

US Pharma Market 2022 and Beyond

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Experts predict macro changes and technology advances to deliver post pandemic boom in the USA, with a 'supercharged' period for partnering, strategic alignment and contract agreements

Introduction

Ahead of the return of CPhI North America, Informa commissioned an in-depth report into the US pharma market focusing on how the pandemic has affected public discourse and political priorities, and how it could alter the pharmaceutical supply paradigm in the medium term. Analysis from six leading US experts – following extensive interviews and data collection – provides an essential guide to near-term priorities, medium-term capacity constraints and longer-term shifts underway in the US pharma market supply chain.

Our expert team includes thought leaders across regulation, advanced pharmaceutical manufacturing, biologics and CDMO capacity, and they provide

a detailed examination of the pharmaceutical innovations that will usher in new methods of manufacturing and future growth:

- **Aurelio Arias**, Engagement Manager, Thought Leadership at IQVIA
- **Bikash Chatterjee**, Chief Executive Officer at Pharmatech Associates
- **Doug Hausner**, Senior Manager Continuous Manufacturing at Thermo Fisher Scientific Inc.
- **Nielsen Hobbs**, Executive Editor, Policy and Regulation at Informa Pharma Intelligence
- **Peter Shapiro**, Senior Director of Drugs and Business Fundamentals at GlobalData
- **Valdas Jurkauskas**, PhD, VP Technical Operations at Black Diamond Therapeutics

Background

Key positives from the last year include the remarkable adaptability of private sector companies, increased global collaborations and the ability of governments to implement policies to meet pressing, real-time public health challenges. However, attention has also been drawn to issues in pharma, especially the United States, that have been bubbling under the surface for some years. For example, how and where drugs are manufactured, and how secure supply chains are in a time of crisis. We have seen a wave of protectionist policies from several countries around the world and not least the previous administration in the White House. Yet, it is expected that with the Biden administration's recent election, such concern will still likely continue to guide policy to an appreciable extent.

It's going to be the most exciting 10 years of our lives. There is no question about it

Looked at holistically, the overall implication is that we are now entering something of a 'golden era' for US pharma and manufacturing. These supply side trends have combined with an inflection point for new technologies and continuous manufacturing. Alongside this, biologics and cell and gene manufacturing are potentially entering a hugely profitable period, but one where greater capacity will be needed. In fact, with these new approaches now proliferating, our experts believe the US is extremely well placed for surging growth as it continues to act as the global centre of pharma innovation.

"It's going to be the most exciting 10 years of our lives. There is no question about it. I think it's going to be unbelievable in terms of the innovation we are going to see. This applies to new drugs and therapies to advanced manufacturing techniques for cell and gene therapies, and continuous processing as well," Bikash Chatterjee, Chief Executive Officer at Pharmatech Associates

Regulatory Environment

The regulatory environment has been stretched by new demands in the last two years, from the macro trends in the market and supply chain security, to spiralling healthcare costs and the urgent need for innovation to advance faster. The pandemic has, of course, accelerated these trends, but it has also introduced an element of national competition between states rarely seen in the past.

“The pandemic has stressed this existing system and highlighted real weaknesses in our current model, fuelling calls to enact reshoring policies to enhance national security. Thus, reshoring is a symptom of many problems in the market, including supply chain resilience, but also geopolitical aversion to reliance on other nations, national employment and industry interests to name a few,” commented Aurelio Arias, Engagement Manager, Thought Leadership at IQVIA.

Added to this, we’ve seen the departure of Scott Gottlieb as commissioner of the Food and Drug Administration and wider awareness among the general public regarding how and where drugs are made. This has brought about a slightly more politicised regulatory environment. So, while Janet Woodcock’s role as acting commissioner of the FDA is a welcome appointment for the industry, with a decade’s experience at CEDR, the insider’s view from our experts is that she is unlikely to be given the role permanently.

The FDA and industry have further improved the collaborative environment, in terms of new vaccine approvals

Nielsen Hobbs, Executive Editor, Policy and Regulation, Informa Pharma Intelligence, reflected on the politics at play, adding: “The downside of Woodcock’s decades of experience is the baggage, and the FDA’s role in the opioid epidemic appears to be blocking her nomination to be permanent commissioner. Several Democratic senators have voiced concerns about her role in FDA’s approvals of opioids, and whether that’s a good shell for underlying objections to agency cosiness with industry or not, those objections have meant that Woodcock isn’t being nominated. The Biden Administration is uninterested in having the intraparty fight that nominating her would cause. Ironically, if Biden’s agenda stalls – if the infrastructure bill sinks and the healthcare legislation doesn’t happen – then you might

see Woodcock’s nomination, since party unity will have already fizzled.”

However, the CPhI North America experts do agree that the FDA and industry have further improved the collaborative environment, especially in terms of new vaccine approvals, but also in advancing new manufacturing. Woodcock is well known as one of the major forces behind the drive towards continuous manufacturing. Although political tensions and uncertainty will continue, Woodcock will remain in her acting role for some time; this is ultimately good for the industry.

Chatterjee in particular was very complementary on her impacts over the last 20-years and believes the predominate industry view is that she is a safe pair of hands. He added, “Industry is very happy with Dr. Woodcock being there. She is very well known to the industry. She was always active in our professional societies and has been the architect of a lot of what we see today. If you were to step back to 2008 the U.S. QbD—Quality-by-Design—would still be a podium presentation, a theoretical concept, without her support for integrating the principles of QbD into the 2011 guidance; to basically make stage 1 Process Validation (PV) QbD was how she enforced these concepts with industry. And she did it having lived through all of the missteps from 2004 to 2011. She understands what it takes to drive us toward innovation, and industry would be happy with her.”

Reshoring is another area where the new administration is so far, in the view of our experts, focusing on incentives rather than punitive measures. Hobbs added, “despite the Biden Administration’s comfort with the Defence Production Act, its efforts at boosting domestic manufacturing have so far focused mostly on incentives, not punitive measures. And Republicans are likely to retake control of Congress in the midterms, so if reshoring legislation hasn’t passed by then, the resumption of partisan gridlock means it probably won’t.”

The Biden administration is using the purchasing power of Medicare, Medicaid, the US Department of Veterans Affairs, and other federal agencies to favour drugs made in the US, but is reversing former President Trump’s onshoring tax codes incentive.

“The majority of small molecule API manufacturing facilities are located in China and India. Shifting all this production to the US would be a huge undertaking

and brings its own risks. Proposals for drastic changes to pharmaceutical manufacturing supply chains underestimate the significant time, resources and other feasibility challenges and complexities involved” Peter Shapiro, Senior Director of Drugs and Business Fundamentals at GlobalData.

The duality of the goals at play is clear, with lower healthcare costs inconsistent with reshored manufacturing. Therefore, only certain types of manufacturing are likely to return, with API and generic production, in all but the most extreme cases, likely to remain in lower cost production hubs; namely, China and India.

“What I’ve seen since last year is more of a sentiment-emotion driven supply chain. Sometimes we hear that ‘we are going to have to reshore it at any cost’ however, it’s not that simple. We have to do technology transfers. If you think of supply chain, it’s from starting materials to intermediates to bulk substances to formulated drugs,” commented Valdas Jurkauskas, PhD, VP Technical Operations at Black Diamond Therapeutics.

cell and gene therapy, API manufacturing and injectable dose manufacturing are the best immediate opportunities for reshoring

What we are seeing, however, is a willingness to accept slightly higher production costs in the most advanced therapies with higher margins. In particular, there is high demand for biologicals, cell and gene therapy capacity, and highly potent drug therapies in the United States. In fact, the pandemic has further aggravated capacity constraints as priority is given to COVID vaccines. Anyone with available capacity in the United States is likely to be booked up well in advance and able to charge a premium. For the CDMO space, this presents huge opportunities with a large number of acquisitions in the last year as well as increased capital coming in from VCs.

Chatterjee reflecting on M&A environment, added: “In 2020, more than 40% of the mergers and acquisitions in the US were CDMOs. In terms of where you need to put your energies in the U.S, cell and gene therapy is going to continue to grow. There are a couple of areas that make complete sense: If I had \$100,000,000, I’d go out and buy a CDMO tomorrow. The amount of CDMO capacity that is available worldwide is very small right

now, and so you’d be busy for years to come. Part of that is driven by the pandemic and the need to find ways to make vaccines.”

To give just one example of the shortage of resources available in the United States, our experts pointed to Paragon, which is understood to have booked up capacity 18 months before their new facility is finished.

Shapiro agrees that cell and gene therapy, API manufacturing and injectable dose manufacturing are the best immediate opportunities for reshoring. He also identified that there will continue to be a trend towards dual sourcing and multi-sourcing arrangements for high value therapies. However, Shapiro argues we’ve not seen evidence of significant volumes of pharma manufacturing moving on shore and instead we will simply see greater flexibility built into the majority of supply lines.

“There are opportunities for the United States to lead in particular for advanced biologicals. But there are also medium- and long-term opportunities for manufacturers capable of manufacturing mRNA-based vaccines and therapies and vector manufacturing for recombinant vector vaccines, gene therapy and gene modified cell therapy. Manufacturing capacity for cell and gene therapies was already strained before the pandemic, and now it’s under further pressure because vaccines use a lot of the same technology and raw materials. This is especially true for recombinant vector vaccines such as Johnson & Johnson’s, AstraZeneca’s and Russia’s Sputnik V, which require a viral vector for their production, just like gene therapies and gene-modified cell therapies. Governments have in aggregate placed orders of approximately 900 million doses for AstraZeneca’s and J&J’s COVID-19 vaccines, and vaccines are understandably being given priority for product slots over cell and gene therapies. So, increasing capacity is very important,” added Shapiro.

Recent research by GlobalData (May 2021)¹ shows that there are currently only 87 viral vector contract manufacturing facilities worldwide. Adding to the shortage of supply is the current inefficiency in manufacturing – including low titres and complexity – with both biopharma innovators and contract manufacturers working on both upstream and downstream process innovations. One suggestion from our experts is for agencies to approve standardized viral platforms that could be used interchangeably by therapy developers, potentially speeding up cell and gene therapies’ development, approval, and technology transfer to CMOs.

Acquisitional Environment

Understandably, with record levels of capital coming into the industry – from public sources for activities related to the pandemic, and private sources including the usual venture capitalists but also many new market entrants – the M&A environment for the best facilities in the United States is particularly hot. US-based contract service providers with specialised capabilities continue to attract the greatest interest and highest prices.

By way of background, Shapiro’s research showed that of CDMO acquisitions “25% of US deals targeted biologics capabilities however, 36% targeted specialized

capabilities such as companies/facilities with containment or solubility enhancement.”

The excitement in the cell and gene therapy sector is best highlighted by Catalent’s \$1.2 Bn (2019) purchase of Paragon Biosciences, and Thermo Fischer Scientific Inc’s \$1.7 Bn (2019) acquisition of Brammer Bio LLC. In fact, the GlobalData research shows a huge disparity in terms of manufacturing acquisitions, with America (55) seeing nearly the same number of acquisitions as the combined totals for India (22), China (19) and the UK (17).

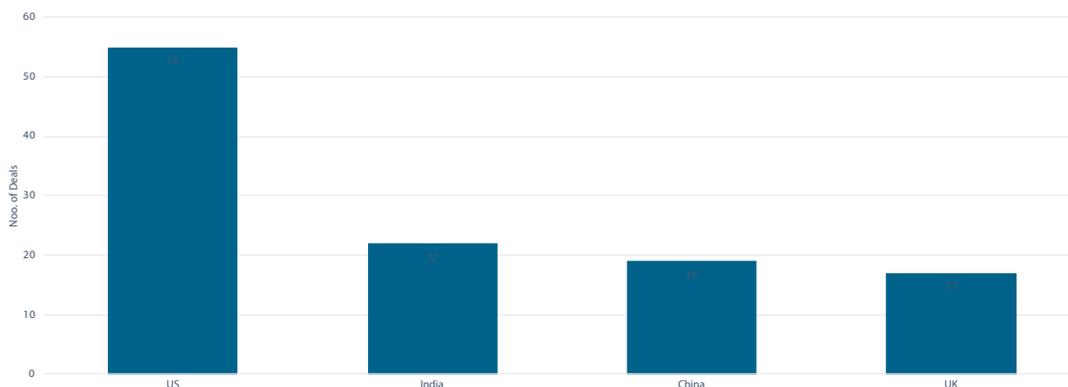


Figure 1: Shows the number of M&A deals and geography per GlobalData research.

Adding to opportunities for US manufacturers, capital (\$10 Bn) from Operation Warp Speed² was designated to increase development and manufacturing capacity within the US. This investment is likely to provide a good deal of stimulus to advanced therapy medicinal products (ATMPs) and the approval of the two mRNA vaccines has validated an entirely new approach to vaccine delivery.

“We expect to see the approval of mRNA-based cancer therapies in the next few years. Furthermore, these mRNA therapies will be able to use the same manufacturing equipment as mRNA vaccines now that the industry has shelled out the high CapEx cost for this equipment, and trained more staff in sophisticated pharma manufacturing,” added Shapiro

Advances in Manufacturing Processes

Our experts predict that the United States is going to play a key role in the development of advanced manufacturing technologies improving the technology base in general and potentially lowering costs. While the country cannot compete on labour costs, it has the scope to bring new efficiencies to advanced biologics manufacturing. Another area of US leadership is continuous processing. Thanks in part to the guidance and flexibility provided by the FDA, this technology can

reduce development timelines while also potentially lowering costs. In fact, American CDMOs are helping bring continuous processes to market more quickly, building trust and providing guidance to biotech partners less familiar with the regulatory process.

“The advantages of CDMOs is that one of the hesitations among innovators is the initial investment. However, once a line is in place with a contract provider, it’s simply

a case of securing that capacity for innovators. So they potentially have a huge role to play in accelerating adoption,” Doug Hausner, Senior Manager Continuous Manufacturing at Thermo Fisher Scientific Inc.

Despite the slow adoption over the last five years, our experts now believe we are at a tipping point as a number of continuous lines start commercial production. In particular, they considered the use of continuous processing and finished dose drug development, where it's predicted that over the next five years, 30% of all new NCEs coming to market will use continuous or semi-continuous processes involved. However, the use of continuous in API manufacturing is more nuanced and likely to be done on a case-by-case basis with developability concerns around dangerous reactions rather than cost taking precedence. The publication of ICH Q13 will also undoubtedly help accelerate adoption as it boosts global regulatory harmonisation on continuous manufacturing filing.

These technologies potentially mean companies can review hundreds of targets simultaneously

Similarly, in the biologics space, the industry is continually looking for new innovations in upstream and downstream processing, with organisations like NIMBLE pushing continuous bioprocessing. This is potentially an even bigger breakthrough than in the small molecule space as production costs are significantly higher and any innovation that lowers this will potentially make US manufacturers more competitive domestically and internationally.

“Innovation in manufacturing will be required for the production volumes necessary for the widespread use of advanced biologics, as well as the reduction in price of these therapies; just as innovation was previously involved in the popularization of monoclonal antibodies. There are already large market-based incentives for success in increasing the efficiency

and volumes of advanced biologic production,” commented Shapiro.

However, Jurkauskas believes that the best immediate option for biologics manufacturing in the United States is for small volume drugs with high margins. He added, “There will be more tolerance to higher production cost in the US, however, that tolerance is not unlimited”. For example, in the oncology space, many drugs, especially in the early commercial life cycle are low volume.

Another benefit for the production of innovative drugs in the United States is that many of these products require entirely new manufacturing processes. This is giving incentives to manufacturers and CDMOs to explore purpose-built facilities to meet the needs of these new drugs negating the cost-advantages of many overseas legacy sites. While at the start of the adoption curve, advances in AI and drug target development technologies are also opening up the potential for some returning discovery and early-stage development work being run in the United States. These technologies potentially mean companies can review hundreds of targets simultaneously and come with the obvious advantages of closer collaboration between innovators and development teams. What we'll likely see over the next few years is the increase in biotechs using US partners for computational processes to explore target options, chemistries and biologics – as opposed to the recent modus operandi of outsourcing chemistry services to Asia.

Emphasising how AI will impact the industry, Chatterjee added: “The biggest prediction I can make in the next five years for the United States is the application of AI. Whether it's on the early precursor chemical synthesis processes, or done in the formulation development processes or in the treatment algorithms that are being used today, it is a huge catalyst to be able to screen and evaluate very, very efficiently. Automation is also taking off quickly and not just in AI-driven drug development. Manufacturing and smart factories are now improving efficiencies and even enabling real-time remote monitoring.”

Innovation Hubs

Unquestionably, the source of the United States pre-eminence in the pharma industry stems from its giant centres of innovation. These centres, coupled with centrally organised incubators, have helped knowledge

dissemination and provide tremendous opportunities for new biotech start-ups. In fact, the country has been incredibly successful in rejuvenating and adding new hubs of pharmaceutical innovation. In addition to

the traditional big four – San Diego, Philadelphia, San Francisco and Boston – globally significant hubs can be found in Texas, Los Angeles, and Chicago as well as Washington and New York³. In fact, host city for CPhI USA, Philadelphia – home to innovators like Spark Therapeutics [who developed the first FDA-approved gene therapy for a genetic disease; LUXTURNA] – is poised to become perhaps the globe’s leading cell and gene therapy manufacturing hub with demand outstripping supply by 5 to 1⁴.

To emphasise the point that the United States continues to accelerate away as the largest centre of innovation, Jurkauskas looked at the number of clinical trials in the fastest growing area of clinical research, oncology. Spanning a three-year time frame, the United States has grown over that period, along with other countries. But as of April 1st, 2021, the total number of clinical studies in the United States is almost double that of China, France and Germany combined.

	USA	China	Germany & France
1 MAR 2018 to 28 FEB 2019	789	221	233
1 MAR 2019 to 11 MAR 2020	823 (+4%)	334 (+51)	268 (+15%)
1 APR 2020 to 1 APR 2021	1015 (+23%)	360 (+8%)	266 (-1%)

Figure 2: The table below summarises clinical studies over three periods of time spanning lung, prostate, colon, breast, skin, non-Hodgkin lymphoma, leukaemia, bladder, thyroid, uterus, pancreatic, oesophagus, and brain cancers and is compiled by Valdas Jurkauskas using data from the ClinicalTrials.gov website.

Most significantly, the pandemic has also seen an acceleration towards collaborative approaches and open innovation. Shapiro suggests that people are collaborating in ways previously unimaginable in pharma and it’s bringing new money and new ideas. Adding, “in the future, we are going to see a combination of academia, incentivised by government spending, and private industry incentivised by contracts and production.”

Shapiro also speculates that although it’s difficult to see what is behind private deal making (we can only confirm dual-sourcing arrangements once products

go commercial), there is likely to be increasing alignment between larger CDMOs and pharma companies for development services. Shapiro concluded, “over the next few years, it’s going to be a really positive environment in the United States with specialised skillsets, whether it’s for advanced dose technologies, advanced biologics technologies or cell and gene platforms. That is where you really want to be, and we are seeing a large number of acquisitions in the United States confirming this trend.”

Conclusion

Looked at holistically, the United States pharma sector, and manufacturing supply chain and associated services are perhaps the biggest beneficiaries of macro changes accelerated by the pandemic. This recent trend reverses the drift away from US pharma manufacturing and domestic contract services observed over the last two decades. Perhaps just as significantly, the innovator and biotech market has reasserted its pre-eminence over emerging hubs with, as of April this year, nearly double the number of oncology clinical trials of China, Germany and France combined.

Looking deeper into the market, we see not only rising relative growth, but growth for high value manufacturing areas, such as high potent and complex APIs, biologics and cell and gene therapies. For example, whilst small molecule CDMOs make up the bulk of the market, relative growth rates in advanced manufacturing will be significantly higher. Globally, Results Healthcare predicts that absolute growth across biologics, biosimilars, and cell and gene technologies will amount to \$133bn between 2019 and 2023. Most significantly, this prediction

pre-dates the pandemic, which has added billions of dollars-worth of contracts for fill-finish vaccines, adjuvants and, of course, viral vectors; adding further capacity pressure to an overstretched sector. Collectively, this means that US manufacturing sites for APIs, biologicals and, most pressingly, cell and gene therapy facilities will demand premiums (over 20 times EBITA in some cases). However, what we will also see, particularly with the convergence of recent manufacturing technologies and private equity capital, is a 'buy', 'build' and 'add' strategy across the North American region. Available pre-existing facilities will be competed for fiercely.

Undoubtedly, both CDMO and innovators will look to expand capacity significantly, whether it's now or in two to three years' time. In fact, such are the potential constraints, particularly across biologics manufacture that we will increasingly see a change in approach from biotech innovators, with capital raised earlier to build clinical and commercial manufacturing sites. Consequentially, this potentially means an increasing advantage for the largest CDMOs, who have the greatest access to capital. It allows them to stretch their capacity advantages – either through acquisition or construction – delivering even greater market penetration and the fastest overall growth rates. So, in the next few years, we would expect to see a growing market dominance from the top 30 CDMOs (by revenue), with the top 10 advancing fastest.

Another significant factor in the future growth of the United States market is the relatively small penetration of biosimilars within the country, which are anticipated to grow at a remarkable 35% over the next three years⁵. In the short term – while capacity catches up with demand in the United States – European CDMOs and Asian giants like WuXi Biologics and Samsung Biologics, will likely continue to see high growth of exports to the United States. Additionally, not only will access to manufacturing capacity continue to be a highly competitive space, but so will access to qualified pharma personnel. The industry is therefore expected to see a high growth in salaries for R&D scientists, as well as for manufacturing personnel both in-house and at outsourcing partners.

For large pharma, this increasingly competitive manufacturing landscape could mean that we will see not only the well documented strategic partnerships, but

also, the pre-booking of reserve capacity in advance of any needs. From a contractual point of view, this means we will see both deeper supply chain partnerships for suppliers, as well as the ability to demand longer contracts and more favourable terms.

Another potential shift in the market is the drive for increased stability and resilience. We may see greater vertical integration by companies in the United States, but also, regional sourcing strategies for starting materials and ingredients; particularly, for essential medicines or in response to governmental pressure and/or incentives for certain aspects of the supply chain. Chemistry and biology R&D and associated biotech support will also see rapid growth as new technologies and advances in targeting offset the previous cost advantages of partnering internationally. But in the short and medium term, as the engine of innovation, the US market will still provide enormous contract opportunities for chemistry, analytical and early-stage discovery CRO services for competitive international companies.

For overseas multi-nationals focussed on innovative drug manufacturing, particularly those without facilities in the country, the United States market still represents the largest opportunity for growth, but also a critical inflection point in strategy. Do they continue to rely on lower costs and operational advantages from existing overseas facilities trusting that any macro changes will be short lived and that there's enough growth for all? Or, is the optimal approach to rapidly build or buy facilities, despite the current high valuations, so that they can ensure a regional supply chain for their US customers that deem this a priority?

Overall, perhaps more than at any point in the last 20 years, the United States represents the single biggest economic opportunity for both domestic and international pharma companies to consolidate and grow. In fact, with the return of international travel and trade events, it is anticipated that over the next 12-18 months, the industry will see a 'supercharged' period for partnering, strategic alignment and contract agreements. The companies that establish supply and partnering networks earliest will undoubtedly see the best medium-term prospects, as well as capturing the majority of the growth from the expected post covid boom.

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