to the Fierce Biotech Layoff Tracker, 2023 logged 187 total layoff events which was a 57% jump from 2022. As of September 12, 2024, 141 layoffs have been announced which is in line with last year's count at this time (138). It is estimated that around 25,000 employees have been let go in the pharma sector in 2024 as of mid-year.

Implications for CRO/CDMO's: Big pharma's continued streamlining means more R&D and manufacturing will need to be done externally. This only helps drive demand for outsourced pharma services.

Big Pharma "Owns" the GLP-1 Space: When asked "what's going on with big pharma?" GLP-1's cannot be omitted from the discussion. While big pharma has not originated all GLP-1's, they are clearly positioning to "own" this space. Several big players are all-in with these therapeutics, and it's not hard to understand why. Goldman Sachs estimates $44 billion, and Barclays' $100 billion by 2030. The current number one player in GLP-1's is Novo Nordisk, and at one point in 2023, Novo's growth exceeded Denmark's entire economic output.
The key big pharma players are Novo Nordisk, Eli Lilly, Amgen, Pfizer, Boehringer Ingelheim, and Sanofi (Antaros). Several have either announced major capital expansions to plan for the ramp in demand, and Novo acquired Catalent specifically for the capacity needed to support growth of its GLP-1's. In addition to the internal investments by big pharma, GLP-1's are catalyzing another wave of major capacity expansions across the CDMO landscape.

Implications for CRO/CDMO's: Given the volumes of GLP-1's anticipated, the amount of capacity required will clearly be a net positive for the CDMO community, and the larger CDMO's will benefit, given their critical mass and ability to for further expansion. Note that manufacture of peptides is not trivial, and require specialized equipment. New technologies are also be developed which can plan an important role here as well.

Other Regulatory Factors Affecting Demand for CRO/CDMO Services

Update on the Inflation Reduction Act: In August of 2022, the Inflation Reduction Act (IRA) was passed in the US. One of the major elements of the IRA is the US government's ability to negotiate prices for top-spending Medicare drugs. The timing for small molecule price negotiations was 9 years after approval, and large molecules would be 13 years from approval. The pharma industry has estimated the potential impact of $10's to $100's of billions in future profit lost.

Iquvia provided an update at a recent JP Morgan conference. They noted that the pharma industry is looking at new clinical trial strategies to combat the impact of the IRA. For example, if a drug has multiple indications, innovators would consider running multiple indications simultaneously and launch simultaneously, rather than running more sequential trials. This is because price protections are by molecule and not by indication

Pharma companies are also looking closer at therapeutics with more marginal economic profiles, and some believe they may start favoring more large molecules over small, given the 4 years of additional price protections for them. Interestingly, the current venture, follow on, and IPO data suggests small molecules have continued a strong bet in 2024. We will see what 2025+ brings.

Implications for CRO/CDMO's: Enhanced regulation and government price negotiations will be a net negative for the financial health of the sector, and generally put downward pressure on CRO/CDMO demand. However, should pharma companies run indications simultaneously, this could lead to increased demand for services.

BIOSECURE Act – US Biotech Now Inextricably Linked to US National Security: Earlier this year, legislators in the US sent shockwaves through the industry with the release of the BIOSECURE Act. It effectively bans the federal agencies and recipients of federal loans or grants from contracting or purchasing goods or services from certain companies seen to be closely associated with adversaries of the United States for national security reasons. A transition period of 8 years (2032) has been proposed for companies of concern. Five companies currently listed in House bill are WuXi AppTec, WuXi Biologics, BGI Group, MGI Tech, and Complete Genomics. The bill passed the US House of Representatives by a very wide margin (306-81) on September 9, 2024. The bill moves to the US Senate next, then on to the Presidents desk.

To be clear, the BIOSECURE Act does not explicitly prohibit all private U.S. companies from working with the companies cited in the bill, provided they have not taken any US grants or loans. However the disruption (and confusion) the bill has caused is as if the ban had extended to the broader biopharma community.

Companies across the industry are re-evaluating their supply chain strategies, and the potential impact of additional companies-of-interest being added to the list. WuXi in particular has been in the spotlight because of the prominent role it plays with US-based companies who are developing therapeutics. WuXi generates about 65% of its revenue came from U.S. customers, totaling $3.6 billion. However, the ripple effect has gone far beyond WuXi as it relates to Chinese suppliers. In my discussions with several Chinese suppliers doing business in the US, few have said their businesses have not been impacted. Many have seen a noticeable downturn in at least parts of their business. They attribute this to US-based customers looking for alternative options, or looking to site new programs in alternate geographies.

Noteworthy however is the sheer scale of what has been built in China in terms of chemical and biologics capacity, and it is not realistic to consider that a wholesale shift will happen quickly. WuXi alone holds over 10% of the global biologics market share as of 2022 according to a Jefferies report. The world relies heavily on China for everything from raw materials to intermediates, to API's, and Biologics for any exodus to be rapid and wide spread.

Implications for CRO/CDMO's: A net positive for US-based CRO/CDMO's, and service providers in countries not considered foreign adversaries of the US. One risk is any retaliatory actions from

China that could disrupt the flow of key raw materials and intermediates.

Demand for CRO/CDMO Services – 6 Key Takeaways for the Coming Year

Given the current biotech, big pharma, and regulatory landscape what are Six Key Takeaways for CRO/CDMO's over the coming year?

1. ***Stability and Growth for Clinical CRO's and CDMO's:*** Demand for CRO/CDMO services focused in clinical development programs should see stability and continued growth in demand over the next year. Both clinical stage biotech and big pharma continue to spend and invest in progressing clinical assets which have been considered less risky bets for investment over the past 18 months. Also noteworthy, is how the capital flows out to the CRO/CDMO community. Typically as spend picks up, the CDMO's will see the first signs as drug substance, then drug product will need to be secured first before the clinical CRO's take over on trial execution.

2. ***Continued Softness for Discovery/Pre-clinical CRO/CDMO's:*** Given early stage funding has been anemic the past couple of years, the early-stage pharma service providers have felt the slowdown perpetuate and even accelerate over the past year. Anecdotally, our discussion with over 50 smaller CRO/CDMO's over the past year have revealed generally consistent feedback of an accelerated slowdown felt mid 2023 into 2024. This is likely to continue for the next 6-12 months before a meaningful rebound in funding flows through the system.

3. ***Stronger Demand for Services in ADC's, Small Molecules, and Biologics…For Now:*** Investors have tended toward more "tried and true" therapeutic modalities over the past 12-18 months as they are considered less risky than CGT's or other advanced therapy platform investments. CRO/CDMO's with focus in R&D or manufacturing of therapeutic modalities such as ADC's, Biologics (Bi-specifics/mAbs), Small Molecules will likely see more stability, and a ramp in momentum through 2024 and into 2025.

4. ***Mixed Bag of Demand for Cell & Gene CRO/CDMO's:*** Those service providers working with advanced therapies such as CGT's will likely see a continuing mix in demand profile which is reflective of the current funding environment. Clinical phase demand for services in this area should continue to improve, however early phase CGT companies have been hit disproportionately hard in 2023 and continuing into 2024. CRO/CDMO's focused here should expect slow demand to continue well into 2025.

5. ***Specialty CRO/CDMO's to Play an Important Role:***

- Radiopharma: CDMO's with capabilities in handling radiopharmaceuticals are seeing strong demand, reflecting strength in these therapeutic modalities. Barriers to entry here are extremely high and could lead to a supply/demand imbalance in the near term as more radiopharmaceuticals make their way into the clinical pipelines.
- Peptides: While peptides certainly aren't considered "niche" or "specialty" therapeutic modalities, the drug substance manufacturing processes require specialized expertise not common to all CDMO's. GLP-1's in particular have gotten most of the attention, and rightfully so given the market size and potential. Traditional liquid and solid-phase synthesis approaches can have scalability issues, and the GLP-1 boom has brought attention to this issue. Technologies like continuous liquid-phase synthesis (ie. Snapdragon Chemistry) are niche approaches that could benefit here. CDMO's who are able to innovate more scalable and cost-effective manufacturing will have clear advantages here.

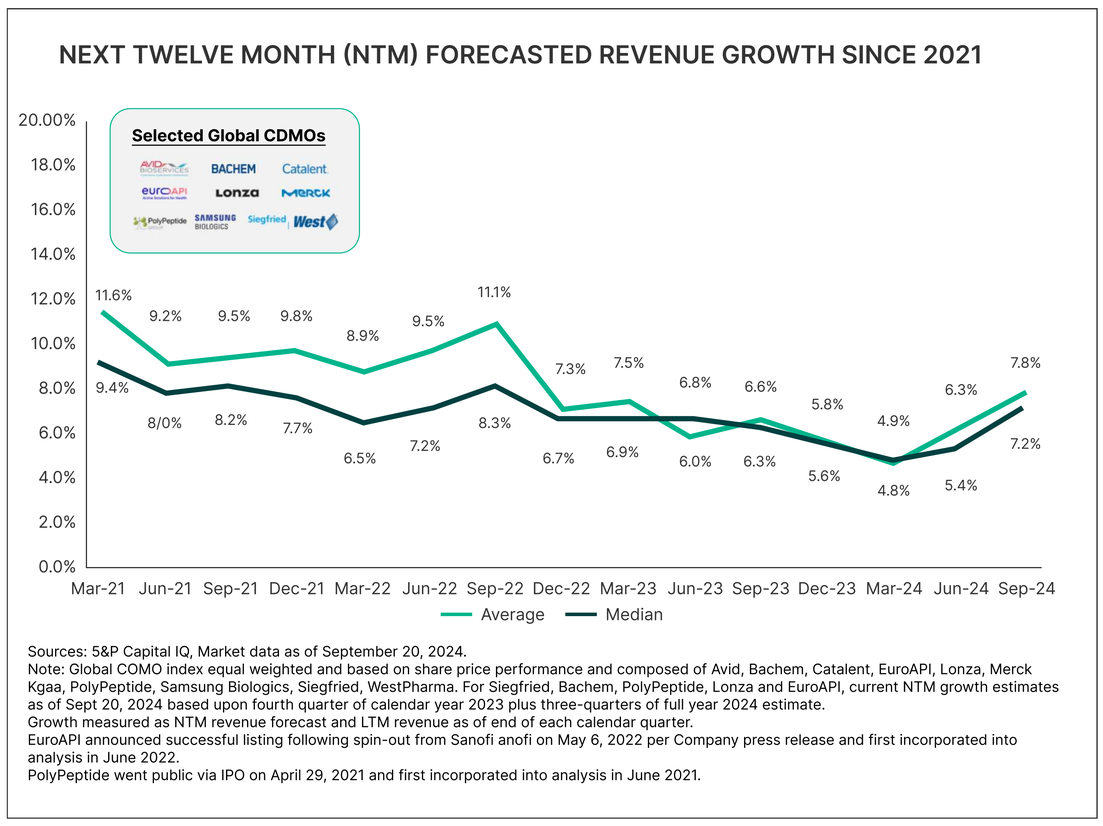
6. ***Biosecure's Ripple Effect to Expand:*** The US BIOSECURE Act is likely to pass in the next year based on the bipartisan political climate in the US. In spite of the limited scope of the bill, misunderstandings around the bill, and the future uncertainty of broader US scope or Chinese government retaliation, momentum could continue to further shift towards alternate sources of supply outside of China. These will inlcude North America, EU, India, or other countries not considered adversarial to the US. The ripple effect is already being felt by Chinese CDMO's (those not referenced in

BIOSECURE feeling slowdown in demand). Conversely, our discussions with several CDMO's in the US, EU, and India have seen programs shifting to these geographies, although not widespread yet.

How are CDMO's Feeling About the Future?

A proxy for the health of the CDMO industry is how the larger public CDMO's are viewing the market and their outlook for the next 12 months (Figure 17).

Figure 17: Public CDMO Growth Outlook



Sources: 5&P Capital IQ, Market data as of September 20, 2024.
Note: Global COMO index equal weighted and based on share price performance and composed of Avid, Bachem, Catalent, EuroAPI, Lonza, Merck Kgaa, PolyPeptide, Samsung Biologics, Siegfried, WestPharma. For Siegfried, Bachem, PolyPeptide, Lonza and EuroAPI, current NTM growth estimates as of Sept 20, 2024 based upon fourth quarter of calendar year 2023 plus three-quarters of full year 2024 estimate.
Growth measured as NTM revenue forecast and LTM revenue as of end of each calendar quarter.
EuroAPI announced successful listing following spin-out from Sanofi anofi on May 6, 2022 per Company press release and first incorporated into analysis in June 2022.
PolyPeptide went public via IPO on April 29, 2021 and first incorporated into analysis in June 2021.

After nearly three years of declines and a low point in March 2024, CDMO's on average, anticipate increased growth over the next 12 months. A good sign generally that the CDMO market is in the beginning stages of the recovery.

CRO/CDMO Valuations and the M&A Climate

[Body] Since last year's CPHI, public CRO/CDMO's valuations have generally improved (Figure 18). 2023 ended with public valuations around pre-pandemic levels for CDMO's and slightly lower for CRO's. 2024 has seen a rebound in public valuations through August TTM with CDMO's up ~35% and CRO's up ~30% from 2023.

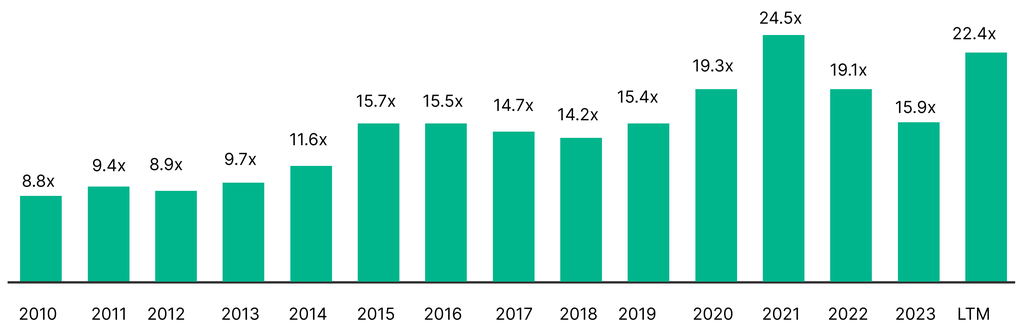
Figure 18: William Blair Equity Research, Pharma Services Update, August

Equity Performance

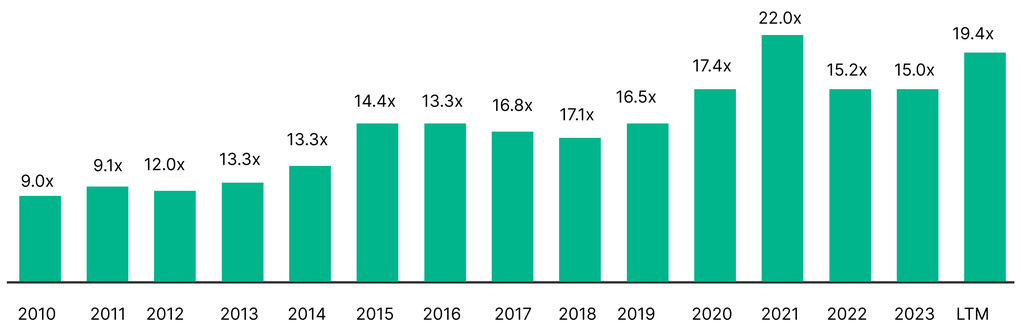
	Companies	Market Cap (SM)	YTD Price Performance	2024E Revenue	2024E EBITDA	23-24 Revenue Growth	2024E Gross Margin	2024E EBITDA Margin	EV/LTM EBITDA	EV/2024E EBITDA
CDMOs	AVID BIOSERVICES	$451	9.8%	$158	$21	15.5%	10.6%	13.5%	NMF	29.3x
	Catalent	$10,161	22.2%	4,385	838	7.0%	17.9%	19.1%	32.2x	17.8x
	Lifecore BIOMEDICAL	$195	(17.1%)	136	18	11.1%	0.0%	13.0%	22.1x	18.3x
	Lonza	$145,251	38.6%	7,283	2,061	(0.9%)	34.1%	28.3%	19.5x	20.9x
	Siegfried	$4,171	8.6%	1,424	314	2.3%	25.8%	22.1%	15.7x	14.6x
	Median	$4,171	9.8%	$1,424	$314	7.0%	17.9%	19.1%	20.8x	18.3x
	Mean	$11,246	13.0%	$2,677	$650	7.0%	17.7%	19.2%	22.4x	20.2x
CROs	charles river	$12,462	(12.6%)	$4,221	$1,272	2.2%	36.7%	30.1%	14.2x	12.1x
	Fortrea	$3,479	(33.1%)	$2.801	$283	(9.9%)	18.4%	10.1%	19.0x	17.8x
	ICON	$25,990	10.7%	$8,645	$1,840	6.5%	29.9%	21.3%	16.8x	15.9x
	IQVIA	$44,081	(8.6%)	$15,477	$3,760	3.3%	35.3%	24.3%	15.9x	15.1x
	MEDPACE	$12,786	34.4%	$2,170	$430	15.1%	28.5%	19.8%	31.2x	29.2x
	Median	$12,786	(8.6%)	$4,221	$1,272	3.3%	29.9%	21.3%	16.8x	15.9x
	Mean	$19,760	(1.9%)	$6,663	$1,517	3.4%	29.8%	21.1%	19.4x	18.0x

EV / LTM EBITDA Multiples Over Times

CDMO Sector

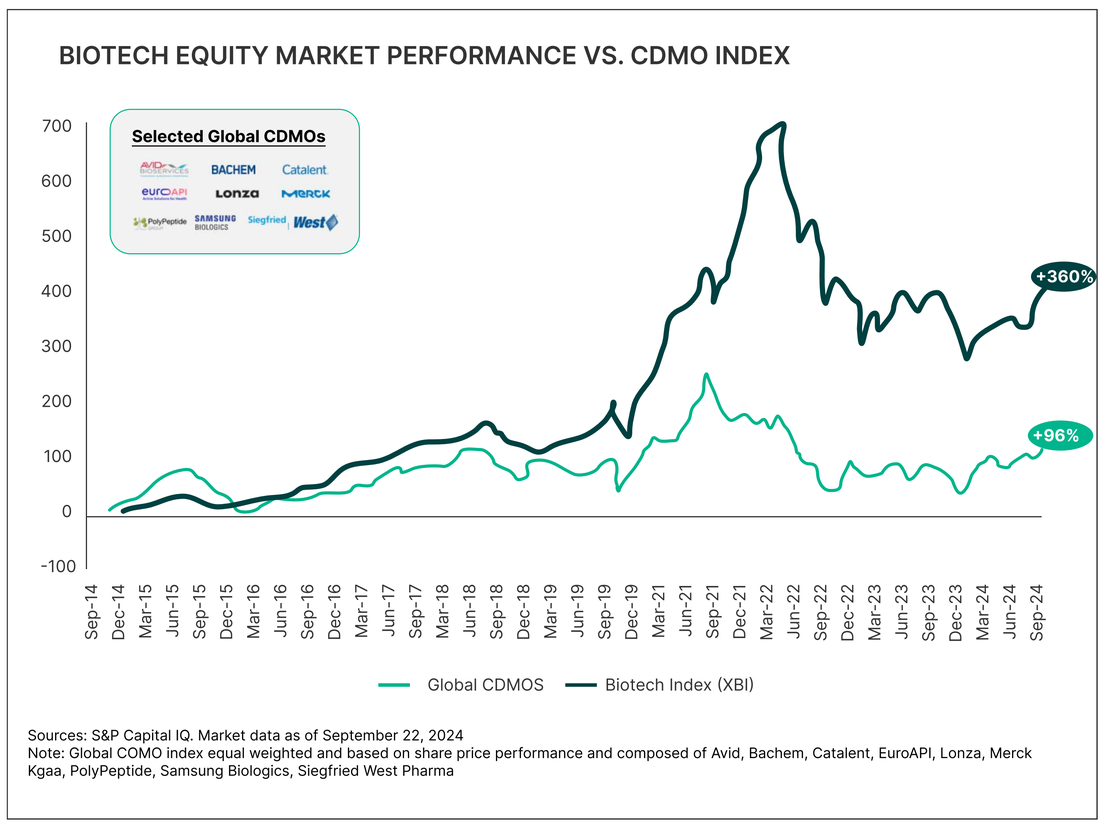


CRO Sector



The Public CDMO sector performance index has also fared well against its biotech cousin, the XBI (Figure 19), reflecting investor confidence in outsourced pharma services versus the underlying therapeutic asset.

Figure 19: Biotech equity market performance (XBI) vs CDMO index.



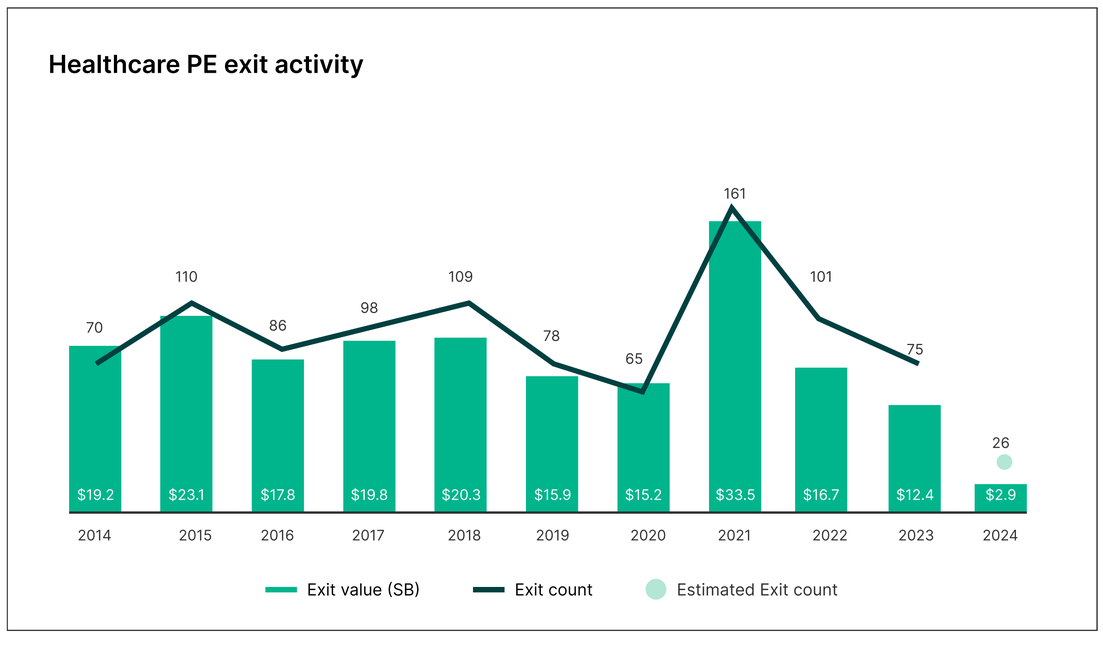
Sources: S&P Capital IQ. Market data as of September 22, 2024
Note: Global COMO index equal weighted and based on share price performance and composed of Avid, Bachem, Catalent, EuroAPI, Lonza, Merck Kgaa, PolyPeptide, Samsung Biologics, Siegfried West Pharma

What's Going on in the Private Equity World?

PE Portfolio Exit Activity:

The private equity (PE) landscape has not been as rosy over the past year, as the number of PE exits continued a downward trajectory with 2024 shaping up to be significantly behind 2023 (Figure 20).

Figure 20: Healthcare PE exit activity; Pitchbook



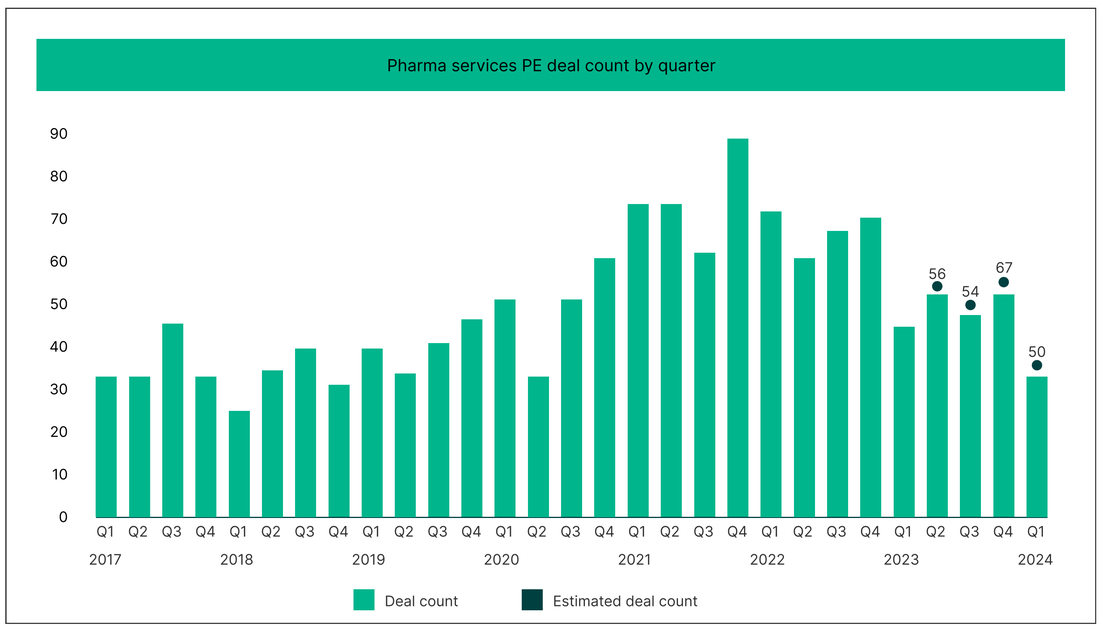
Given the clogged exit and activity, Pitchbook notes the median hold period of PE investments reached a record of 6.4 years for US PE middle-market assets in 2023. Correspondingly, the exit/investment ratio fell to 0.36x in Q2 2024, a new low that reflects the sluggish PE exit climate, and the number of unsold portfolio companies is getting large, preventing distribution to investors.

While the economic climate has not been cooperative for PE exits, their portfolio companies have been using the past two years to improve operational efficiencies in light of increasing interest rates, inflation and dealing with a generally more tepid market impacting their performance. According to Bain Capital as rates ease in the coming year, exits should recover faster than they did in the wake of the global financial crisis.

PE Pharma Service Deal Activity:

In terms of Pharma Services PE activity, the number of deals per quarter has generally been trending down since the record quarter logged in Q1 of 2022. Q1 2024 was among the lowest number of deals in the past six years (Figure 21) in spite of the large amount of dry powder available for M&A.

Figure 21: Global PE Pharma Service Deals, *March 2024; Pitchbook

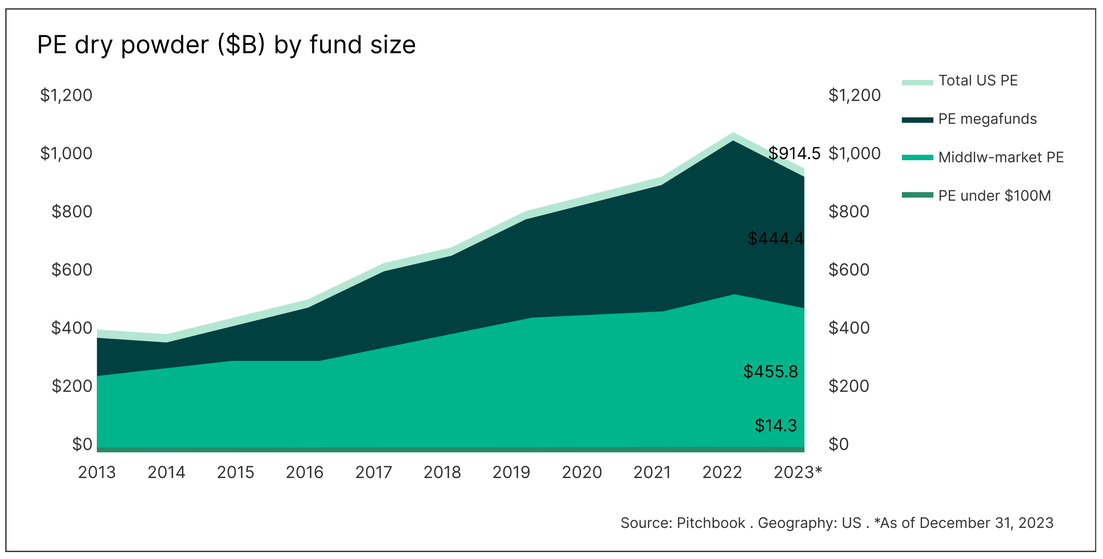


The PE Pharma Service subsector deal activity reveals an uptick in the percentage of minority capital investments in the CDMO sector over the past three years, with percentage of platform investments in CDMO generally shrinking. In the CRO sector there has been an increase in the percentage of add-on M&A activity as PE's pivot their focus on their growing their existing portfolio companies rather than more platforms in this environment.

PE Dry Powder Still Near Record Levels:

However there still remains plenty of dry powder in PE, and US PE firms are still sitting on nearly a trillion dollars of dry powder (Figure 22).

Figure 22: US PE Dry Powder; Pitchbook



Source: Pitchbook . Geography: US . *As of December 31, 2023

According to Bain Capital, 26% of global PE dry powder is four years or older, and general partners are under increasing pressure to deploy capital. At the same time LP's are looking for a return on invested capital, however the M&A environment has been clogged on both sides.

Last year we noted that the investment banking community was signaling an increase in pitch volume later in 2023 and the expectation of PE deal volumes to increase in 2024. While this has not materialized, the broader economic landscape, lower inflation, improving funding into the biotech sector all point toward a better overall picture today versus last year's CPHI. As a result, there is room for more optimism around and an improving PE M&A climate over the next 12 months.

Summary on the Health of the CRO/CDMO Sector:

Since last year's CPHI, there are more clear signs that the funding environment is indeed improving, and the long-term demand drivers continue very positive for CRO's and CDMO's. As such, demand for services should generally improve in the CRO/CDMO sector the coming 12 months, however not all segments will feel this equally. A steadier improvement should be seen by those focused on supply services into clinical/ commercial phase programs, and with expertise in more traditional therapeutic modalities (ADC, Biologics, Small Molecules). Those service providers focused in earlier stages of development and advanced therapeutics (such as CGT's) will likely sluggishness continue until investors dial back their risk profile on early R&D and platform therapeutic investments. Note the recent US Federal Reserve rate cuts in September 2024 should act as a catalyst to accelerate investment (and optimism) into sector.

Public CRO/CDMO valuations have generally improved somewhat versus last year, and for private/PE-owned companies, we are hearing that valuations have modulated a bit, but quality businesses with some scale (>$5M EBITDA) are generally trading at strong multiples.

For private equity, both deal volume and exits have continued sluggish over the past year, while PE is still sitting on near record levels of dry powder. However as the economic landscape improves, Fed rate cuts take hold, and portfolio company performance and valuations improve, the outlook is favorable for both PE exits to start to start flowing again, and M&A activity to pick up in the coming 12 months.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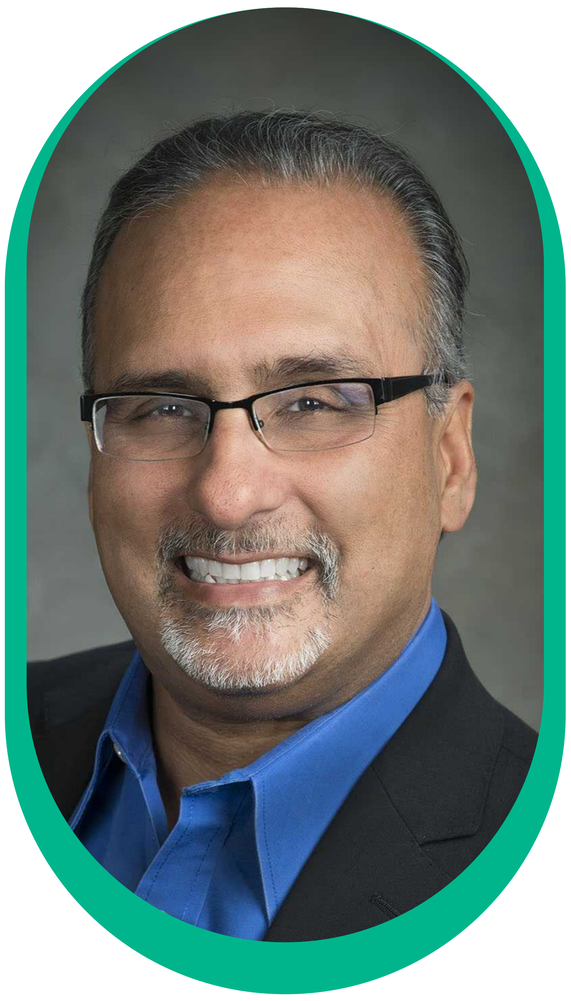
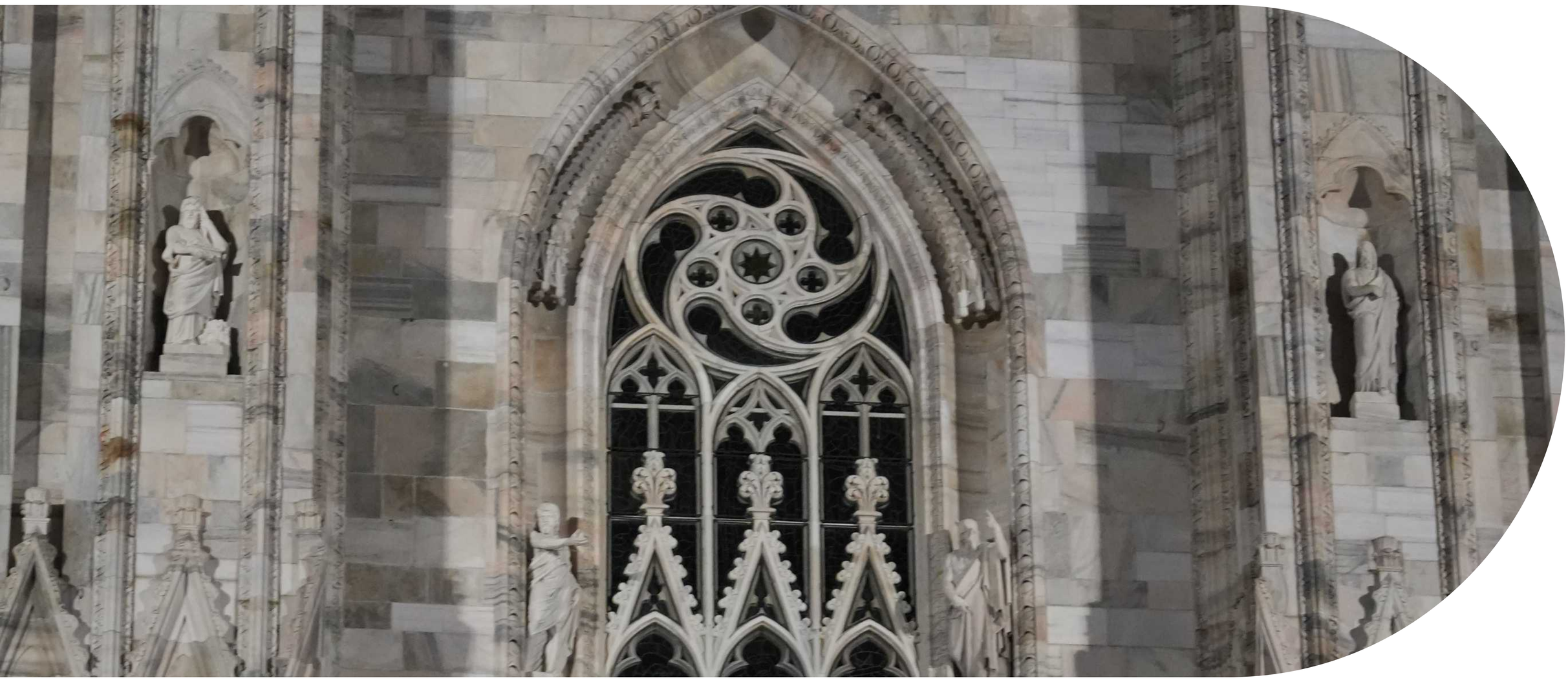
Digital Transformation

Data Harmonization Will Accelerate Drug Development In The Next 5-Years



Bikash Chatterjee

President and Chief Science Officer,
Pharmatech Associates- a USP company



The pharmaceutical industry has yet to fully realize the transformative potential of its most innovative tools despite unprecedented advances in science and technology. Artificial intelligence, organ-on-a-chip technologies, and advanced predictive modeling promise accelerated development of pharmaceuticals by simply performing key steps in the development process better.

What motivates us is the cost of drug development that continues to rise. A recent study concluded that the average cost of developing a new therapeutic agent has nearly tripled in the 21st century, from $1.3 billion in 2003 to $3.4 billion in 2013 (adjusted to 2023 U.S. dollars).1 The fact is that 90 percent of all drugs in development never make it to market2 and the industry has been pursuing a fast-to-fail strategy for decades with meager success. The potential for innovations lies in identifying safe and effective compounds, but regulatory, compliance, and organizational barriers exist and full deployment may be years away. In the interim, an enhanced ability to understand a drug's viability has value in combination with conventional tools and approaches in today's drug development. Structured portfolio management for early development programs has often drifted toward art over science; however, applying innovation tools that bring insight into higher probability compounds could divert capital to lower risk programs that reduce the high costs that dog drug development.

The Innovation Paradox

Ours is the only industry where the consumer assumes the product is both safe and effective. The pharmaceutical industry considers itself innovative, but much of the innovation is in discovery with drug development remaining risk averse as programs move to later clinical phases. This is a unique paradox, in part driven by the conservative nature of health authorities. The framework for developing drugs has been in place for decades and straying means potentially overlooking a risk or deficiency with consequences on patient safety or drug efficacy. This creates a dichotomy where drug innovators seek to minimize risk exposure as imposed by regulatory compliance, while the same regulatory machine expects drug companies to innovate.

Innovations can create new and greater understanding that challenges what we know and what we perceive of as risk. With the emergence of new complex modalities health authorities have become more comfortable with innovative solutions; however, industry has been slow to pounce on the shift in thinking. One need only observe the sluggish adoption of PAT, or of rapid microbial testing and pharmaceutical continuous manufacturing as proof. Health authorities continue to look to industry and academia to characterize and address the difficult questions in hopes of providing enough guidance and direction for industry to continue to innovate.

Digital Models

As part of the FDA Modernization Act signed into law in December 20223, the FDA stated it would no longer require animal testing for new drug applications— an opportunity to replace a poor predictive model with a better approach. Animal models are poor proxies to humans as they themselves are complex systems. By logic, the output of an operating complex system should provide insight but without full knowledge of system mechanics. When paired with an innovation tool such as the organ-on-a-chip for example, these new tools approach a more representative human mimetic partially because they lack the dynamic of a complex system. This affords drug developers a human light model. It is both the lack of complexity and more approximate human mimetic that scares risk averse developers and regulators alike. It is left to industry to argue the merits of a surrogate approach to animal testing, which has been tough sledding for a drug development framework built upon risk aversion.

Shifting to more predictive digital models, whether at the molecule selection stage or at the manufacturing stage is a step toward greater insight and greater uncertainty at the same time. Most organizations embarking on digital transformation only realize a small percentage of the opportunity. A McKinsey survey4 concluded that only 16 percent of respondents say their organizations' digital transformations have improved performance and equipped them to sustain changes in the long term. The reasons for not realizing the full benefits range from no

clear vision as to why these innovations are being pursued, to poor change management, lack of a digital expertise, or a lack of a digital culture and infrastructure. While there is no problem generating data sets, data translation is the issue.

What is the Missing Link?

Impediments to adoption arise as new approaches spread across an organization, with innovations typically evaluated in isolation. Combining new technology or a new analytical approach with a traditional methodology would provide a comprehensive view and reduce uncertainty for a more informed choice about which drug candidates to advance, prioritize, or discontinue—ultimately leading to more efficient and successful drug development processes.

Innovations Shaping Drug Development

From CRISPR to Chat GPT, advanced technologies affect our industry in many ways. The following innovations have the potential to impact our industry's ability to identify molecule candidates with a high probability of success:

Artificial Intelligence (AI)

AI is beginning to revolutionize drug discovery and development by improving the efficiency and accuracy of data analysis and decision-making. It can accelerate target identification, lead compound discovery and drug repurposing through analysis of large datasets that create predictive models to address specific drug attributes that impact safety and efficacy. In drug development, AI enriches predictive modeling to deliver faster and more successful clinical trials. By integrating diverse data sources, AI enables real-time analysis and reduces risks by predicting potential failures early, ultimately lowering costs and speeding the development of new therapies.

Organ on a Chip (OOC)

OOC technology creates miniature, lab-grown models of human organs on microchips that mimic real organ functions. Using living cells and tissues, these chips provide physical human-like predictive modeling of drug behavior in a human system, reducing the reliance on animal testing. This leads to more precise drug testing, better identification of side effects, and a lower risk of late-stage drug failures, ultimately improving the drug development process.

Quantitative Systems Pharmacology (QSP)

QSP is an interdisciplinary approach that combines computational modeling with experimental and publicly available clinical data to understand drug interactions with biological systems and diseases. In drug discovery, QSP predicts how drug candidates will interact with biological targets, optimizing drug design and identifying potential biomarkers. In drug development, QSP can simulate clinical trials virtually, helping to optimize dosing, select appropriate patient populations, and reduce trial failures. Overall, QSP enhances drug development by improving predictive accuracy and supporting more informed decision-making.

Digital and Predictive Modeling Techniques

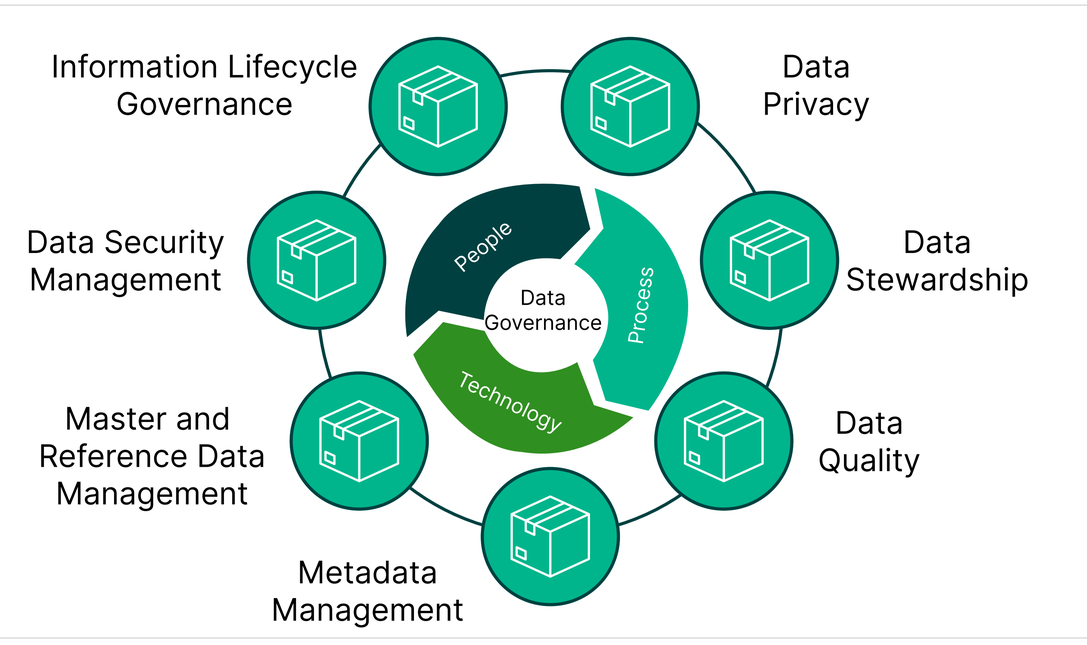
Pre-dating AI, this approach to drug development involves using computational techniques to simulate biological systems and predict drug interactions, as well as efficacy and safety. These models can integrate data sources across the drug development lifecycle for a comprehensive understanding of drug behavior. By simulating drug responses and optimizing clinical trials, digital models enable faster, more accurate decision-making, reduce development time and costs of bringing safer, more effective drugs to market.

Data as a Product: Intelligent Data Management

An intelligent data management framework is essential to create and manage high quality data and to realize their value. Beyond accumulating and aggregating this incorporates managing and maintaining the data under processes designed to ensure quality and integrity. Intelligent data management implies that the organization invest in systems and infrastructure to ensure the quality, accuracy, and consistency of the data. This may start organically by focusing upon each element within the information masterplan or innovation pilot, but, if managed under the umbrella of data governance, it can catalyze the

complete data governance framework are shown below in figure 1:

Figure 1: Data Governance Framework



Organizations that approach intelligent data management should view data as a precious asset to be carefully curated, managed, and leveraged. Intelligent data management practices ensure that data is high-quality, well-governed, accessible, and continuously improved. These factors can drive innovation in drug development, where data is the foundation for making informed decisions, optimizing processes, and ultimately bringing safe and effective drugs to market more efficiently. Intelligent data management in drug development will help organizations better manage their data assets, leading to more successful outcomes for patients.

Even with focused initiatives like Big Data and Pharma 4.0, many small to mid-size organizations confront data management in piecemeal fashion. The notion of curating data is relatively new in our industry. As we realize the benefits of accumulating and analyzing data to understand where targeted improvements can be made, data confidence and data integrity have moved to the forefront, driven less by compliance and regulatory requirements and more from the need for high quality data to give confidence in our analyses. Whether deployed as pilots or continuing across the value chain, as more islands of targeted innovation emerge, cogent and consistent data management becomes a priority. Data quality is an imperative in formal processes such as data profiling, data hygiene, and data obsolescence, and a precursor to deploying data intensive innovations. Such organizational understanding is the foundation for evaluating and accelerating the process while providing confidence in the results obtained.

Complementary Strategies for Drug Portfolios

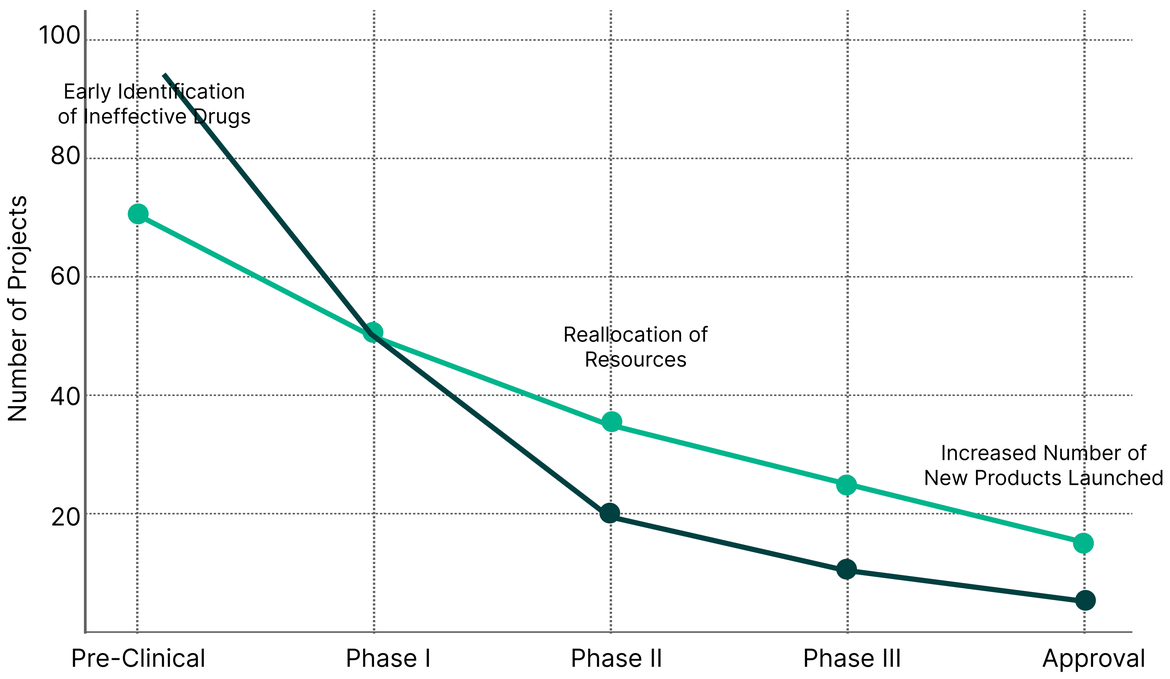
Some reasons the pharmaceutical industry lags other industries in adopting potentially impactful innovations range from lack of clarity in strategic leadership and communication, to cultural resistance, poor change management, and regulatory risk aversion. Adoption would be easier if the success of pilot evaluations shifted from technology or methodology assessments to improvement analysis by identifying early program failure modes. If it were possible to screen out safety or efficacy issues earlier, the probability of a later stage program being successful could go up substantially. This would help drug sponsors manage their portfolios more effectively and invest in programs with a real chance of reaching the market.

Setting a framework to evaluate a technology or adopt a new approach in drug development requires calculating a pilot project's potential value in relation to its cost. Metrics such as internal rate of return (IRR) or return on investment (ROI) directly measure the amount of return relative to the investment's cost. On the other hand, net present value (NPV) measures an investment's value through its lifetime discounted to today's value but does not allow comparison of the level of investment between projects. All these metrics are commonly used by drug development portfolio managers to determine which projects will be more valuable, with NPV being the most common metric. These metrics can be used either in a nominal matter (evaluating value assuming success of a project), or risk-adjusted/expected value (evaluating value including the risk of failure). Today, the risk-adjusted metrics provide a truer measure of an investment's value. A recent study analyzed clinical trial data from 2010 to 2017 and revealed four possible reasons for the 90 percent clinical failures of drug development: lack of clinical efficacy (40%–50%), unmanageable toxicity (30%), poor drug-like properties (10%–15%), and lack of commercial needs with poor strategic planning (10%)[5,6]. Addressing any of these root causes would affect the cost and time required to bring a new product to market. By considering the impact of an innovation or novel approach to a drug development problem in terms of its ability to improve the risk profile, impact to the risk-adjusted value (expected IRR, expected ROI,

eNPV) will show a significant improvement. However, nominal NPV analysis will not show the impact of these risk profile improvements, which can shift decision-making the success criteria away from innovation technology and reduce future value.

The impact would be fewer programs in the development funnel with the remaining having a higher probability of success and better funded as the existing budget is reallocated across the remaining programs. If done correctly this would also translate to more product launches as we look to move the needle on the 12% acceptance rate to market. The principle is illustrated below in Figure 2:

Figure 2: Impact of Early Program Filtering on Portfolio Success



Thinking outside the box, there are several areas in our drug development lifecycle where technology in its current state of maturity could bring greater insight into the potential for success of a program:

1. AI Combined with Real-World Evidence (RWE)

- **AI Alone:** Artificial Intelligence (AI) has been increasingly used to predict drug efficacy and identify potential drug candidates. However, relying solely on AI can result in models that don't fully capture the complexity of real-world scenarios.
- **With RWE:** When AI is combined with real-world evidence (data from actual patient outcomes outside of controlled clinical trials), the predictions and insights generated are more robust and actionable. This combination allows for better decision-making in portfolio management by identifying drug candidates that are not only theoretically promising but also likely to succeed in real-world settings.

2. Digital Twins Combined with In-Silico Trials

- **In-Silico Trials Alone:** In-silico trials use computer simulations to model the effects of drugs, reducing the need for some physical trials. However, these models can be limited by the assumptions and simplifications they require.
- **With Digital Twins:** By adding digital twin technology—virtual models that replicate the biology of individual patients or patient populations—the accuracy of in-silico trials is greatly enhanced. This complementary innovation provides deeper insights into how a drug will behave across different patient demographics, improving decision-making regarding which candidates to advance in the development pipeline.

3. Quantitative Systems Pharmacology (QSP) Combined with Biomarker Development

- **QSP Alone:** Quantitative Systems Pharmacology (QSP) models integrate biology, chemistry, and pharmacology to predict drug behavior in the human body. These models are powerful, but they can sometimes lack specificity when it comes to individual patient responses.
- **With Biomarkers:** When QSP models are paired with the development of specific biomarkers (biological indicators of drug response), the ability to predict which patients will benefit from a drug improves significantly. This combination allows for more precise decision-making in clinical trials and better portfolio management by focusing resources on candidates with the highest likelihood of success in targeted patient groups.

4. Predictive Analytics Combined with Advanced Portfolio Management Tools

- **Predictive Analytics Alone:** Predictive analytics can forecast the potential success of drug candidates based on historical data and trends. However, without the right tools to apply these predictions strategically, the full value may not be realized.
- **With Portfolio Management Tools:** By integrating predictive analytics with advanced portfolio management software, companies forecast outcomes and optimize their entire portfolio in real time. This integration allows

for better resource allocation, prioritization of high-value projects, and clearer decision-making regarding which candidates to advance, pause, or terminate.

5. Organ-on-a-Chip Combined with High-Throughput Screening (HTS) or Small Animal Modeling:

- **OOC Alone:** Organ-on-a-chip systems mimic human organ functions using human cells, providing more accurate insights into how a drug might behave in the human body. This technology can detect potential organ-specific toxicities that may not be evident in animal models. By closely replicating human biology, organ-on-a-chip models can predict human-specific responses, reducing the risk of late-stage failures due to unforeseen safety issues.
- **With HTS:** When combined with High-Throughput Screening (HTS) technologies that allow for the rapid testing of thousands of compounds, the OOC can validate and refine the findings from HTS. This combination helps narrow down candidates more effectively, ensuring that only the most promising compounds move forward, thus improving decision-making and portfolio management.
- **With Small Animal Modeling:** By using OOC models alongside small animal testing, researchers can gain a more complete picture of a drug's safety profile. The OOC can highlight human-specific toxicities early, while animal testing confirms these findings and provides additional systemic and long-term safety data. Combining both methods reduces the risk of false positives (where a drug appears toxic in animals but is safe in humans) and false negatives (where a drug seems safe in animals but is toxic in humans). This dual approach enhances decision-making by providing more reliable data on potential safety issues, allowing for earlier identification of high-risk candidates and improving the chances of advancing safer, more effective drugs through the development pipeline.
- **With AI algorithms:** Complex inputs from vertical integration of OOC, HTS, and animal modeling create difficult to interpret data sets. AI offers a unique approach to resolve valuable outcome patterns that would otherwise go unrecognized.

To Sum Up

The pharmaceutical industry has stepped into the digital innovation world cautiously, but we have made steady progress. The industry is gaining insight on the requirements to support new digital approaches and understand how to reap the full benefit. And there is a common thread across all these innovations: the need for highly reliable data. Building a centralized intelligent data management approach and infrastructure to support new technologies will allow all programs to enjoy the benefits of continued learning as it relates to data management and data quality best practices and allow a plug-and-play approach to considering new innovations.

While these innovations present the potential to fully replace outdated or ineffective tools and development steps, resistance is to be expected. As health authorities create new frameworks for evaluation it is left to industry to determine how these innovations can improve. Shifting the success metrics for any innovation pilot to include its potential impact on a program's ultimate success will allow the industry to fail faster and shift the focus and resources to programs with the best chance of reaching the market. The synergies we propose between complementary approaches are just scratching the surface of what is possible. If done properly these additive insights can be quantified and valued as part of the portfolio management process reducing uncertainty and enabling informed choices as to which drug candidates to advance, prioritize, or discontinue, ultimately leading to more efficient and successful drug development.

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Additional Question and Answers Section on implications and trends ahead

Which of these will deliver the fastest change and by when – what might their impact be in the next two, five, and 10 years? By when might these combination approaches be widely used by the industry? [NOTE: Bikash – you mentioned these in your article this year and last year, too -- AI Combined with Real-World Evidence (RWE); Digital Twins Combined with In-Silico Trials; Quantitative Systems Pharmacology (QSP) Combined with Biomarker Development; Predictive Analytics Combined with Advanced Portfolio Management Tools; Organ-on-a-Chip Combined with High-Throughput Screening (HTS) or Small Animal Modelling]

"For drug development and clinical trials, I believe that AI combined with real-world evidence, and predictive analytics linked to advanced portfolio management tools will deliver the most immediate improvements—particularly for trial efficiency—while predictive analytics will accelerate drug pipeline prioritization significantly. Look for adoption of these innovations and emerging technologies to grow in the next two to five years.

However, over the next five to 10 years, digital twins with in-silico trials and organ-on-a-chip technology will deliver the most profound long-term impact by fundamentally altering how drugs are tested and trialed, reducing both cost and time. At the same time, quantitative systems pharmacology (QSP) combined with biomarker development will make treatments more precise, improving overall trial success rates."

CPHI) Looking five years ahead: Do you think the drug development industry will have moved beyond the current 12% acceptance/success rate? If so, what might that figure be? What should we be aiming for?

"I believe if adoption of advanced technology continues it is reasonable to improve by 8-10% and push the success rate from 12% to around 20-22% over the next five years. Longer term ten years from now when in-silico trials, digital twins, and organ-on-a-chip models are fully validated and integrated into the regulatory framework I believe a 30-40% success rate is possible. Achieving this would bring a fundamental shift in how we conduct trials, using precise predicative models in combination with human trials, early program filters to fail faster and shift programs to fewer but potentially more effective drug therapies."

CPHI) Pharma is slow to change, but by when do you think we might be able to pass the symbolic 100 FDA approvals per year? [obviously our record every year was circa 70 approvals in 2018]

"Drug approvability is a result of many factors. I believe we will see incremental improvement in the next year as industry and regulators gain a comfort level with data-driven modeling. Technological innovation will spur regulatory innovation, that is, the regulatory pathways to in-silico modeling and predictive modeling will become clearer for both health authorities and industry, resulting in approval acceleration. Along with more effective portfolio management tools to filter and prioritize high potential drug therapies, I would not be surprised to see industry and FDA break the magic 100 approvals barrier in the next eight to 10 years."

CPHI) What are the implications of an "optimized funnel" for biotech companies? What work should they retain in-house versus – which parts are more suitable for CRO or CDMO partners?

"By an 'optimized funnel' I assume you are referring to an improved and streamlined drug development pipeline, where drug sponsors maximize efficiency in moving candidates from discovery to approval. The strategy asks the questions 'what do we do well? What are our core competencies? Where should we bring in outside expertise?' Unfortunately, there is no one-size-fits-all answer. The industry will see an increase in licensing and acquisitions as corporations look to speed up the development pipeline by acquiring promising new drug modalities. The question becomes 'do we build in-house expertise, or bring in outside expertise?' I have seen both strategies work, as when large biotech began to embrace cell and gene therapy. I think CRO, CDMO—and now CRDMO—will have a large impact on a drug sponsor's ability to bring a program to market. And I do believe the recipe for success will not change for some time to come: that is, IP regulatory and commercial strategy should stay with the drug sponsor, while supply chain—including forecasting, manufacturing and clinical trial execution—could be led by a contract service provider. Soaring with your strengths has proven to be the most effective equation for most outsourcing strategies."

Looking just two years ahead what do you think we can realistically achieve and what does the industry (regulators, pharma, biotech's or outsourced companies) need to do to accelerate this type of new drug development approach [Bearing in mind how slow things like continuous have moved]?

"Biotech and pharma industries are likely to see modest but meaningful progress toward optimizing the drug development funnel and leveraging emerging technologies to streamline processes. While significant transformation will take time due to regulatory, technical, and cultural hurdles, there are key areas where we can realistically achieve tangible progress within the next two years. For real acceleration we will need to see broader investment and adoption of in-silico solutions, and seriously begin shifting drug development to embrace the notion of data as a product to drive data standards and interoperability. We must evolve our cultural aversion to regulatory interaction and recognize we cannot be successful without shared understanding and insight. As industry and regulators develop a framework for real-world evidence, this can have a profound impact on intelligent risk management and improve portfolio management for early programs. When nine out of 10 programs are likely to fail, we are looking for that needle in a haystack. Harnessing innovative technology capabilities will improve the measurement and resolution of our filters and allow drug sponsors to shift resources to drug therapies with the highest likelihood of success."

Part
05

Excipients Prediction

GMP Risk Assessments

Iain Moore

Senior Advisor EXCiPACT & former IPEC Chair

What next for Excipients?

In this report I'll share my perspectives on what we can expect for excipients in the future.

Excipients have always been an important part of drug product formulations but have not always had the same level of focus as the drug substance. Even regulators in many countries don't have the time or resources to put them higher on their agenda. Whereas this may have been an acceptable approach in the past it's not going to be a sustainable approach in the future because their role and function in modern drug products is ever more important, critical even. Excipients are being brought into the development of new medicinal products earlier and this requires that their quality is established, including the standards for GMP [good manufacturing practice] and GDP [good distribution practice].

What we are also seeing is that greater regulatory oversight and burdens are likely to follow, as the importance of excipients in delivery of newer therapies has never been more critical.

Alongside this greater security with have the tragic backdrop of, yet again, too many infant deaths, through economically motivated adulteration of pharmaceuticals - notably the majority of blame has fallen upon the excipients used in the most recent cases.

It is therefore a regulatory, industry and moral imperative that all parties involved will need to increase their oversight of excipients and remain vigilant long into the future.

What is an excipient?

The traditional definition is anything that is not the active substance in the drug product. However, as I have long argued, this is rather too simplistic definition. I prefer the International Pharmaceutical Excipients Council definition as *"substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system"*. Some key words here include "intentionally" – that is these substances are deliberately added to the drug delivery system. And thus, they must serve some purpose in the delivery of the drug. The legal definition is open to defining anything in the drug product that is not intentionally added as an excipient, such as impurities or contaminants! I don't find that thought very helpful. The other key part of the IPEC definition is that they have been appropriately evaluated for [patient] safety.

However modern technology is pushing the boundaries of these simplistic views of the components of a drug product. No example better than the mRNA vaccines that protected so many of us from the worst of COVID-19 infections. Here, the excipients that created the lipid nanoparticles that carried the mRNA into our bodies had such an important role that they ranked equally as important as the mRNA. It's not hyperbolic to say that without them, there would have been no therapy. So it's a great example of the purpose of excipients and the reason why they are included in the drug product – becoming much more than a simple filler. Thus, we should perceive them as a delivery enhancement vehicle essential to many medicines' efficacy.

The challenge, as many of you will be aware, is that as new medicines come to market how do we ensure the excipients we use remain fit for purpose. Newer technology requires newer excipients that best fit the purposes of that unique formulation – not a make do approach with what we already have. Sadly, there remains no easy or effective way to develop new and novel excipients and demonstrate their suitability and patient safety except through a new drug application. This disadvantages the excipient manufacturer and ties them into one customer who then has to include all the details including the novel excipient safety date in their dossier. Only a handful of novel excipients have been introduced in the past years despite the need from the new technologies.

At least the US FDA has recognised that this is an unhealthy situation and have instigated their Novel Excipient Review pilot programme to see if another way forward can be engineered. In Europe too, the proposed revision to the pharmaceutical regulations would generate a Drug Master File approach for novel excipients. Let's hope that both these are successful and are implemented because we need to reduce the barriers for delivery of new excipients.

Another example of the blurring of the distinction between excipients and drug substances includes the adjuvants often used in vaccines. Such materials are not inactive in the manner usually associated with excipients but are not traditionally “active” either. So, are these excipients? There is no doubt these materials do have greater regulatory scrutiny, not least because their route of administration will be parenteral, but also because of their critical function in the delivery of effective vaccines.

Another example of a non-traditional excipient can be found in medical devices. That name can be misleading because some medical devices are indistinguishable from drug products. In such medical devices there can be a “critical” component which is the key to delivery of the therapy to the patient. The delivery of that critical component requires use of other materials that are inert. Such substances are being called excipients by the industry! And why not? The traditional definition fits these materials too. And then there are combination products which fuse medical devices and drug products into one delivery mechanism for the patient. Here excipients may be found in both the drug product and the medical device part of the product.

The use of biological therapies also continues to increase, but the methods of manufacture here are very different to those used in the chemical industry where many small molecule active ingredients are made. Many substances are used in the biotransformations, and these are removed from the active ingredients. Yet their intimacy with the active ingredient requires that they be treated as excipients too; they need to be of known purity and quality and be made according to a relevant GMP. These materials too have a purpose, albeit not directly in the delivery of the active substance to the patient. EXCiPACT has adapted its Certification Scheme for excipients to include these substances, coining the term “Pharmaceutical Auxiliary Materials” (aka PAMs) to describe them. This step was prompted by the leading organisations in the industry who needed to demonstrate the purity, quality and GMP used in the manufacture of PAMs. They considered EXCiPACT GMP to be a good standard to apply to the manufacture of these substances.

With these examples we can begin to see that the definition of what an excipient is has been extended, and that the simple limitation that an excipient is only present in a traditional drug product is unhelpful, because if these substances used in medical devices, vaccines and so on are not excipients, what are they? And where do they fit into the existing regulatory frameworks?

But there are some common characteristics for these substances in these diverse cases:

- Defined quality and purity
- A purpose in the medicinal therapy (used here to mean drug products, medical devices or any other therapeutic treatment)
- Be manufactured to a suitable standard of GMP

Thus, a wider definition for an excipient that can accommodate all these other uses could be:

> “Excipients are substances that are intentionally added to a therapeutic product to serve a purpose in aiding the delivery of the therapy to the patient. They have been appropriately evaluated for patient safety.“

This permits excipients to be present in relevant medical devices, as well as traditional drug products. But key is the emphasis that the excipient is added to the therapeutic product for a purpose. Be that protection of the active component(s), solubilisation, encapsulation etc. It is this purpose which determines the attention given to the excipients in the regulatory approval process. The purpose is paramount in determining quality, purity and most critically the standards of GMP used in its manufacture.

Thus excipient GMPs such as IPEC-PQG GMP and EXCiPACT GMP for pharmaceutical excipients are suitable in the vast majority of cases where the purpose and function of the excipient lies within well-known boundaries. Where the functionality is novel, or the excipient is new, then the GMP that needs to be applied will be much the same as for Active Substances,

i.e. ICH Q7. A good example here, is those lipid nanoparticles used for the mRNA COVID-19 vaccines. Excipients? Yes, but all the regulatory submissions were evaluated the same way as for the Active Substance and they had to be made to ICH Q7 standards.

With an increased scope of what an excipient can be, the huge variety of functions that excipient perform then how then can we determine what GMP should be used in its manufacture? There is already an official and an excellent guideline that can cope with this dimension:

- Guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use

If you consider an excipient in this wider sense, and input the purpose of the excipient into the formalised risk assessment guideline along with the and the source and security of the excipient supply chain, then the result will give be the correct answer for the GMP and GDP that is required.

Conclusions

Modern technology is broadening the definition of what an excipient is, and how we should assure its quality. By revising our definition of an excipient the existing guidelines and risk assessment guidelines can applied to all these new applications for excipients. And with that **will come the assurance that all excipients are fit for purpose and safe for use.**

[1] IPEC Glossary 2021

[2] CDER Conversation: Novel Excipient Review Pilot Program | FDA

[3] Reform of the EU pharmaceutical legislation - European Commission (europa.eu)

[4] EU and PCI/S

Additional Q&A

With these suggested changes as the backdrop, what are your predictions for novel excipient development over the next 2-3 years?

"We will see increasing numbers, by historic standards, of novel excipients being introduced, especially if an excipient master file system is introduced."

Do you have any predictions on what we can expect from a regulatory perspective in the next 2-3 years?

"Curiously, in the developing world many regulatory authorities do oversee excipients directly (e.g. China, Brazil) but in the developed world this is quite rare. With France now having broken ranks and implemented routine excipient GMP inspections then I would anticipate other authorities following their lead."

Do you foresee, without change, a situation whereby drug development programmes are being slowed because we don't' have the excipients fit for purpose with the more complex therapeutics in the pipeline – e.g. as more mRNA and third and fourth generation MAbs advance through clinical development. For which drug types and indications might this be most critical and, by when might such a reality come to pass?

"I have heard it mentioned that some new drug products have not made it to market because there were no effective excipients, but this sort of matter is rarely made public so it is hard to judge how frequent it may be. The COVID-19 vaccines do demonstrate just how fast everyone can work when there is an urgent unmet patient need, and the learnings from that experience have to be implemented into future developments."

Alternatively, do you believe that for that for the industry to advance at the same pace we have in the last few years (with circa 50-ish approvals per year) we need much greater partnering early in the development – one where the excipient companies are involved as early as pre-clinical [especially for biologics – i.e. as soon as you identified the MAb and want to screen in assays]

"Absolutely, when things were simple, in terms of what the excipient function was in a drug product, then one way communication from the supplier worked. But with increasing functionality and the need to tailor and design that as part of the delivery mechanism, two-way exchanges of information and greater partnering will be required."

How many novel excipients you think we ideally need to see over the next 5 years and how many do you envisage we will actually get introduced? Essentially, do you think there will be a short fall?

"As this is the crystal ball question! Not sure I have close enough perspective to judge. But, certainly many more than we have seen in the last 5 years."

Part
06

Drug Delivery and Devices

CPHI Annual Report 2024: Drug Delivery Trends and Insights from a Device Perspective

Chris Hurlstone

Director of Drug Delivery, Team Consulting

Overall picture – growth and new opportunities on many fronts

Significant growth in the drug delivery sector is predicted for many areas, with headliners including cell and gene therapies and the GLP-1 blockbusters. Small molecule-based formulations still dominate innovator pipelines, but advanced biologics are also growing significantly. In terms of therapy areas, many pharma companies are targeting oncology, immunology, cardio-vascular and cell and gene therapy.

Given these predicted advances in drug formulation, what are the implications for drug delivery devices?

Oral presentations are simple, effective and currently account for as much as 90% of the global market share of all pharmaceutical formulations for human use. Where these are not suitable, companies will seek to deliver these drugs using established delivery systems. Injectables include pre-filled syringes, auto-injectors, pen injectors and infusion systems, while for respiratory drug products there are many existing device technologies including capsule, reservoir and blister-based inhalers, nasal delivery systems and nebulisers.

Injectables

Nobody wants to develop a new device if they can avoid it. Hence in the injectables sector formulators will target 1ml subcutaneous delivery or similar where possible, as this is an area very well served by existing devices. But for some new formulations, including those driven by a desire to move treatment away from IV delivery in the hospital or clinic to the home, increased volumes and/or viscosity are often necessary. Such payloads are falling into the space between autoinjector and on body delivery systems, so new developments of both are in progress, with some devices now appearing on the market.

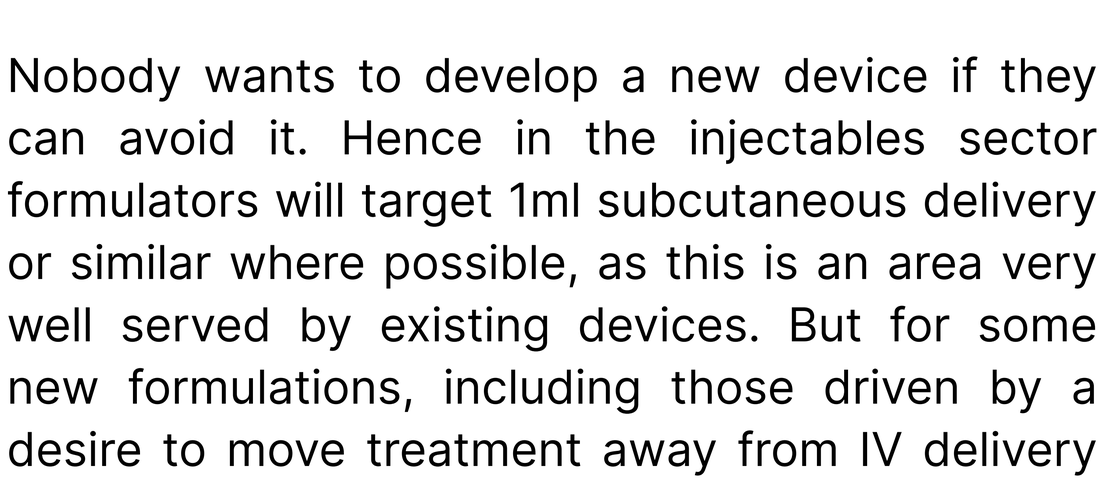

Figure 1: the recently approved Ypsomed 5ml autoinjector (Ypsomed)

Sustainability and cost

Two of the challenges that need to be addressed by new device technologies are cost and sustainability. In an increasingly competitive market, the need to minimise cost per dose delivered is more important than ever. Meanwhile, the sustainability of such devices, typically measured by carbon footprint analysed across the product lifecycle, is becoming a real - and high - priority for many pharma companies. Optimising device designs for the most effective use of materials and manufacture from highly efficient production systems can be one way to achieve both cost and carbon footprint savings. However, in some cases more sustainable solutions can be more expensive (e.g. the use of specialist bio-feedstock materials or multiple, more localised supply chains).

One other way to reduce the cost and sustainability impact of devices is to re-design them to include ‘retained’ or ‘durable’ elements as well as the disposable element, which usually contains the primary pack. This approach is not new – the UCB ava Connect was launched some years ago for biologic treatment of rheumatology and dermatology – but it is being pursued by a number of companies. This includes Phillips-Medisize (Aria), The Smartclic® device licensed by Pfizer in Australia for Enbrel, and the very recently announced Elexy™ from SHL, all of which include electro-mechanical and software elements.

Balancing the digital benefits

Meeting cost and sustainability targets for these larger and more complex devices, including on body delivery systems such as patch pumps, is difficult without moving away from the entire device being single use. There is scope in such systems to provide additional value though, through the use of digital tools and device connectivity. However, the high levels of activity seen in this area in recent years seem to be abating to some extent. This is partly due to ‘cost and carbon constraints’, but also because the ways to realise or demonstrate true user benefit have proven difficult to establish. Challenges over data capture and handling also present a barrier. Efforts to resolve these challenges will continue but, in the meantime,

opportunities to leverage other digital tools and approaches are being developed, e.g. through the use of smart labelling and packaging, sometimes linking to mobile apps and website support materials.

Other areas of activity in parenteral drug delivery include intradermal delivery, using patches and micro-needles, and also ocular delivery. The latter is of particular interest for new gene therapies, following on from FDA approval for Luxturna in 2017.

The October medical technology conferences are likely to feature announcements of new device developments in a number of these of these areas.

Respiratory

The respiratory device sector has seen less innovation in recent years, with much of what has been happening focused on the development of generic devices for asthma and COPD. This is beginning to change, however, in both inhaled pulmonary and nasal drug delivery. Alternative therapies for conditions including lung cancer, idiopathic pulmonary fibrosis, Parkinson's disease, and more advanced antibiotics appear to be getting closer and there are signs that device developments are progressing to match the particular requirements of these new therapy areas.

One example of device development in this area is in intra nasal drug delivery of both liquid and dry powder dose forms, targeting both CNS (via the blood brain barrier) and systemic delivery. Significantly, these have been extending to treatment areas which were previously the preserve of injectables only, including vaccines and emergency use devices. One example of the latter is the recently FDA-approved neffy® epinephrine nasal spray for the treatment of severe (Type 1) allergic reactions including anaphylaxis.

Figure 2: Neffy® epinephrine nasal spray[1]

A new challenge for drug delivery devices arises from advances in formulation techniques for larger molecules such as peptides and nucleic acids, which require devices capable of handling higher dose sizes of often delicate formulations. This has led to a shift in the design landscape for inhaled pulmonary drug delivery systems, many of which have been developed to deliver no more than 10–15mg of powder per use. The emerging need for effective aerosol drug delivery devices which can deliver higher masses of formulations, often in excess of 25mg, cannot be easily accommodated by simply re-engineering currently available products.

Targeted drug delivery

One significant area of device innovation, driven to a large extent by developments in both oncology and cell and gene therapies, is that of drug delivery direct to target sites in the body such as organs, tissues and tumours. The need for innovation in this area is due to a number of key factors.

Firstly, many of the target sites are difficult to get to, both in terms of physical access but also due the need for accurate targeting in an environment which is highly variable and personalised. The use of surgical robots is becoming more commonplace and, in some cases, can be utilised for such delivery techniques. However, the fact that there are often differences between such systems, and how they are implemented, means that standalone delivery devices may present a flexible approach that can be deployed more broadly, such as through the use of standard laparoscopic methods. Guidance systems of various types, forming part of or used in conjunction with the delivery system, are often also required and will make use of a range of imaging and navigation tools.

[1] https://ir.ars-pharma.com/news-releases/news-release-details/ars-pharmaceuticals-receives-fda-approval-neffyr-epinephrine

Figure 3: DaVinci robot system (Intuitive Surgical)

Another reason why it is highly unlikely there will be many (or any) one-size-fits-all device solutions is the huge variation in payload that such devices will need to deliver. This is both in terms of delivered dose volumes but also the drug's physical characteristics, including viscosity, single/multi-phase, sensitivity (e.g. to temperature, to shear) and stability.

Once the drug has been delivered, there is then the need to control distribution and retention within the target site. This is partly to ensure the necessary amount of drug is delivered but also in some cases to ensure neighbouring non-target tissue is not at risk of damage or contamination. Given the huge range of tumour and organ types this again points to a need for bespoke solutions, and also the need to fully understand tissue characteristics. This can be very challenging and is best approached through a combination of experimental and analytical methods.

These and other challenges, such as the need to ensure that delivery technology can be deployed across a wide range of varying healthcare settings, mean it is critical to begin device developments very early, alongside the development of the formulation. This is frequently the case but not always appreciated.

Drug manufacture

Historically, and in most current cases, drug manufacture can be considered separately to the drug delivery device. Most of the challenges relate to selection, design, manufacture and filling of the appropriate primary packaging (e.g. syringes, cartridges, vials, capsules, powder reservoirs, blisters), and how these are then incorporated into the device technology.

mRNA is extremely sensitive to contamination and needs to be produced to cGMP, but may at the same time be highly personalised and hence must be handled and tracked carefully.

Manufacture, packaging, transportation and handling of radiopharmaceuticals also needs to be handled extremely rigorously, for different reasons. In addition, the time sensitive nature of the drug preparation due to the half-life of the radioisotopes within them means that the effective shelf-life can be extremely short – sometimes just a few hours. This has major implications for the location of the manufacturing site, and the supply logistics.

Regulatory drivers and hurdles

Perhaps the main regulatory factor impacting the development of new drug delivery devices is the continued adjustment to the introduction of the Medical Device Regulation (MDR). Whilst the introduction of the MDR did increase the focus on the medical device aspects of drug delivery systems and combination products, which we believe is a good thing, it has led to challenges in a number of areas.

The need both for full notified body review of any new Class 2 and 3 devices, alongside re-certification of existing devices, is putting excessive pressure on an insufficient number of approved notified bodies. Coupled with this, companies are new to the process and hence submissions are frequently incomplete and need further work (75% according to a European Commission survey).

Both of these factors are leading to long delays in device approval which will have major implications. The pain is felt particularly by start-up companies looking to commercialise their first product, and one result is that many such organisations are looking to the US or other non-EU markets for their first launch.

Companies entering the US market need to bear in mind new guidance from the FDA. New draft guidance documents covering Essential Drug Delivery Outputs and Use Related Risk Analysis were published in June and July 2024 respectively, with the industry given 60 days to submit comments. Meanwhile, the interpretation and application of the “five nines” draft guidance for demonstrating reliability of emergency use injectors, published in April 2020, is still a source of discussion and debate within the industry.

Despite all the challenges faced, the pharma industry continues to make huge progress in helping more people live healthier lives. It will be interesting to see how many of this year’s trends will still be impacting the industry in years to come.

Additional Question and Answers section – predictions ahead

CPHI: what is your prediction for use and innovation in inhalation market over the next 2-years [as noted in the article you mentioned there had only been limited innovation to date]

Jamie Greenwood, Managing Consultant: *"It will be interesting to see whether the recent approval of an intranasal spray for delivery of epinephrine to treat Type-1 anaphylaxis will open the door for other systemic therapies which have previously been the preserve of needle injection systems. This may include device and formulation innovation to expand the epinephrine delivery options beyond liquid dose forms e.g., dry powders and even delivery via the pulmonary route rather than intranasally.*
Of further interest may be whether device and formulation co-development can help overcome the practical challenges for delivering new modalities via the orally inhaled route, such as advanced therapy medicinal products (ATMPs) for pulmonary diseases and vaccine delivery. Many ATMP candidate formulations are sensitive to environmental conditions and mechanical stressors during storage and delivery, so novel approaches to formulation and device design may be needed to support their delivery through the respiratory route."

Do you foresee a new wave of innovation in 2025 for microneedles, patches and ocular delivery – what is your prediction for these in the next 2-3 years.

Kate Hudson-Farmer, Director, New Business Development: *"Ocular delivery is definitely on the increase, which is driven by a number of factors including the increase in eye disease, improved ways to get drugs and therapies into the eye and formulations to enable longer term treatment of these diseases, also the growth of gene therapies for the eye diseases and the need to deliver these very accurately and effectively"*

Thomas Grant, Senior Human Factors Consultant: *"With regards to microneedles, in order to achieve the high accuracy it is particularly true for ocular delivery to the subretinal space, which is an area I believe we will see increase in the coming years. The use of microneedles, including positioning and depth, is critical to deliver to the targeted retinal or subretinal layer."*

Chris Hurlstone, Director of Drug Delivery: *"A number of companies continue to develop and offer solutions for transdermal drug delivery based on the use of patches and micro-needle arrays. Different approaches include dissolvable micro-needles moulded with an integrated API, solid needles coated with API, or hollow needles through which drug is injected. For drug formulations and payloads suited to this form of delivery there are a number of potential advantages offered by the approach. A common challenge however is that of dose volume - getting enough payload onto a realistic patch size - even bearing in mind the fact that intradermal delivery can sometimes give improved bioavailability and hence a lower required dosage."*

What do you anticipate the effects of continued innovation in biologics to have in the market over the next 18-months – e.g. continued use/growth of high viscosity autoinjectors etc etc?

Kella Kapnisi, Project Manager: *"Novel modalities will continue to increase as a proportion of the pharmaceutical pipeline and innovation in biologics will continue to trend towards personalised medicines. This will drive up the demand for advanced delivery approaches, such as high viscosity autoinjectors and direct to organ administration (ocular, intratumoural etc). This will*

encourage greater investment and more sophisticated manufacturing solutions. All of which will help to propel the longer-term trend of driving down costs and simplifying the current regulatory and reimbursement challenges that biopharmaceutical developers face."

Kate Hudson-Farmer, Director, New Business Development: *"I think there will be a continued rate of growth and innovation in biologics for sure and some of these will need different delivery devices due to factors such as increased viscosities, and volumes due to the drive to less frequent injection. Sustainability is also becoming a driver so in the medium term there could be an increase in the types of materials used in such devices and the move to more reusable and durable options.*

In the longer term there will be an increase in newer products starting to get into the market that may see more ways of orally delivering such biologics, which to date is challenging due to their nature, but there are numerous researchers working on ways to achieve this. In addition will see the rise in cell and gene therapies that will require some very precise delivery options and some very robust and repeatable ways to ensure these highly valuable and very infrequently given therapies are administered."

Jamie Greenwood, Managing Consultant: *"I think it is likely that device and formulation developers will continue to explore opportunities for biologic therapies beyond the injection route e/g., orally inhaled or intranasal administration. While both these routes present challenges for formulators, in particular, there appears to be a real driver for drug delivery product developers to present a broader menu of treatment modalities to patients."*

How do you anticipate the effects of continued innovation in peptides affecting the device market in the next 2-years – we saw nine approvals last year after none the year before – so they really have come from nowhere?

Kella Kapnisi, Project Manager: *"While the approvals have jumped recently, the number of peptide-based therapeutics in clinical trials has continued to grow over recent years, indicating a continued interest in them as a therapeutic class. Recent technological advancements are addressing the inherent limitations of peptide therapeutics. Alternative routes of administration have helped to overcome bioavailability challenges and advances in structural biology have helped to improve their stability. With hundreds more still in development, expect more approvals to come."*

CPHI Milan

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