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US Pharma Market Trends 2021:

Ten emerging trends shaping the US pharmaceutical manufacturing and outsourcing sectors

Gareth Carpenter

Introduction



2020 will go down in history as a pivotal year for the US pharmaceutical manufacturing sector. Firstly, the emergence of the global coronavirus pandemic provided a seismic shock to the industry and forced major rethinking on several lines. And secondly, a bitter and hard-fought Presidential election saw Joe Biden defeat Donald Trump to usher in a complete change of approach towards pandemic management and healthcare delivery.

The outlook had been so much different at the start of 2020. The pharmaceutical

industry was locked in the process of re-defining its business models, with precision medicines and greater uptake of digital technology coming to the fore. In the outsourcing sector, contract development and manufacturing organisations (CDMOs) were extending their reach along the product lifecycle and in some cases, re-inventing themselves as 'one-stop-shop' collaborative partners of the talk around pharma supply chains was how to eke out further efficiencies from a generally well-oiled and productive machine.

As the first wave of the virus swept over the country, US pharmaceutical manufacturers initially had to balance the priorities of keeping their staff safe and transitioning the majority to a remote work environment with ensuring ongoing operation of facilities so patients could continue to receive essential medicines.

And they also had to contend with the unpredictable logistical challenges brought on by national lockdowns, border closures, export bans and drug and ingredient shortages.

Pharma's response to the pandemic in terms of vaccines development and distribution of treatments grabbed the most headlines in 2020. As the industry looks ahead to the future, coronavirus will provide a sombre backdrop to many of the immediate hurdles and obstacles it will face. And looking at the crisis through the lens of pharmaceutical manufacturing, capacity – or lack of it – will be a huge cause for concern as the weight of expectation falls on the sector to roll out enough doses of vaccines and therapies to control and suppress the virus.

More than a year on from the start of the pandemic, the sector is now seriously gauging what the longer-term implications of COVID-19 might be, especially now that a post pandemic world is coming into view as vaccine production and administration is scaled up.

It could be argued that the pandemic has acted as a catalyst to accelerate adoption of trends that were already emerging before the crisis struck.

The industry has embraced digital technology to ease the logistics burden of clinical trials (which for a period ground to a halt) and COVID-19 has accelerated drug development timelines in ways previously thought impossible.

One of the key drivers behind the rapid development of COVID vaccines has been the global exchange of ideas. Everything from the sequencing of the virus' genome back in the early part of the year to vital patient data from trials and new therapeutic applications like RNA – all of which was underpinned by a level of proprietary exchange that would have been unthinkable pre-COVID.

With what has been accomplished in under a year, it does have many in the industry thinking about the long-term benefits of continued open access R&D. Is 2021 the start of a revolution in thinking amongst the industry and academia in how we approach the discovery, development, and commercialisation of new therapies?

In interviews with key industry experts, this report identifies ten major and emerging trends that are sure to be prominent in 2021, as US pharmaceutical manufacturing and outsourcing continue to respond not only to the challenges that the ongoing global crisis has presented, but also to evolving obstacles and hurdles that are typical in such a highly-regulated sector.

Gareth Carpenter,
Editor - Pharma, CPhI

1 Biotech research to hot up in 2021

The US approval and validation of both mRNA vaccines against COVID-19, developed by Moderna and Pfizer, has been a watershed moment; not just in the fight against the disease but more broadly in bringing these new platform technologies forward for consideration in use across many therapeutic indications.

“While they are now known for vaccines, the biggest potential applications for RNA platform technologies lie in other areas, notably oncology and genetic disease. The only potential question in terms of development of course, is can they be made in a cost-effective manner, as obviously the vaccines rightly had tremendous government backing and this helped keep the unit cost down,” says **Bikash Chatterjee, Chief Executive Officer of Pharmatech Associates.**

Companies such as Moderna have in the past suggested that they would be able to commercialise RNA platforms much more quickly than previously thought and what COVID has done is validate this approach on a massive scale.

Parrish Galliher Managing Director, BioProcess Technology Group says the past year has been really quite remarkable and the approved mRNA vaccines “have really opened the door to the potential of other treatments using the same approach.”

Personalised medicine is another major growth area especially as the industry adapts and learns how to scale-up – not out – therapies. In fact, there are more than 100 in late-stage development with around at least 10 approvals expected per year from 2022 onwards.

Growth in the advanced therapy space is being expedited by lower cost trials, but also, by new genomics and diagnostics. Patients over the next five years are predicted to be diagnosed far earlier and have specialised diagnostic tools to identify the best therapies for the disease pathways unique biology.

“Globally genomics is delivering a remarkable pace of innovation – one only need look at the mere week it took China’s scientist to sequence COVID – with AI also bringing potentially step change improvements in early-stage work,” says Chatterjee. “It means chemistry services and early discovery will be less reliant on PhDs – work that is often conducted at the other side of the world (in China and India) to the sponsors – and even small companies can explore advancing more potential targets simultaneously. In fact, many commentators expect FDA approvals of more than 100 targets per year to become commonplace within the next decade.”



Another factor that will accelerate activity in the latter half of 2021 is the bottleneck of investment decisions that were put on hold in 2020, which translates to a lot of ‘pent-up liquid capital’ being made available.

2 Increasing CDMO/CMO demand poses manufacturing capacity and skills questions

According to **Valdas Jurkauskas at Black Diamond Therapeutics**, the biggest manufacturing bottlenecks are moving away from whether therapies can be funded and whether the requisite technologies and knowledge are in place to advance them into the realms of whether enough service companies meet the demand: “CROs are extremely busy and CMOs are at capacity in some instances. I think the opportunity for CROs and CMOs to grow is incredible. Will they grow and reinvest in their capacities and capabilities?”

He says the challenge for CDMOs and CMOs is not only to enlarge equipment capacity to make more drugs, but also, to diversify equipment and a set of skills to address the need for large molecules, antibody drug conjugates, cell therapies and personalised medicines. “The question for both CROs and CDMOs is whether to remain very focused on one area or expand and grow with the industry, because right now there is an avalanche of clinical trials,” he says. “My instinct is that the constraints will first come in terms of people – which will drive wages higher and mobility – but then also facilities.”

He says single-use technologies do potentially offer some solutions, both in terms of helping CDMOs set up for demand and for innovators thinking of going it alone on manufacturing. The shift to single-use in particular, coupled with increased funding, has accelerated the re-evaluation amongst innovators. Improved approaches in biologics manufacturing and titre mean that facilities can now be operated on a smaller footprint with smaller, less expensive equipment.

“What we have seen in the last five years is an overall reduction in available CDMO bio capacity, as a result of a big jump in pipeline that has come into commercial production,”

adds Parrish Galliher at BioProcess Technology Group. “Consequently, what we now hear is a lot of activity around building your own capacity versus outsourcing, with biotech exploring building first early stage and then later stage manufacturing facilities. Understandably, that has resulted in a re-examination of the economics of plants and what types of facilities are best. Obviously single-use becomes very attractive as a less expensive option initial option.”

3 Pharma industry to largely embrace ‘predictable’ new Biden administration

Joe Biden’s victory in the US Presidential Election was the biggest story as the monumental year of 2020 came to an end, but what are the implications of this power switch for the US pharmaceutical industry?

“President Biden is a known commodity in Washington; he was a US senator for a long time and a vice president for eight years and he was a critical part of the Affordable Care Act, so the US pharmaceutical industry knows what they’re getting,” says **Peter Loge, Associate Professor of Media and Public Affairs, School of Media and Public Affairs, George Washington University.**

Biden’s predecessor, Donald Trump, had at best a strained relationship with pharma. While on the surface, it appeared he had close ties with the industry – as illustrated by his appointment of former Lilly president of US managed care services, Alex Azar, to US Secretary of Health and Human Services – he did have a number of high profile spats with Big Pharma during his tenure, particularly over the issue of drug pricing.

Loge says that if money is an indication of how people feel, the US pharma industry will not miss Donald Trump, explaining that pharma executives contributed more than \$2.5 million in total to the Biden campaign, and only just over \$500,000 to the Trump campaign.



“Maybe smart political money follows power; you always want to bet on a horse that is about to win,” says Loge. “But if you look at what the industry wanted, President Biden will be a lot better for them than President Trump. One of the things about Biden is we know what we’re getting; he’s unlikely to get into public spats with the industry and he is predictable. All any industry wants is to know what the rules are and how to follow them. President Trump constantly shuffled the rules, he would issue statements and releases and then back off them.”

The Biden administration has also ushered in a new approach to dealing with the largest public health crisis the world has faced in over a century, the coronavirus pandemic.

“There is a trust in science from this new

administration and a recognition that experts come from all corners,” says Loge. “If you’re a biomedical researcher or if you’re interested in supply chains in the pharma industry, you can work in government, universities or industry. President Biden is going to draw from the best in all of those fields for a predictable, deliberate response to the pandemic that is driven by science.”

4 Early stage development companies dominating biotech investment

According to **Valdas Jurkauskas at Black Diamond Therapeutics**, the 21 preclinical development companies that launched IPOs in 2020 enjoyed more than ten-fold difference between their market capitalizations in mid-January of 2021 (\$41.7 billion) and the total proceeds at the time of their IPOs in 2020 (\$4.0 billion).

“The total proceeds for all preclinical companies in 2020 was \$4 billion at the time of IPOs; yet as of mid-January [2021], the combined market capitalisation for the same companies had risen over ten-fold to \$42 billion,” says Jurkauskas. “The implication of this is that these companies have the resources to hire CMC and clinical research professionals far earlier and therefore further speed-up development timelines. It also means that the next few years look extremely promising for both CROs and CDMOs that can expect to help conduct the trials and making ingredients and clinical materials for these potential therapies.”

In the medium-term, this will present some interesting conundrums for successful CDMOs who will need to decide whether, where and how to invest for future growth. Typically, in the past, CDMOs have often waited for a pharma customer before investing in facilities – to reduce risk and unused capacity – but we might now see attempts to ‘follow the molecule’, and get a head start over competitors on where and for what future capacity is needed.

5 Supply chain resilience to take precedence over reshoring of API manufacturing?

With the majority of ingredients and intermediaries still produced in Asia – particularly India and China – certain drug shortages caused by the COVID-19 pandemic in 2020 accelerated the debate about whether API and intermediate production should be reshored to the US and Europe to reduce dependency on large suppliers such as China and India. With a presidential election looming at the tail-end of the year, the issue took on an increasingly political nature in the US, with a group of senators promoting a bipartisan bill to reduce reliance on China for finished products and drug ingredients.

Much of the thinking appeared influenced by the perception that global pharma supply chains had been severely weakened by the crisis, and remedial action needed to be taken given the huge uncertainty over how long the disruption would last.

However, with vaccine candidates inching ever closer to fast-track approval and distribution, 2021 could be the year when companies operating in the pharma supply chain start to reimagine a post-COVID world and take a step back from committing themselves to what would be a huge investment to bring facilities and technology closer to home.

René Zoetmulder, Procurement Manager at Aspen Oss, believes that companies would be better served by active maintenance and reinforcement of their supply chains by dual sourcing – the practice of establishing at least two sources for key ingredients to have fall-back options in case of outages – rather than reshoring production.

“If you have control of your real supply chain as far as possible down the chain, I think that’s a better guarantee of continuity and availability than reshoring to Western countries, which I think should be considered but will not change the game,” he says.

6 Supply Chain Security and Patient Focus

Much of 2020’s headlines focused on how COVID-19 exposed the weak links in pharma supply chains rather than the myriad success stories. Proactive forward planning by companies in preparation for such emergencies over previous years meant that medicines distribution was overall unaffected.

“The pandemic challenged drug supply chains throughout all regions”

The pharma industry has shown great agility during the COVID-19 pandemic, and 2021 will be the year when companies need to keep building on that by remaining patient-focused and putting carefully laid out plans into action, according to **Rajesh Sadanandan, Head of API Sales for US and Europe, Dr Reddy’s**.

“The pandemic challenged drug supply chains throughout all regions,” he says, explaining that Dr. Reddy’s has been working on several initiatives to mitigate supply chain risks by integrating key starting materials, establishing strategic sourcing and logistics partnerships, and improving its manufacturing units’ capacity management.

“These past years’ efforts have helped us normalize supply to meet customer and ultimately patient demands during the pandemic,” he says. “We continue to mitigate geographical risks by leveraging our manufacturing assets throughout India, Mexico, and the UK for our APIs and in India the US for our formulations.” He adds that redundancy, reliability and responsibility are key to de-risking the supply chain for global pharma companies: “Continually monitoring the situation, potential issues (e.g. genotoxic impurities) and anticipating and addressing their short-term and long-term impacts with agility and speed will continuously accelerate access to affordable medicines.”

"[COVID-19] sped up how companies had to embrace digitalization, and it will stay critical for companies to keep the digital strategy high on the list and further improve on it," he says.

7 Cure vs. treatment model shifts CDMO contracts from volume to value

The CDMO sector has seen significant activity in cell and gene therapies (CGT) in recent years; Catalent and Thermo Fisher have combined for more than USD3 billion in acquisitions in that space and are making additional investments in those new businesses.

As **Gil Roth, President of the Pharma & Biopharma Outsourcing Association**, explains, while there is a great deal of pipeline work in this space and much promise for patients, there are challenges ahead.

"In addition to the complexity of manufacture, the evolving regulatory landscape for CGT products, and the lack of trained reviewers at FDA for these candidates, there is also the very different business model they represent," he says. "Many CGT candidates are being developed as cures, rather than treatments. While this presents reimbursement challenges and new assessments of the value of these drugs, it also creates a different model for client-CDMO agreements."

He adds that a cure implies a front-loading of the patient population, with many patients treated upon launch, and diminishing volumes required over time as fewer patients remain to be treated: "Such a model means that CDMO contracts must mirror this approach, which is a change from the ongoing volumes typically treated in contract relationships."

He says that the clearest example of this so far isn't actually in the CGT space, but from a small molecule drug product: Gilead's Sovaldi, and the follow-on drugs in that space, which effectively cure hepatitis C. This remarkable achievement shepherded a new world for drug manufacturing as well as drug pricing, he argues.

"Drug license-holders and CDMOs weren't necessarily accustomed to a drug like Sovaldi, which required a massive bolus of manufacturing services in its early years, only to see demand drop off as so many patients were cured at the end of their 12-week course of treatment," he says. "Advances like this were almost unimaginable 20 years ago, but they do bring new market realities with them." The question of how CDMOs and customers will develop contracts that reflect this new model of cure vs. treatment is likely to gain ever more prominence as we head into 2021.

8 A gradual breakthrough for continuous manufacturing of APIs?

2021 could see more API manufacturers invest in continuous technology, enticed by the perceived advantages of maximizing throughput and eliminating labour and cost implications of starting up and shutting down production between batches by running the manufacturing process 24/7 until the project volume is complete.

This also includes the potential to reduce the likelihood of any discrepancies in quality and process reliability, meaning the risk of discarding a portion of a batch or an entire batch is considerably less.

"By running reactions on a smaller scale, you can reduce the amount of product you lose in the event of mechanical failure," says **Bikash Chatterjee, Chief Executive Officer of Pharmatech Associates**. "This can mean huge savings in terms of money and raw materials. Smaller scale equipment can translate into less infrastructure and facility cost, although this is offset by the characterization and control challenges associated with continuous manufacturing."

With US government support coupled with a defined regulatory framework aiding anyone looking to leverage continuous manufacturing technology, it is poised to break through in the pharmaceutical industry, says Chatterjee.



However, he is of the view that in terms of large-scale operations, uptake in 2021 is likely to be slow because of the complexity associated with process development, and the control and paradigm shift required by quality assurance.

"Perhaps the most challenging aspect for widespread adoption of continuous manufacturing is the strong business case to make the investment," he says. "The business continuity component of business strategy should move to the forefront of this conversation, where the ability to operate even in the face of catastrophic events, is the basis for the investment in continuous manufacturing capacity."

He adds that continuous manufacturing does provide a potential avenue for chemical manufacturers looking to make the jump to pharma APIs and chemical pre-cursors, as the technology removes the human component from the process.

"According to where the process falls within the GMP cascade, this could require a more manageable paradigm shift in quality thinking. The wild card is whether private/public partnerships such as Civica Rx gain a foothold and convince CDMOs to invest in the capital and expertise required to support continuous manufacturing," he says. "In such a scenario, I would expect the advantages of continuous manufacturing to become more apparent and become more broadly adopted. What I do believe we will see is a re-energization of Process Analytical Technology (PAT) as the practical knowledge of moving to real-time releases becomes better defined within the continuous manufacturing's control strategy."

Amid the anticipated huge demand for COVID-19 vaccines and therapies, how likely is it that continuous platforms will be utilized in 2021 for these products?

Chatterjee says that while billions of dollars are being invested, it is not clear how much is being invested in novel manufacturing continuous processes for the first generation of vaccines that will be approved.



“While initial approvals will most likely be for vaccines manufactured using traditional batch processes, BARDA is investing in continuous process development for the production of the raw materials or building blocks (ribonucleotide triphosphates, NTPs) used to produce mRNA vaccines (Moderna),” he says. “mRNA vaccines are produced through chemical synthesis and thus are more amenable to continuous processes.”

HE adds that for vaccines produced using more traditional biotechnology processes (Protein, and viral vector-based vaccines) the use of continuous processes in their manufacture is less likely.

“Continuous or intensified processes are in early feasibility stages currently, with investments in research being provided by CEPI and the Gates Foundation,” he concludes. “Most likely, with the continuation of the pandemic and the extremely high demand for vaccines, we could see a push to incorporate these processes post approval.”

9 Industry fight against antimicrobial resistance to gain prominence?

2021 may be the year when governments and pharmaceutical companies really start to show some tangible progress in their efforts to fight what is developing into a major issue.

A report by ex-Goldman Sachs economist Lord Jim O'Neill in 2016 estimated 700,000 deaths per year due to AMR and predicted this could rise to 10 million by 2050 if left unchecked.

“Antimicrobial resistance (AMR) is a major global health crisis and antibiotics represent one of the most important medical tools in the tool-kit and we’re at risk of either diminishing their effectiveness or losing them altogether,” says **Steve Brooks, advisor to the AMR Industry Alliance**, formed in 2017 and comprising around 100 life sciences companies and trade associations committed to tackling the problem. “There’s really a call to action to address AMR. The pharmaceutical industry is one of the stakeholders with a role to play in this.”

Brooks says that AMR Industry Alliance members have committed to implement the work products that it has developed, which lay out good environmental management practice to minimise the risk of antibiotics getting into the environment. For example, Predicted No-Effect Concentrations (PNECs) can be used in environmental risk assessments to calculate whether the residual antibiotics in a facility’s wastewater is safe and acceptable to discharge.

However, current membership only represents one third of the global antibiotic manufacturing base so more needs to be done.

“We would encourage antibiotic manufacturers who are not part of the Alliance to either consider joining or at least look at the framework or the PNECs, which are freely available on our website, and challenge themselves to commit to meeting the targets,” says Brooks.

In terms of what is in store for 2021, the AMR Industry Alliance is working on developing its framework and PNECs into a consensus standard and hopes to have this ready by the end of the year.

10 Continuing consolidation in the CDMO sector

Peter Bigelow, President of xCell Strategic Consulting and Chairman of the Pharma & Biopharma Outsourcing Association (PBOA) is of the opinion that M&A activity in the CDMO sector will continue at a brisk pace into 2021 based on several resilient drivers.

He explains that valuations of pharma services companies remain high, incentivizing small and medium sized companies to transact, and large and medium sized pharmaceutical innovators have less desire than ever to continue to own non-strategic assets so carve outs and divestments should continue at a high rate.

He also points to the growth of advanced technologies such as cell and gene therapy and mRNA, which “creates an exciting opportunity for those companies that can capture customers early in the cycle.”

He adds that COVID-19 and other unseen factors will drive growth in injectable manufacturing and other segments of the business.

But is there any risk the current COVID-19 situation will have any effect of the recent trend towards consolidation?

“I do not believe COVID-19 will have a substantial long-term structural effect on the CDMO sector,” he says. “However, the impact of increased government funding for access to essential medicines and the desire to build regional and country specific supply chains has yet to play out – and could have some impact.”

With CDMOs trending towards strategic partnerships with a broad service offering, some have questioned whether the current crisis will force them to specialise in services directly connected with pandemic management.

However, Bigelow says that companies with diverse offerings will continue to build strategic partnerships and serve important customers broadly.



“There will be a much greater ‘reservation concept’ whereby capacity elements for some suppliers will become unavailable to their general customers,” he says. “This is a result of governmental and non-governmental pandemic management functions maintaining available capacity in case it is needed. Assuming that this capacity will be acquired at a fair rate whether it is needed or not, additional investment will be made to create new capacity. There may be some short-term capacity constraints (as we see currently for vaccine fill/finish) but the market should correct over the next two to three years.”

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