CPhI insights

CPhI Annual Report 2020: Postulating the post-COVID pharma paradigm

CPhI Pharma Industry Rankings & Annual Industry Report 2020

CPhI Festival of Pharma, 05 - 16 October 2020

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Overview

The findings from this year's CPhI Pharma Industry Rankings come as the world experiences unparalleled economic and healthcare shocks. COVID-19's implications for pharma growth, revenues and the supply chain are still emerging. Despite this, the industry has been remarkably quick to act. International supply chains remain robust, innovation has accelerated and global partnerships are proliferating. In a year of uncertainty, insight into how executives view the industry's resilience, its opportunities and relative strengths of the major global pharma economies could not be more valuable.

The 2020 survey results include Informa's largest ever cohort of industry executives with more than 550 taking part, bringing perspectives from over 30 countries.

The rankings assess the major pharmaceutical markets across a range of key indicators – from 'market growth potential' to 'quality of API manufacturing', 'innovation', 'competitiveness', and 'finished product' quality – culminating in overall scores for each country.

Significantly, for the first time in its four-year history, the Annual Survey reveals the **overall industry index has fallen**. The overall index measures accumulated scores across each country in the five main solid dose indices; growth, API manufacturing, finished dose manufacturing, competitiveness, and knowledge of professionals.

In addition, the rankings also provide detailed data on biologics across 'quality of bioprocessing', 'knowledge of professionals', 'growth' and 'innovation'.

The report is published alongside the inaugural CPhI Festival of Pharma, which will take place virtually between October 5-16. This will be the world's largest ever virtual pharma trade event, playing host to more than 20,000 attendees and over 700 exhibitors.

Pharma market growth potential

This year's report sees a significant shift in the growth potential across the major pharma economies. India (7.37) for the first time, has topped the rankings, despite a slight score decrease (0.85%). China, the leading nation in terms of growth across all previous surveys, suffered from a sizeable score decrease of 11.93%, the biggest of any market since the survey began. However, falling from a high base, China is still well-set for growth. Only the much talked about supply chain de-risking has acted as a potential drag factor.

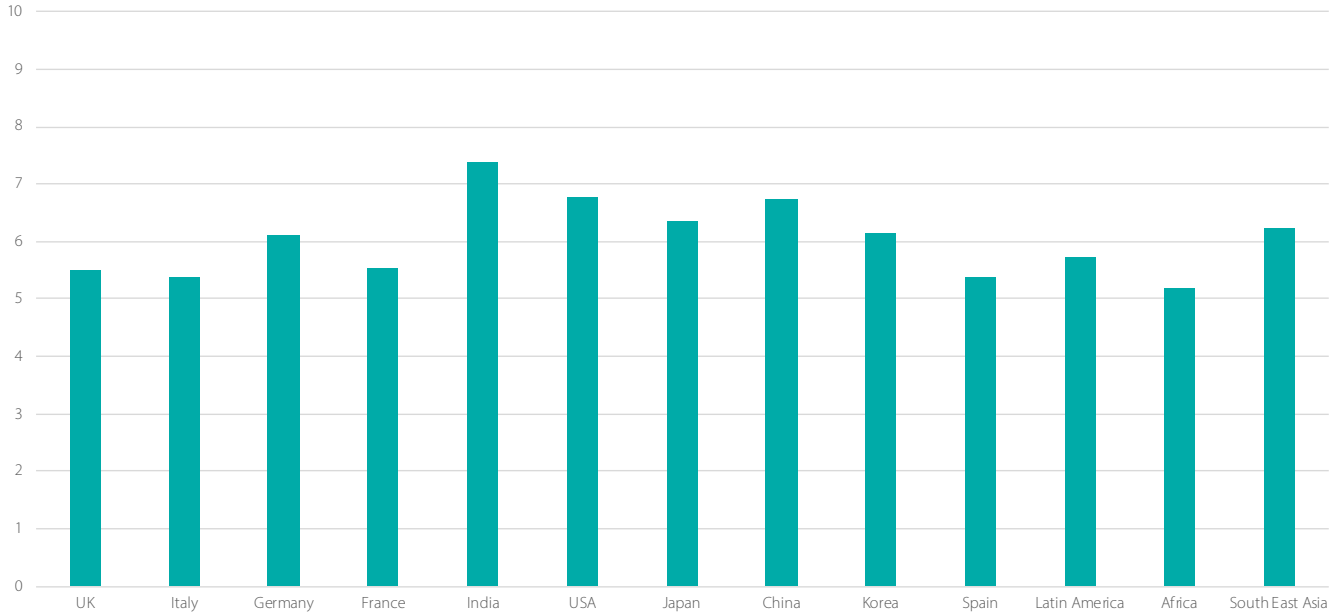
For API manufacturing and CRO chemistry services, India is viewed as the primary beneficiary of the rebalancing of outsourcing away from China. However, this is offset by continued strength in China's domestic healthcare market, with overall drug consumption rising and many new innovative biotechs launching. This could mean in 5 years time exports are likely to make up a less prominent percentage of China's overall pharma market size.

Germany (6.12) was another negative mover, down over 11%, falling from 3rd to 7th in the rankings. Germany has appeared to suffer as pharma markets look increasingly towards domestic sources of manufacturing to de-risk the global supply chain. The reason behind Germany's sudden shift? It could be that it is unfeasible for advanced economies like the USA – which according to many analysts and commentators is exploring ways to increase domestic production and is still by far the largest market – to bring home low-cost, high-volume manufacturing

from emerging markets. However, the USA may be able to bring some of the advanced high-value manufacturing home from relatively expensive and developed pharma economies such as Germany.

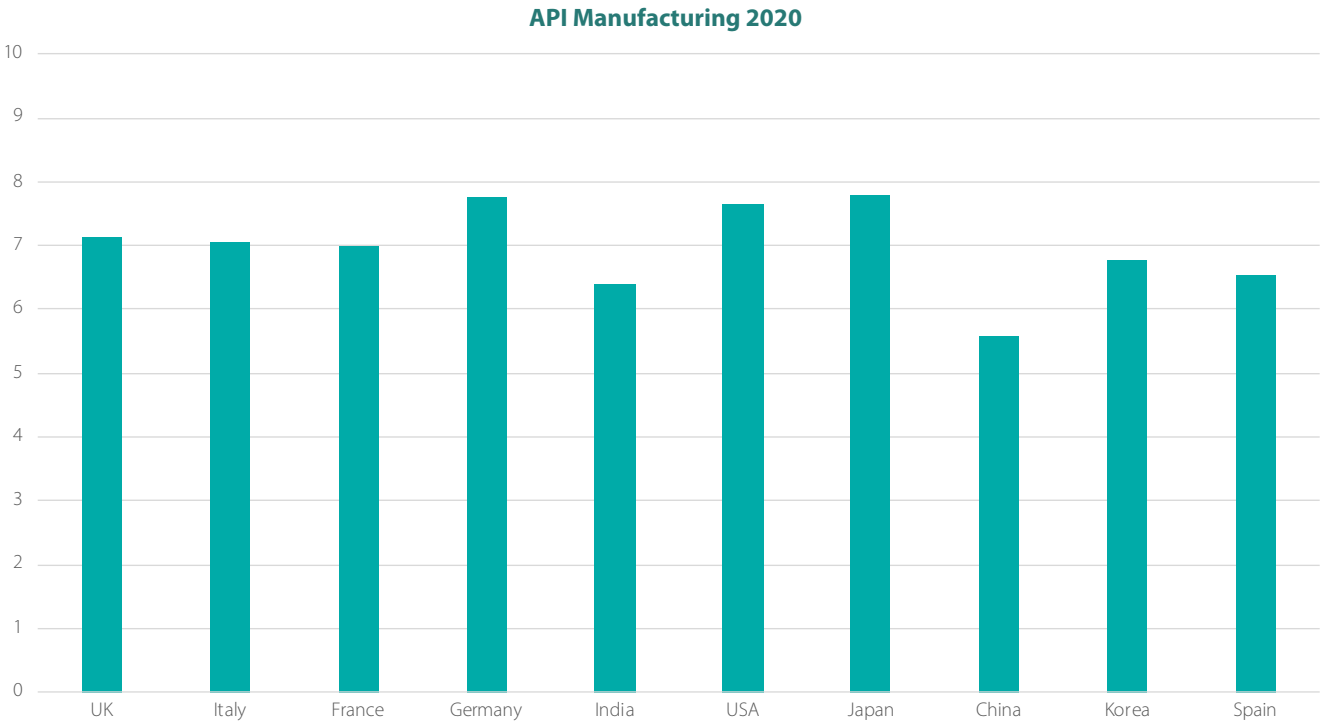
Significantly, Italy (5.37), the largest producer and exporter of APIs in Europe, saw its growth potential increase rapidly by more than 16%. This suggests that it may see near-term growth as a result of diversified ingredient sourcing strategies (i.e. as a regional alternative to Asian hubs). Japan (6.35) and the UK (5.50) can also be satisfied with respective score increases of 6.53% and 6.07%. Although conducted prior to the most recent developments in Brexit negotiations, the survey suggests Britain is rebounding on its previous three years' performance, which clearly reflected concerns over Brexit downsides.

Growth Potential of pharma industry 2020



API manufacturing

API manufacturing quality is always a one of the most eagerly anticipated rankings for CPhI audiences. The top three – Japan (7.78), Germany (7.75), and USA (7.64) – remain unchanged from 2019 with India (6.39) and China (5.57) in 9th and 10th, bringing up the rear. Scoring year-on-year has remained reasonably consistent barring Spain (6.54), the only country to see a decrease (8.68%), and Italy (7.04), the only country to experience a significant score increase (5.58%). Italy's performance sees it move from 8th to 5th place in the rankings. It looks well-set to benefit from global supply chain de-risking, with European markets looking to bring sources of affordable APIs closer to home and away from Asia.

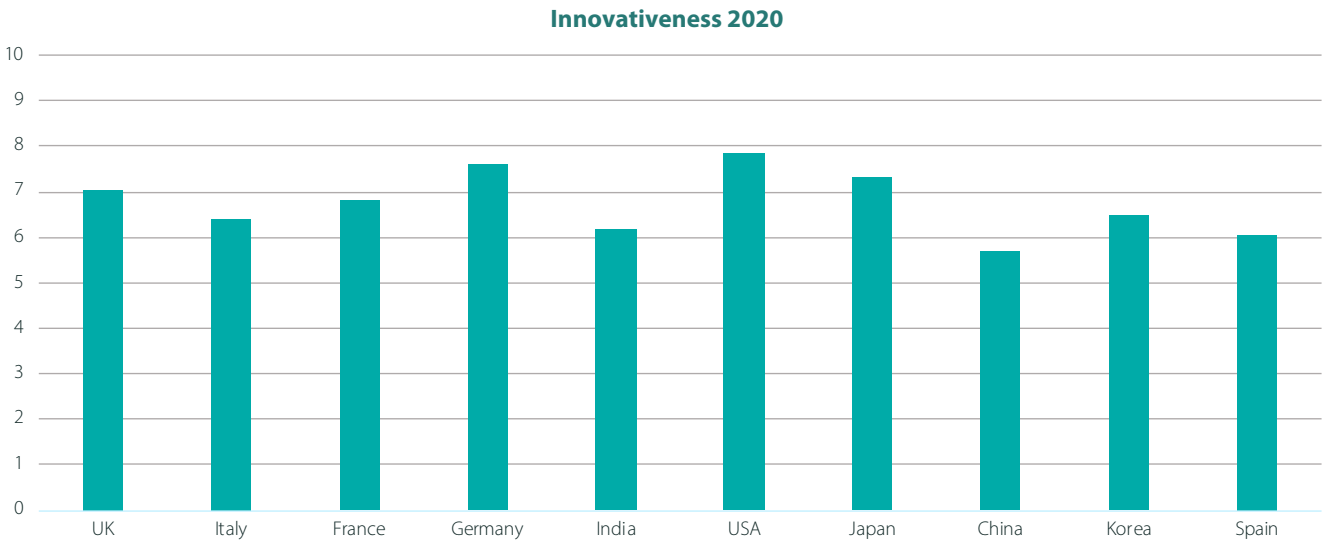


Innovation

Unsurprisingly, the USA (7.84) dominates in innovation. As the world's most prominent big pharma economy, it retains its top position in this year's report, despite having the second biggest score decrease (-3.38%). Germany (7.59), however, has overtaken its nearest rival Japan (7.34) to take 2nd place. The UK (7.04), France (6.79), Korea (6.48) and Italy (6.42) all retain their places from 2019, further consolidating their positions as tier two, innovation-led pharma economies.

The emerging innovative markets also remain largely unchanged. However, India (6.16) did rise from 10th to 8th with a respectable 2.35% increase in score, leapfrogging Spain (6.05) and China (5.68). Surprisingly, China saw a decrease of 6.57%. This falling perception of China as an innovation centre may reflect adverse coverage of the nation in 2020 – rather than the reality – as the numbers of biotechs, global CDMOs and mAb approvals has continued to rise extremely quickly (see BioPlan Associates, Vicky Xia's CPhI 2020 Report contribution).

Improved perceptions of India are likely in response to the government's increased R&D initiatives. For example, the Indian Pharma Secretary is planning new R&D centres of excellence and policies that strengthen industry-academia linkages – with incentives for R&D scientists that allow them to commercialise and profit from their discoveries[i].



Competitiveness

The competitiveness index evaluates each country's tax environment, quality of employees, infrastructure, research potential, labour costs, accessibility and access to funds. The USA (6.82) retained the top spot, in spite of a 3.09% decrease in score from 2019, with Germany (6.49) regaining 3rd place having dropped down to 4th in 2019. China (6.21), suffering a decrease of 5.37%, fell back on its 2019 gains into 4th place, while Italy (5.74) improved by a remarkable 9.38%, overtaking Spain (5.60) and scoring comparably with France.

Finished product manufacturing

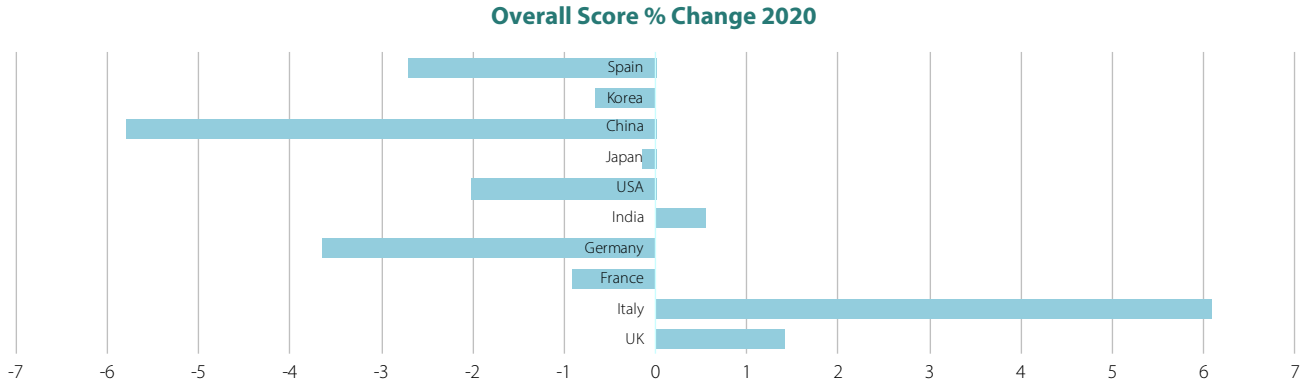
The leading names in high quality production – Germany (8.14), Japan (8.13) and USA (7.96) – are again ranked as the only tier one nations in terms of finished formulations. In terms of the rest, Spain (6.33) saw the largest score decrease of 6.79% from 2019, whilst India benefited from a strong 3.34% rise; the biggest increase out of all markets. The quality of finished products in India is seen as rising, and the country famously has the most USFDA-approved sites outside of the US[ii], accounting for an incredible 40% of generics imported into the country[iii]. The UK (7.66) and China (5.35) were the only other markets alongside Japan and India to better their scores from the previous year, with increases of 0.18% and 1.35%, respectively.

Change in Country overall score: the CPhI Pharma Index:

To calculate the CPhI Pharma Index we compile the findings from each of the five small molecule categories with equal weighting given. The USA (7.41), Japan (7.15) and Germany (7.10) make up the top three, with Japan just displacing Germany in 2nd place, as the latter suffered a substantial overall score decrease of 3.65%. Germany's performance might seem surprising at first glance, but it is driven by the11.67% decrease in the 'Growth Potential' category. However, all three leading countries performed exceptionally well in quality of finished product, quality of API manufacturing and level of innovation, further consolidating their positions in the elite tier of pharmaceutical economies.

The UK (6.66) – only one of three countries with an increased score from 2019 – has climbed above France (6.60), taking second place among the European Pharma markets behind Germany. What cannot go unnoticed, however, is the rise of Italy (6.33). The country boasts largest percentage increase in this category (6.08%), which sees it move from 10th to 8th in the global rankings. It is possible that such a significant increase is not only down to global macro changes, but reflect Italy's undervaluation in last year's survey (a 2018-19 score decrease of 5.02%).

But it is China (5.91) that has suffered the biggest score decrease of 5.80%, which sees them fall down the rankings into 10th place. This is the largest year-on-year fall in any year of the survey, with significant score decreases in all categories except for the categories relating to quality API manufacturing and finished dosages. Respondents believe that the global pandemic has negatively impacted the Chinese pharma market's reputation in nearly all major sub-sectors. These effects are unlikely to be felt long into the future as China's fundamentals remain too strong. We expect a dramatic bounce for China in 2021, as while the pandemic has altered many short-term realities and perspectives, the long-term trends in China remain extremely strong. We expect continued innovation in biotechs and growth in manufacturing production. But what the crisis may have done, is to accelerate the switch towards a pharma economy led by domestic – not international – sales.

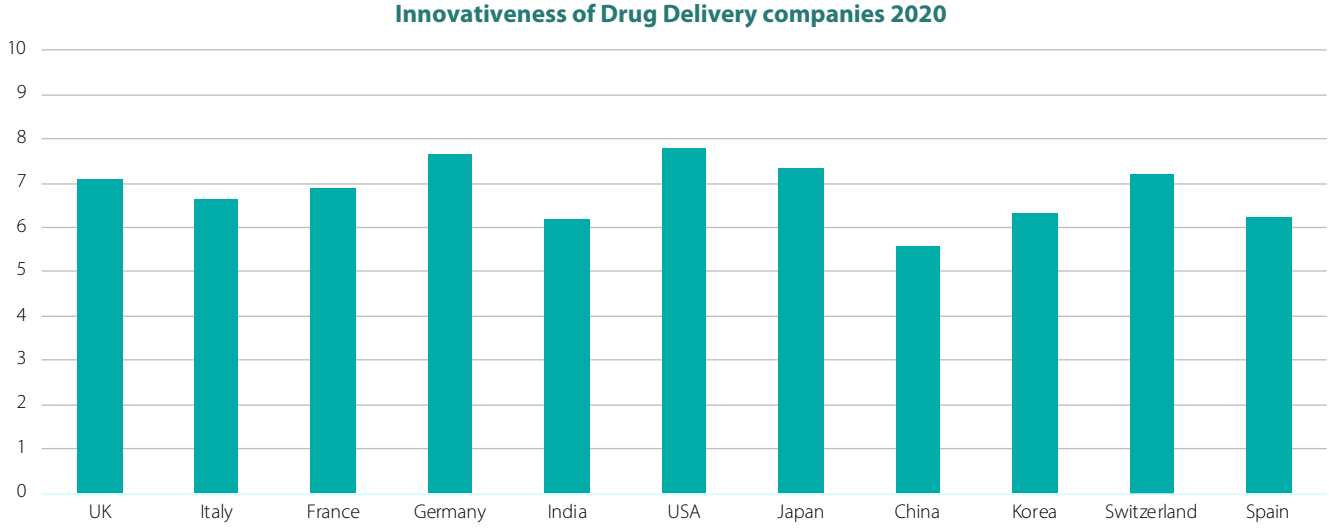


The CPhI Pharma Index: what do the collated findings mean for the global industry in 2021?

When collated across all markets and all primary survey categories (solid dose categories), the industry as a whole has experienced, for the first time, an overall decrease of 0.86%. This is perhaps to be expected given the global impact that COVID-19 has had, not just for pharma, but all industries and economies. Yet overall, the resilience of the global pharma supply chain is commendable. Moreover, looking forward, there is plenty of opportunity for global market growth through the development of novel therapies and vaccines targeting COVID-19. It is also worth noting the many of the leading pharma economies have scored strongly in knowledge and pharmaceutical quality statistics and much of the fall on 2019 results reflects reduced confidence in growth rather than quality.

Innovativeness in drug delivery

The United States maintains its position as the world's pre-eminent drug delivery economy with a score of 7.79. However, Germany (7.66) has closed the gap, overtaking Japan (7.32) and moving into 2nd place thanks to a 1.24% increase on 2019. Surprisingly, Switzerland (7.19) drops down to 4th place due to a 6.69% decrease in score. The reasons for this remain unclear, but may reflect reduced focus on drug delivery in the last 6-months. It nevertheless heads a second tier of countries with the UK (7.08) and France (6.89), who both retain their places of 5th and 6th respectively. The market with the biggest score decrease, however, is China (5.57), which sinks to the bottom of the rankings, with a score decrease of 7.29%. India (6.18) failed to break away from the bottom tier in the rankings, despite having the largest score increase of just under 6%, which sees them climb one place to 10th.

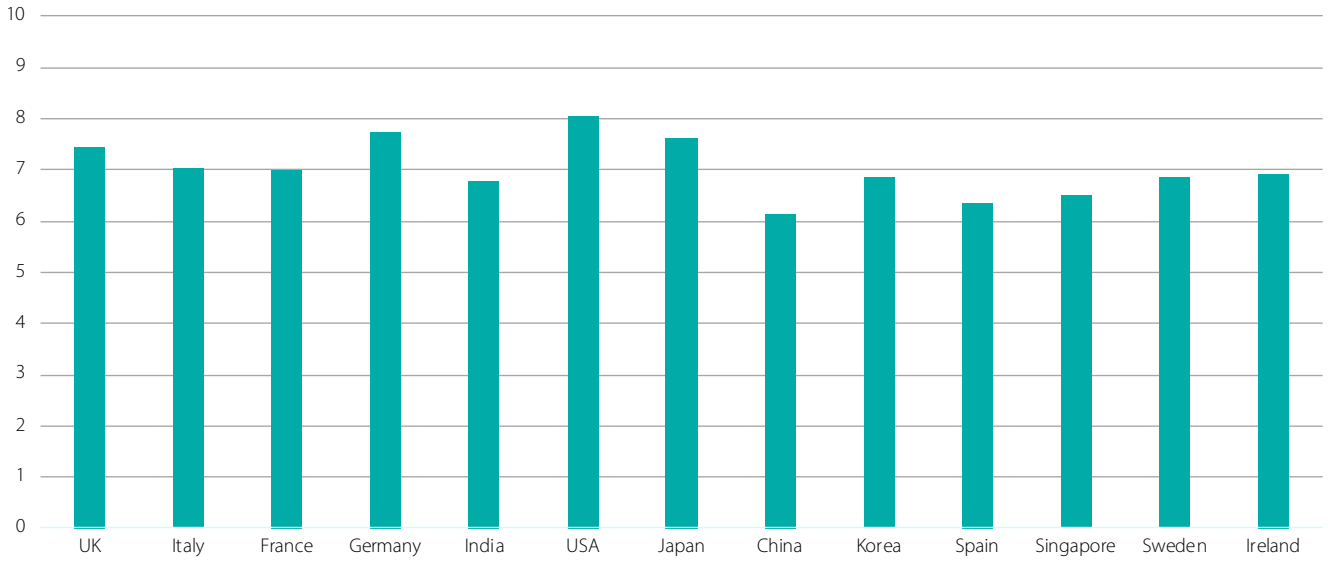


Knowledge of Biologics Professionals

For the last four years, the United States has been far and away the global leader in biologics and it retains this position for 'knowledge of biologics professionals', despite a score decrease of 3.78% (8.03). They were once again closely followed by Germany (7.73) and Japan (7.63), which concludes the top-tier markets. An exclusively European tier-two market includes the UK (7.44), Italy (7.02), France (7.00) and Ireland (6.90). Italy observed the biggest score increase, rising up four places from 9th to 5th. The industry's other key movers are India (6.78) and China (6.16) with score increases of 7.30% and 6.50%, respectively. India has a very well-established biosimilars market and currently has around 100 approved domestic biosimilars – the highest of any country in the world[iv]. This has laid down the foundations for continued investment in knowledge and scientific expertise in India's biologics space, of which the overall Indian biologics market was estimated to be valued at $386bn at the end of 2019[iii].

Three of our report contributors, Vicky Qia, Leo Yang and Eric Langer all of BioPlan Associates, provide some context to China's score increase, with returning bio professionals fuelling dramatic rises in manufacturing. *"The Chinese biologics market is forecast to quadruple in value to 120bn RMB by 2025, by which time the country will also expect as many as five domestic CDMOs to be classified as 'tier-one' contract providers (i.e. those with FDA and EU approvals) – up from just one at present."*

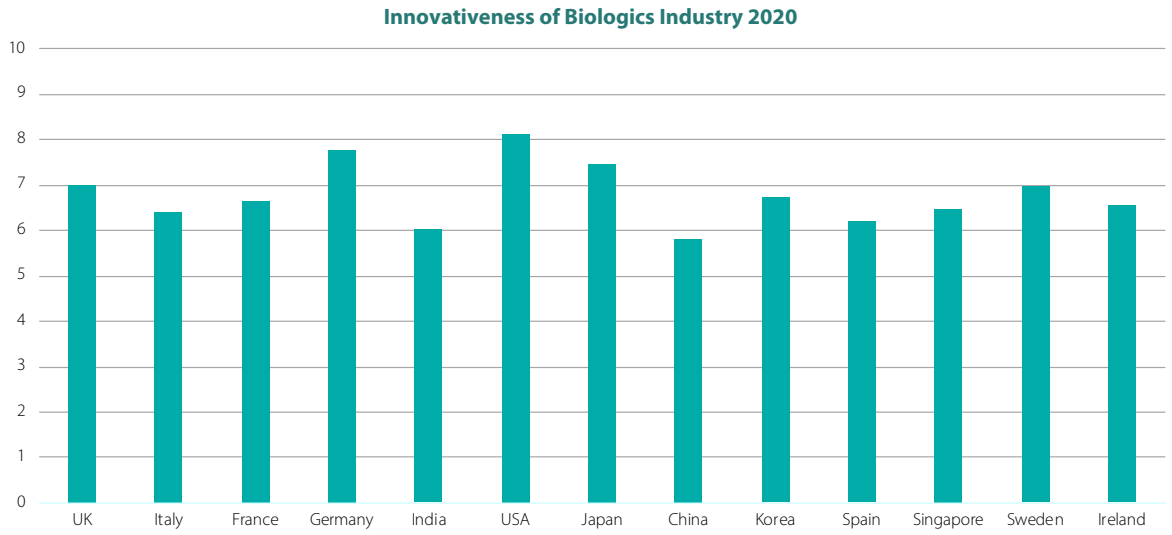
Knowledge of Biologics Professionals 2020



Innovativeness of Biologics Industries

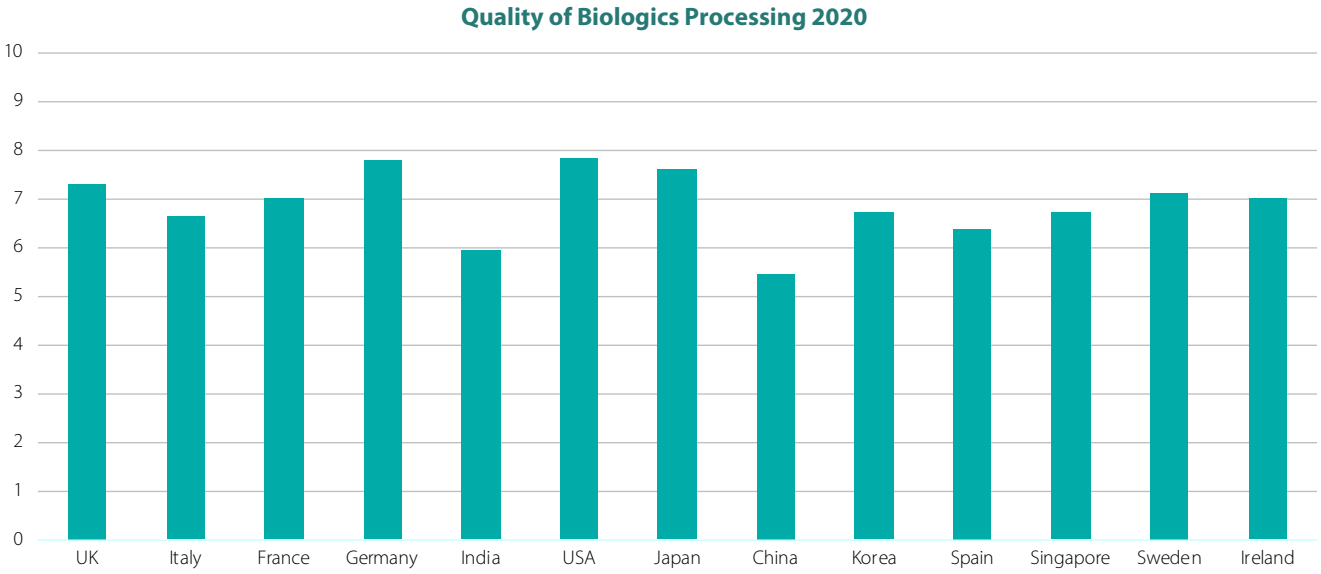
Yet again, the US (8.12), Germany (7.76) and Japan (7.48) rank in the top three; this time in the 'Innovativeness of Biologics Industry' category. What should also be highlighted are the gains made from the UK (7.00) and Korea (6.71) – the former moving up from 6th to 4th with a 2.50% increase in score, and the latter soaring from 9th to 6th thanks to a 4.45% increase in score.

Of course, one of most high-profile biologics innovations today is the University of Oxford's COVID-19 vaccine, ChAdOx1 nCoV-19. AstraZeneca, partnering Oxford, has just began enrolment for phase III trials in the US[v], and there are optimistic aims to have a commercially approved COVID-19 vaccine before the end of the calendar year[vi]. This vaccine, alongside Moderna's mRNA technology, is widely seen as the most promising to counter COVID-19 and is contributing considerable profile on the UK's biologic innovation centres. Italy (6.42) again received the biggest score increase, with a massive 13.19% gain lifting them from 13th to 10th, leapfrogging Spain (6.21), India (6.02) and China (5.82).



Quality of Biologics Processing

The most significant move in the rankings sees the UK (7.30) overtake Sweden (7.13) in 4th place thanks to a 3.51% increase in score from 2019, ranking the UK second in Europe behind only Germany (7.79). Korea (6.72) also deserves commendation for another respectable 2.37% score increase – the second biggest increase in the category only behind the UK – which sees them displace Singapore (6.71) and Italy (6.65) and move up to 8th. The country's continued year-on-year improvement may be a result of the rapidly growing status of Samsung Biologics and Celltrion as CDMO and biosimilar heavyweights.

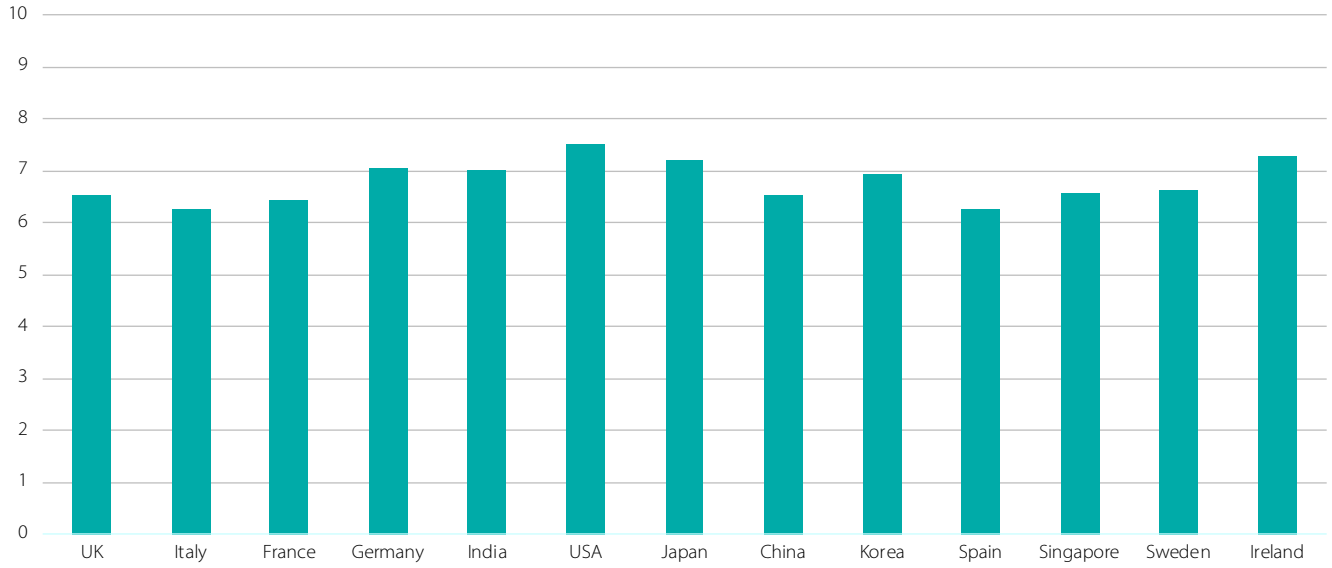


Growth Potential of Biologics Manufacturing Industry

The U.S. (7.53), thanks to its leading bio innovation hubs in Boston, San Francisco and San Diego, ranked first for growth potential in their biologics manufacturing industry, whilst Ireland (7.27) consolidated itself in 2nd, despite both markets suffering from minor score percentage decreases from the previous year. Ireland has become a major biologics manufacturing hub with WuXi Biologics having invested heavily in both biologics manufacturing and vaccine production sites[vii].

The 2020 table, however, sees Germany (7.03) drop out of the top 3 due to a substantial score decrease of 5.62%, which also coincides with their score decrease in the growth potential in their pharmaceutical market. Capitalising on score decreases seen in the middle-tier markets, Japan (7.21) has jumped from 8th to 3rd, with only a small score percentage increase of 2.46% from 2019. Italy (6.27) and Spain (6.26), both with large score percentage decreases of around 12%, fall into 12th and 13th place respectively to form the bottom-tier.

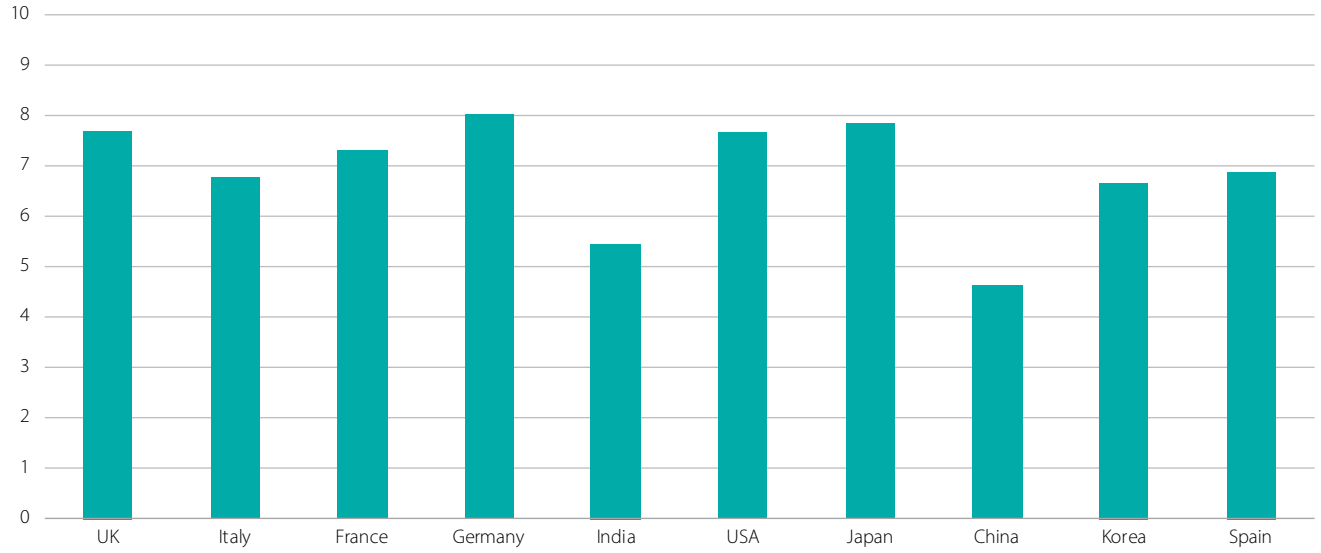
Growth Potential of Biologics Market 2020



Transparency Index

This year's survey sees the addition of the 'Transparency Index' category. Respondents ranked each market out of 10 based on the degree of corruption, business transparency and regulatory adherence, with 1 being the most corrupt and least regulated, and 10 being the least corrupt and most regulated. There is a clear trend of the traditional Western markets being ranked the highest, with the high-growth Asian markets significantly lower. The top three markets consist of Germany (8.02), Japan (7.85) and the UK (7.72), which are closely followed by the US (7.66) and France (7.30). India (5.45) and China (4.62) rank in at 9th and 10th to form the bottom-tier.

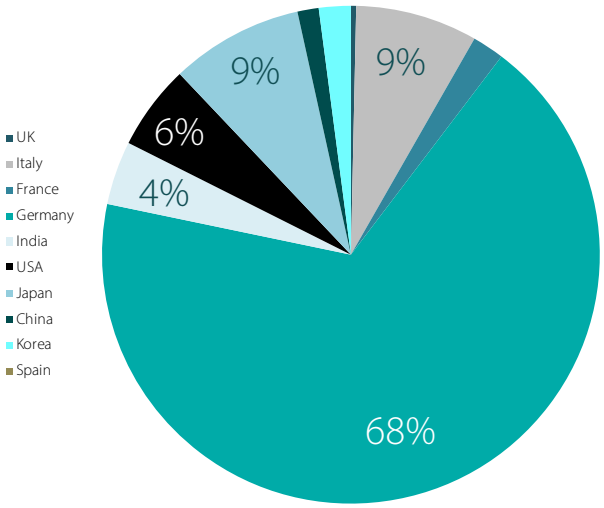
Transparency Index 2020



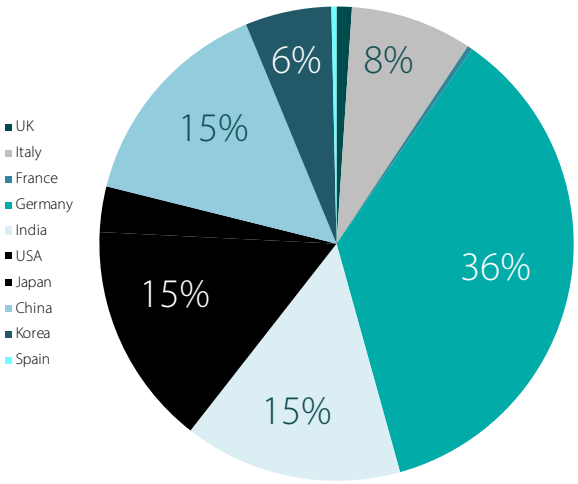
Quality and innovativeness of pharma machinery

Machinery is a crucial component of the pharma industry. Development of newer and more efficient machinery is helping to reduce manufacturing costs of medicines. Germany has again secured the vast bulk of the vote for quality of pharmaceutical machinery in this year's survey, taking an incredible 68% of the respondents' votes. Japan and Italy rank in 2nd and 3rd respectively – both with roughly 8% of the votes – these are followed closely by the US (5.5%) and India (4%). It doesn't come as a surprise that our respondents also voted for Germany as the country displaying the most innovation in the machinery space, where they take 36% of the votes. Interestingly India, the US and China each took 15% of respondents' votes, and were closely followed by Italy (8%) and Korea (6%).

Nation that produces the highest quality machinery 2020



Most innovative nation for pharma machinery 2020

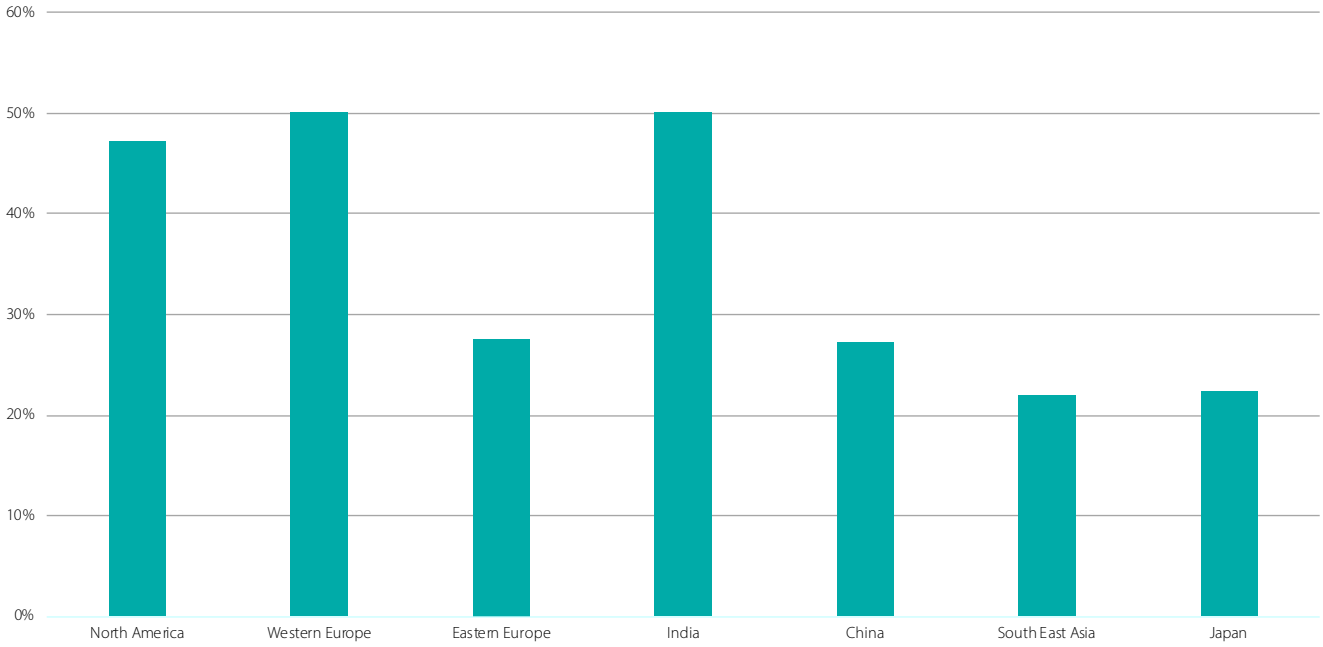


How COVID-19 may impact the global supply chain

The global supply chain in such a fragmented and internationalised industry as pharma, with complex ingredients and high levels of regulatory scrutiny, is always a key focus. Yet in 2020, this is likely to be the largest single contingency the industry needs to evaluate due to the long-term implications of COVID-19. Flexibility in supply from ingredients to finished dosages is now being considered, alongside how reliant we are on certain geographies for critical parts of the supply chain. So undoubtably, there will be some redistribution of resources and partners to further secure networks. We asked our respondents which major pharma regions would or could benefit from such supply chain de-risking with regards to both ingredients manufacturers and CDMOs. India topped the charts for ingredients suppliers, with 68% of respondents believing that they would benefit from changes to the global supply chain. 42% of respondents also believe that Western Europe would benefit, most likely as European markets will increasingly look to domestic sources of ingredients as a safe measure. What is interesting, however, is that 42% of respondents also believe China will benefit from supply chain changes – suggesting that the country's sizable role as the globe's ingredients production centre is to remain. Our annual reports experts believe that economies of scale and how margins in high volume products mean that many ingredients or starting materials can be viably made in China. For example, China accounts for 70% of India's API imports[viii], as well as 18% of the US's API imports[ix].

However, in the contract services space, where manufacturing may deliver far higher margins – particularly for innovative drugs or complex generics – there is a more notable reordering. Here, only 27% of respondents believe China's CDMO industry will stand to benefit from changes to the supply chain – this is significantly lower than India and, significantly, Western Europe, both of which scored 50%, and who were closely followed by North America (47%). This indicates that North America and Western Europe will certainly look to bring a substantial amount of contract manufacturing back home, led by innovative formulations, contract services and final dosage forms of commercial supply. In the short- to medium-term, our experts have previously suggested that discovery chemistry services and early stage clinical trial supply may still be outsourced to Asia, but increasingly, hybrid approaches will be sought. This is likely to be particularly true for final dosages supply, packaging and commercial productions – with the USA and EU CDMOs the biggest potential winners. For API and clinical stage supply, Asian hubs are likely to continue to see growth in part thanks to more expedited trial timelines (i.e. is there enough development resources – scientists – at western CDMOs to meet demand).

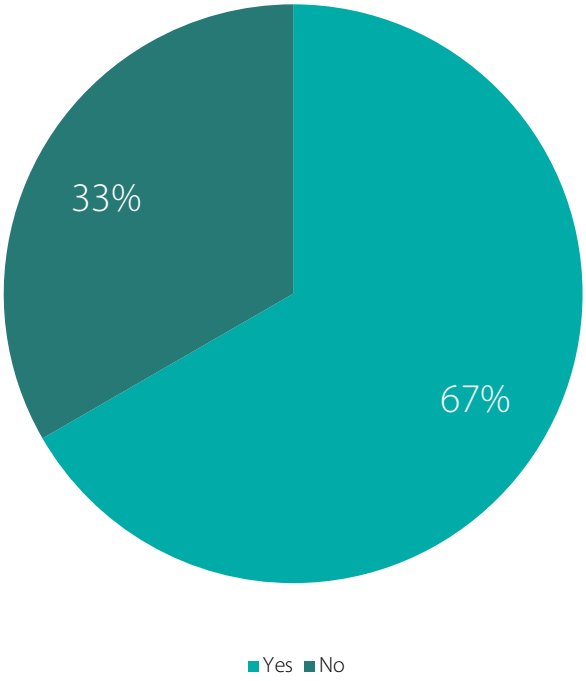
Which countries CDMOs will benefit most from COVID-19-driven supply chain changes



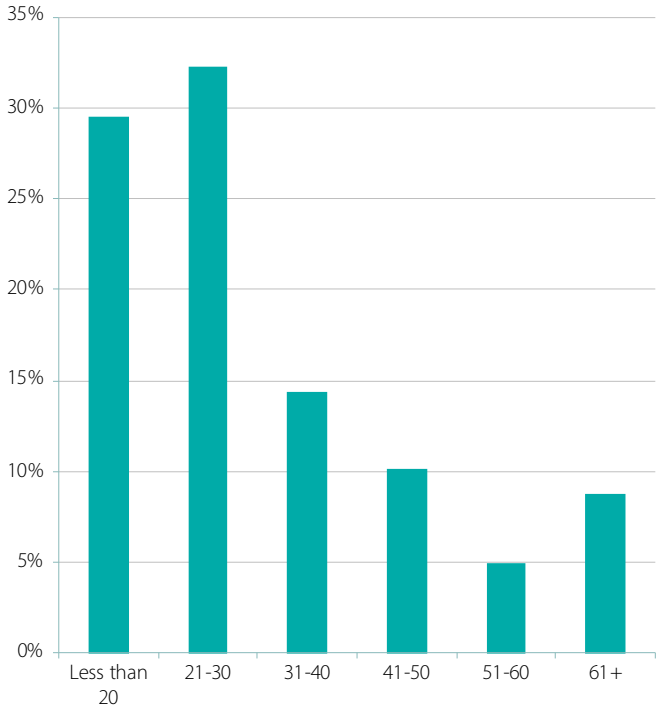
What are the longer-term implications for pharma manufacturing of COVID-19? (Tick as many as appropriate)

Question	Percentage that agree
1 - More of the supply chain will be repatriated to domestic sources	56.27%
2 - R&D will be slowed as chemistry services move away from China	36.27%
3 - API sourcing will remain internationalised, but final dosage manufacturing will towards domestic providers	43.73%
4 - There will be short-term disruption, but pharma manufacturing will continue with a significantly international supply chain	49.15%
5 - European and US-based CDMOs to be big beneficiaries	35.25%
6 - Big pharma will deleverage its risk exposure in Asia	32.20%
7- Biotechs and start-ups may come under VC pressure for localised development (national level) to reduce risk	30.51%
8 - None of the above - too early to say for sure	6.10%
9 - Other	3.05%

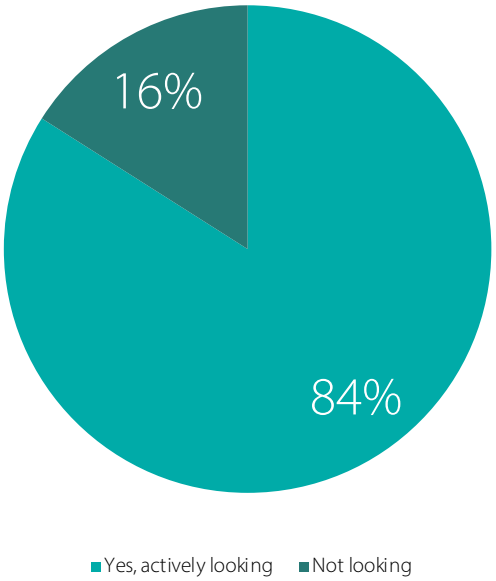
Is the government in your country attempting to bring manufacturing home?



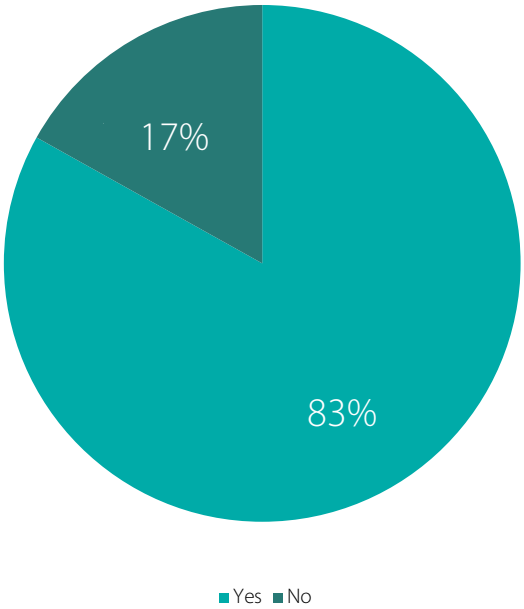
How many FDA drugs do you think will get approved in the calendar year 2021?



As a result of the pandemic are you searching for new supply chain partners (to increase contingencies and robustness)?



Do you think the pandemic has caused an increased level of innovation and agility in the industry?



CPhI insights

Part 1.

Global biologics and Chinese CDMOs

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PANEL MEMBER
Eric Langer, President and Managing Partner, BioPlan Associates.

Global trends and growth opportunities in the biopharmaceutical product development and manufacturing

Introduction

The biopharmaceutical industry and its bioprocessing sector are healthy and continue to grow in size/revenue, breadth, importance, and diversity. Worldwide sales of biopharmaceuticals are now over $300 billion, growing globally at about 12% annually. This growth has been relatively consistent over the past 15+ years, which is why the segment is attractive to investors.

In this year's 500+ page *Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production*, from BioPlan Associates, we include surveys of 130 bioprocessing decision-makers, both developers and contract manufacturing organizations (CMOs), in 33 countries; and 150 industry supplier/vendor respondents.

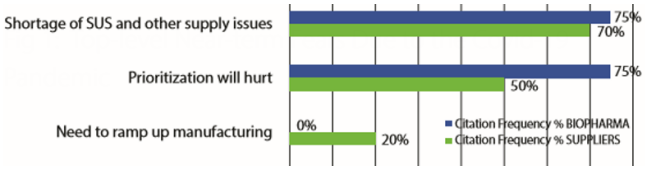
Just a few of the key areas where we see bioprocessing trends affecting growth:

- **Hiring in Bioprocessing** will continue to create significant bottlenecks. Finding qualified staff at global facilities continues to be a problem.
- **Biological products**, often each with smaller markets, including more orphan and even personalized products
- **Bioprocessing facilities** worldwide, especially in major markets and in China, where 20% annual expansion is the norm (See: http://top1000bio.com/top100china/)
- **Cellular and gene therapies** facilities and products, including now commercial manufacturing
- **Use of single-use systems,** including fewer new commercial scale stainless steel-based facilities
- Growth of GMP facilities in developing countries (see www.top1000bio.com)
- **Biosimilars, biobetters and biogenerics**, are capturing growing market shares in bioprocessing
- **Adoption of continuous processing**, including upstream perfusion and continuous chromatography increasing adoption for commercial manufacturing in coming years

Industry Adapting to Address the Pandemic:

In a recent White Paper covering Covid impacts[2] we found the bioprocessing sector and biopharmaceutical industry have effectively adapted to the ongoing pandemic, including making needed staff and operational

changes and paying greater attention to assuring robust supply chains. Key activities have largely continued as before, including R&D and manufacturing often being increased to address the pandemic. The most commonly cited fears are shown in the following figure.



Source: White Paper on Covid Impact on Biopharmaceutical Industry, June 2020, BioPlan Associates, Inc. Rockville, MD www.bioplanassociates.com

The top fears noted were "Shortage of SUS (single use system) and other supply issues," concern about inability to obtain needed single-use supplies in a timely manner, and "Prioritization will hurt." Prioritization concern refers to the new fact-of-life that nearly all suppliers and many developers are now prioritizing their orders and activities, pushing pandemic/biodefense-related activities to the front of the line. Prioritization combined with expected worsening of ongoing shortages, including high-purity polymers, will result in many facilities having longer wait times for suppliers to fulfil orders, particularly for single-use supplies.

Long-term Biopharma Industry Changes Due to the Pandemic:

Big changes will come in the longer term as the industry does its part in resolving the Covid-19 pandemic. The major response will be an expansion of biopharmaceutical R&D and manufacturing activities worldwide – whish is displacing other bioprocessing work to alternative facilities. For example, smaller CMOs not involved in pandemic-related work are seeing increased future demand as pandemic/biodefense projects are undertaken by larger CMOs.

A few of the factors on the list of major long-term effects of the Covid-19 pandemic on the bioprocessing sector include:

- **"More outsourcing,"** with 70% of developer interviewees citing this
- **"Changes in supply chains,"** with 60% of developer interviewees citing this, including more concerns about and involvement with suppliers, and securing '2nd sources
- **"More regionalization,"** cited by 50% of developer and 45% of supplier interviewees. This refers to more manufacturing facilities, both developers' and suppliers', being located in more countries, such as a plant in U.S. supplying the U.S. market while plants in China and India handle the Chinese and Indian markets.
- **"SUS supply crunch,"** cited by 50% of developers and 35% of suppliers, including worsening of current single-use equipment shortages

Productivity continues to increase:
Bioprocessing productivity, particularly in terms of upstream titers and downstream yields (to a much lesser extent), continue to incrementally increase. The Figure below shows year-to-year changes in survey respondents reporting the average mAb titers at larger scales at their facility. Keep in mind that titers back in the later 1980s-early 1990s were still usually only in the few 100s of milligrams (mg)/L, less than 10% of current average titers.

Related survey findings this year include:
Average titer for new commercial-scale monoclonal antibody (mAb) upstream bioprocessing this year is 3.53 g/L: and 3.96 g/L for new clinical-scale mAb upstream bioprocessing.

"Improving production titer." Was cited by 56.5% as a key "Factors having the greatest impact on reducing your cost of goods for biotherapeutic products,"

Follow-ons Bring More Products and Players:
Biosimilars (and biogenerics in lesser- and non-regulated international markets) are resulting in many new products and players entering the biopharmaceutical industry, including new facilities being constructed. Our Biosimilars/ Biobetters Pipeline Directory (www.biosimilarspipeline.com) [3] now reports 1,099 biosimilars (including biogenerics) in development or marketed worldwide, with 588 now in clinical trials or marketed in 1 or more countries. There are also >560 biobetters in development or marketed

worldwide, with 296 in clinical trials or marketed. Over 800 companies worldwide are involved in follow-on products.

Capacity Crunch" for Cellular and Gene Therapies:
The distribution of capacity among survey respondents reporting that their facilities perform cellular/gene therapy bioprocessing is insufficient. BioPlan has projected a worsening cellular and gene therapies "capacity crunch" similar to the crunch in mainstream bioprocessing that was feared but avoided in the early 2000s. This shortfall will increase in 5 years.

Continuous Bioprocessing Optimism and Skepticism:
When asked in our annual report and survey what bioprocessing innovations are most needed, respondents this year continued to most frequently cite aspects of continuous bioprocessing. "Upstream Continuous processing/perfusion" was cited by 44.2%, and "Downstream: Continuous purification/chromatography" systems were cited by 40.0% as expected to be evaluated/tested by their facility within the next year. It can be assumed that a majority of bioprocessing facilities will evaluate at least some part of continuous processing this year.

But there is also considerable skepticism about continuous bioprocessing, with over 60% citing it will "require many years development to become truly continuous." And in response to rating concerns regarding perfusion, fully 71.8% cited "Process operational complexity" as their top concern, reflecting that perfusion adds considerable mechanical, technical and regulatory complexities to bioprocessing.

Single-use Systems Use Still Growing:
Single-use systems (SUS) continue to make advances into biopharmaceutical manufacturing, and now dominate at pre-commercial scales (e.g., clinical, and preclinical). Again, this year well over 80% of survey respondents reported considerable current use of single-use bioprocessing equipment. Fully 84.3.% now report use of single-use bioreactors. Use of these generally indicates much wider applications of single-use equipment as part of the same processing lines. BioPlan estimates that ≥85% of pre-commercial (R&D and clinical) product manufacturing now involves very substantial single-use systems-based manufacturing.

Hiring Challenges Creating Significant Bottlenecks

As the industry expands, hiring will present major problems, especially where growth is involved, such as in cell and gene therapy. We asked respondents which job positions are currently difficult to fill. Of the 25 areas covered, Downstream Process development staff was again cited as the most difficult to fill at 39.5% of respondents, (slightly down from 45.1% in 2019). Followed by "Process development staff, upstream" and "Process engineers." Reasons for these shifts, the apparent lessening of hiring problems in some areas, may be that companies are being more successful in streamlining their processes, making them more automated, and less expensive. This can reduce pressure on already minimized staff.

Source: 17th Annual Report and Survey of Biopharmaceutical Manufacturing, April 2020, BioPlan Associates, Inc, www.bioplanassociates.com/17th

The steady growth in bioprocessing will be suppressed by demand for staff. The need for trained bioprocessing expertise has remained stubbornly in place, year after year. And it will likely worsen as many of the most experienced 'baby boomer' staff retire, and pandemic vaccine and therapeutics bioprocessing, as well as growth in developing regions such as China, add to demand.

Biologics CDMOs in China
Growth of the domestic Chinese Mab pipeline, regulatory reforms and new investment opportunities are changing the region's landscape for Biologics CDMOs. Both multinational and domestic Chinese biopharma companies are assessing the new business opportunities in China's booming contract bio-manufacturing segment. New biologics CDMOs are setting up as investors' interest in the sector rise with recent regulatory reforms and growing market demand (See http://bioplanassociates.com/china-top-60/)1. BioPlan's research for its Top 100 Biopharmaceutical Facilities in China Directory now shows well over 100 biopharma companies in China, both new

and established, that have started mAb development projects[4] .

Many of these product innovators have limited experience in actually manufacturing a biologic, so, as with Western innovators, they are increasingly turning toward CDMOs. The Chinese government also provides subsidy programs for CDMO companies. Boehringer Ingelheim, the first multinational CDMO to test water in China in 2016, announced plans to expand its capacity due to growth in demand in 2019. Lonza, the global giant in the CDMO industry, made a strategic move to enter China at the end of 2018. Korea-based Celltrion also announced plans to build bioproduction facility in Wuhan in 2019. Dozens of domestic companies, existing CRO companies as well as brand new start-ups, kicked off their biologics CDMO business as more mAb therapeutics entering the clinical pipeline and reaching commercial scale.

Since the successful launch of Langmu in 2013, Chinese developers have submitted IND applications for 109 Class I biological therapeutics, so the need for CMOs is likely to continue. Because biopharma is a global segment, the trends and bottlenecks experienced by Western facilities, if not already present in China, will impact that segment in the near future, as well.

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CPhI Festival of Pharma Questions and Answers

2025 outlook

CPhI Question: In which markets will the capacity shortfall for cell and gene therapies be felt most (US, Europe, Asia)?

"The largest capacity shortfalls will occur where the cell and gene therapy pipeline is furthest advanced. This capacity crunch will be especially acute in North America, and parts of Europe."

CPhI Question: Do we therefore anticipate many more CDMOs building cell and gene therapy arms in next two years or will this come much later (too late)?

"CMOs with dedicated cell or gene therapy expertise in these regions are already expanding. The current acquisitions of technologies and facilities focused on these novel platforms, by large CMOs, as well as their high valuations, are an indication of the interest and expectation in this area. Physical capacity may not be the bottleneck, however, as the need for more production of these highly technical and specialized platforms expand, the problem will be finding, training and hiring staff with the required expertise. Further, for some facilities in these emerging areas, the equipment required for expansion, and up-scaling may not exist, nor are the regulatory authorities fully aligned with issues around patient treatments, etc."

CPhI Question: Looking ahead we might only start to realise the potential of continuous bioprocessing by 2025 onwards (as development is years away from mainstream use)?

"Continuous bioprocessing has been in use for over 30 years, so it is not new. And according to our 17th Annual Report, 39% of global facilities are planning on actively evaluating continuous bioprocessing upstream unit operations in 2020 (37% for downstream operations). This is up from 30% and 24% respectively, in 2017. So evaluations continue. However, large-scale, mainstream installations are not likely a near-term outcome."

CPhI Question: With 85% of pre-commercial manufacturing now undertaken using single use systems what does that imply for commercial drugs coming to market in the next 2-years? (e.g. quicker completion on final phases of development?)

By when will virtually all new biologics be developed with single use systems?

"The 85% of facilities, according to our 17th Annual Report, (www.bioplanassociates.com/17th) that are using substantial SUS technologies for their clinical and smaller scale production are the 'pipeline' for commercial-scale production using SUS. However, still, many biologics and scales simply are not effectively produced using disposable devices. The economics or scale justify using stainless fixed equipment, for example. Further, because preclinical and clinical pipeline products require flexible manufacturing, SUS lends itself to these scales. Many of which will fail as they progress through the pipeline. So, yes, more commercial-scale biologics are going to be made in SUS platforms, or hybrid systems, etc. over the next 2+ years, but stainless platforms are, and will remain critical to bioprocessing."

CPhI Question: will China's domestic MAb pipeline (that requires experienced CDMOs) spur not just new domestic CDMOs but many further international market entrants (like BI etc) over the next 2-3 years?

"Our recent study, Growth of Biopharmaceutical Contract Manufacturing in China defines the opportunities and challenges in China's rapidly emerging markets. Many of the 160+ domestic, innovative facilities in China do not have the capacity or staff to produce internally. So this is a key driver toward CDMOs' expansions. However, the attractiveness of the China domestic healthcare market, with its expanding insurance systems, increasing middle class, and sheer size makes it an important market to all global CDMOs. Whether the existing CMO capacity will be sufficient for the next 2-3 years is a key question."

CPhI Question: What effect could more regionalisation, desire for 2nd sources and increased outsourcing mean by 2025 for manufacturing (i.e. will it mean more primary CDMOs in main customers markets (i.e. 1st US CDMO for NA, 2nd European for Europe, China for Asia etc)?... will this give advantages to Asian CDMOs that might already have approvals for USA, China and Europe (or others with multiple market approvals)?

"From our Annual Report, outsourcing has been growing significantly over the past 11 years. For example, the percentage of facilities outsourcing at least some of their microbial bioproduction increased from 40% in 2009, to 64% in 2020. For mammalian systems, those outsourcing up to half of their bioproduction rose from 29% in 2009 to 42% in 2020. And this trend is only continuing to grow. As outsourcing becomes a norm, considering a 2nd source, or establishing facilities for bioproduction in regions like India or China for local manufacturing or for second source production becomes a logical strategy."


PANEL MEMBERS
Vicky Xia, Project Director **and Leo Cai Yang,** Project Manager – BioPlan Associates, Inc.

Growth of Domestic Mab Pipeline, Regulatory Reform and New Investment is changing the landscape of Biologics CDMOs in China

Introduction

Both multinational and domestic biopharma companies are out to grab business opportunities in China's booming contract bio-manufacturing industry. New biologics CDMOs are setting up as investors' interest in the sector rise with recent regulatory reforms and growing market demand (Table 1)[1]. BioPlan's research for its Top 100 Biopharmaceutical Facilities in China Directory now shows (http://www.top1000bio.com/top60china) there are well over 100 biopharma companies in China, both new and established, that have started mAb development projects[2].

Table 1 Investment into the China Biologics CMOs in Recent Years[1]

CDMO	Amount of Funds Raised	Financing Route	Time
Asymchem	Over USD $100 million		2018
CMab	Over USD $10 million	Series A Financing	Jan and April, 2018
Genescript Biologics Center			July, 2019
HJB	Over USD $100 million	Series B Financing	June 2018
JOINN Biologics	Over USD $50 million	Series A Financing	Dec 2019
Mabplex	Over USD $50 million	Series A Financing	Jan 2019
Mab-venture	Under USD $10 million	Series A Financing	March, 2017
Oobio	NA	New OTC Market	Dec, 2016
Opm biosciences	Over USD $10 million	Series A Financing	April, 2018
ShellBiotech	Under USD $10 million	Angel investment	Jan 2019
TobioPharm	Over USD $10 million	Series A Financing	Jan 2019
ToT Pharma	Over USD $100 million	Series B Financing	August 2018
WuXi Biologics	Over USD $1 billion	Going Public	June 2017
Yaohai Bio	Over USD $50 million	Series A Financing	March, 2019

Many of these product innovators have limited experience in actually manufacturing a biologic, so, as with Western innovators, they are increasingly turning toward CDMOs. Chinese government also provides subsidy programs for CDMO companies1. With returnee scientists, VC/PE investment as well as government support, the biologics CDMO industry in China is going through a phase of quick and strong growth.

Boehringer Ingelheim, the first multinational CDMO to test water in China in 2016, announced plans to expand its capacity due to growth in demand in 2019. Lonza, the global giant in the CDMO industry, made a strategic move to enter China at the end of 2018. Korea-based Celltrion also announced plans to build bioproduction facility in Wuhan in 2019. Dozens of domestic companies, existing CRO companies as well as brand new start-ups, kicked off their biologics CDMO business as more mAb therapeutics entering the clinical pipeline and reaching commercial scale.

Since the successful launch of Langmu in 2013, Chinese developers have submitted IND applications for 109 Class I biological therapeutics, including 61 therapeutic mAb, 9 ADC, 4 bi-specific antibody and 1 PD-L1-Fc, as well as 26 recombinant proteins, 13 fusion proteins and a number of gene therapy products, therapeutic vaccines and oncolytic viruses2.

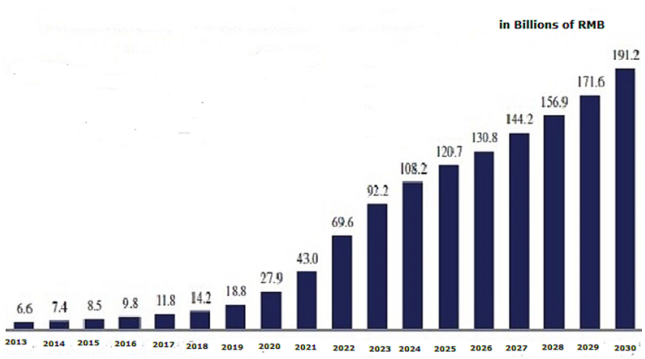
In Table 2 we can see the launch of mAbs onto China market has clearly picked up pace in recent years, with 2019 alone witnessing 7 mAb therapeutics from domestic developers getting NMPA's approval to be on the market, a record high number for a country which approved its first made-in-China mAb therapeutics beginning in 2005. Such a trend is likely to continue, as multiple industry insiders project that China may be home to 5-10 new mAb annually within the next 5-10 years, creating greater demand for the biologics CDMO industry.

Table 2 mAbs from Domestic Developers Launched in China1

Company Name	Project Name	Time of Launch
Bio-Thera Solutions	Adamulimab biosimilar	Launched in 2019
Shanghai Henlius Biotech	Herceptin (trastuzumab) biosimilar (HLX-02)	Launched in 2019
Hisun Pharma	Humira (adalimumab) biosimilar	Launched in 2019
Innovent Biologics	IBI-308, PD-1 mAb	Launched in 2019
BeiGene	BGB, tislelizumab, a PD-1 mAb	Launched on Dec 2019
Qilu Pharma	Avastin (bevacizumab) biosimilar (Qilu)	Launched on Dec 2019
Shanghai Junshi Biosciences	JS-001, a PD-1 mAb	Launched in 2019
Hisun Pharma	Enbrel (etanercept) biosimilar	Launched in 2015
Kanghong Pharma	Langmu (conbercept), a Lucentis biobetter	Launched in 2014
Celgen Shanghai	Enbrel (etanercept) biosimilar (Qiangke)	Launched in 2011
BioTech Pharma Beijing	Taixinsheng (cancer mAb)	Launched in 2009
3S Guojian	Enbrel (etanercept) biosimilar (Yisaipu)	Launched in 2005

With new projects entering clinical stage and clinical projects maturing, the market size of mAb therapeutics is also expected to grow significantly. From Figure 1 we can see that though domestic mAb industry starts from a low baseline, its growth has been quite robust in the past decade, and is poised to continue this trend as more and more mAb therapeutics, once regarded as luxury drugs which have to be paid out of pockets of consumers, start to enter the National Reimbursement Drug List.

Fig 1 Market Size of mAb Therapeutics in China (2013-2030)1



CAGR between 2013-2017: 15.6%
CAGR between 2017-2022: 42.6%
CAGR between 2022-2030: 13.5%.

As most early-stage biologics developers in China lack manufacturing facilities, the need for contract manufacturing services would be certainly on the rise. Total capacity in China has grown by over 10%, based on our analysis of facilities under active construction. BioPlan's Top 100 Biopharmaceutical Manufacturers in China (http://(http://www.top1000bio.com/top60china) directory shows continued capacity expansions and upgrades at a majority of biomanufacturer facilities through 20192. But growth of the biologics outsourcing services market is even more significant, with projected CAGR over 30% for the period 2016-20211.

Regulatory reforms are crucial for the growth of China's biologics CDMO industry. With both global and domestic demand on the rise, Chinese regulatory authorities made the move to permit contract bio-manufacturing in China in 2016. That year, China started the pilot Market Authorization Holder (MAH) program, under which holders of a CFDA biologics approval number now have the option to either manufacture the drugs or use a CMO. The MAH breakthrough is a pilot running in 10 provinces and municipalities, and by the end of 2019, the updated Drug Administration Law removed regulatory hurdles for contract manufacturing of drugs in China (vaccines excluded). Both domestic developers and CDMOs hope there will be future reforms making outsourcing of bioprocessing an easier decision. At current stage, it is mandatory that drug substance and drug products be manufactured at the same place, which makes sub-contracting difficult. In 2020 with COVID-19 pandemic, some industry insiders also hope NMPA will make contract bioproduction of vaccines legal in China in a move to speed up innovative vaccine development amid increased public awareness of public health issues[3].

Industry Dominated by a Leader, But Others are Catching Up

The industry is led by returnee scientists, so it is more Westernized then other manufacturing sectors in China. We can see that the majority of China-based biologics CDMOs are founded by returnee scientists with Western industry experiences, including the industry leader, WuXi Biologics, the first China-based biologics CDMO, AutekBio, Chime Biologics, MabPlex, etc. The flow of returnee scientists builds the industry and significantly increased the know-how of bioprocessing in China. The industry is currently dominated by one leader, WuXi Biologics, but other companies are growing quickly, as new investment comes into this sector. WuXi's domination is clear in revenue, capacity as well as qualification/certification. As far as revenue is concerned, in 2019 WuXi Biologics realized 35.3% of its total revenue USD 0.57 billion from China, which is ~USD 0.2 billion and would translate to ~35% of the total biopharma outsourcing service market in China1.

We can categorize China-based CDMO into following groups. However, we note that, in this emerging, rapidly changing environment, these tier analyses can also shift quickly.

Industry leader and MNC CDMO: WuXi Biologics, MNC CDMO including Boehringer-Ingelheim Shanghai, Lonza, Merck Millipore, Celltrion. These companies are considered as having the quality comparable to international standards, or will have when they are in full operation (Lonza and Celltrion just started construction of their facility in China). When capacity expansion is completed, WuXi will have 280,000 in capacity4, and the other companies will also have at least thousands of capacities.

Second Tier Domestic CDMO: Chime Biologics, CMab, MabPlex, One Thousand Aks, Transcenta, 3SBio, etc. These companies have already established their brand name in China and have thousands or even tens of thousands of capacity.

Third tier CDMO: Shell Biopharma, Canton Biologics, Chempartner, Hualan Biologics, ToT Pharma, Genescript, JOINN Biologics, etc. These companies are relatively young or started biologics CDMO operation recently and they are working to build their reputation and track record in the industry. Chempartner started CDMO division

Smaller CDOs: Autekbio, OPM, T-Mab, Quacell, etc. These companies are smaller and do not have commercial bioprocess capacity currently, so they are better considered as CDO. Some of them have government support; Affiliated

with an industrial park they work as a CRO/CDO platform for biotech companies in the industrial parks, including T-Mab Quacell, etc.

Significant pricing structures exist in this industry in China. As far as price and perceived quality is concerned, WuXi Biologics and Boehringer-Ingelheim Shanghai form the first-tier companies. The second-tier group usually charge significantly less than what WuXi charges, and the third-tier companies charge less than that1. Again, these pricing structures are also likely to change as CMOs in China align more closely with GMP standards; in the future, as in Western markets, price differences for services will narrow as the focus on quality standards, service delivery and expertise become more critical decision factors.

WuXi is projected to have 280,000 L capacity by 2022, which would make it by far the biggest biologics CDMO in China. Combined with the fact that it is the only FDA/EMA certified biologics CDMO in China, its No.1 status would not be replaced by competitors in the foreseeable future. However, we can see that other biologics CDMOs are also making progress, and multiple industry insiders have stated that though WuXi is expanding quickly, its total market share in China is gradually decreasing. With no immediate plan for FDA/EMA certification, 2nd or 3rd tier domestic CDMOs at present try to compete through price discounting, by integration of production of cell culture media, resin, etc. Perfusion technology is also being seen as a way to reduce production costs, though whether it will become a mainstream option remains unclear. Industry observers expect more competition in the sector, with the ones with real expertise and good track record becoming stronger.

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Project Director, BioPlan Associates has her MS in biology from University of Texas-Houston, MBA from University of Pittsburgh. She has experience in consulting, business development, as well as alliance management in China's bio-pharmaceutical industry. Her expertise includes developing research and analysis on multiple global market segments, and has managed a team of industry experts, and projects.

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CPhI Festival of Pharma Questions and Answers

2025 outlook

CPhI Question: How many approved MAbs in China by 2025 (if current trends continues 5-10 over year)… similarly, will we see 10+ approvals annually by 2025?

"We project that in the years leading to 2025, there will be around 10 approvals of mAb annually. The number may be less than 10 in 2020, but more than 10 close to 2025, as the pace of approval speed up."

CPhI Question: we expect the market size of MAbs to quadruple by 2025 (risking from 27.9bn to 120.7bn by 2025)… do we not anticipate any slowing in demand caused by COVID slowing global economies and by knock-on effect slowing growth in China overall (as a partially export driven economy – slowing medicine consumption growth)… what's driving such rapid growth (any obvious opportunities/threats to these headline figures)?

"COVID-19 will have negative impact; we also agree that China's economy will gradually cool down in the next few years. However, this would not necessarily translate to slower growth in mAb market. First China's mAb consumption starts from a relatively low baseline; Second the national drug reimbursement list (NRDL) is updating which starts to include more mAb drugs, which has clearly been a trend and will significantly increase the market demand of mAbs. Industry insiders have long complained that the NRDL includes too many old, safe but useless drugs, which is a waste of national healthcare insurance."

CPhI Question: will the mandatory manufacturing of drug substance and product slow China's development pipeline over the next 2-3years. Do we foresee regulatory changes to alleviate this pressure?

"No, this is mostly a barrier for the domestic CDMO industry, but not much impact on pipeline development. CDMOs and developers alike would love to see regulatory changes in this aspect, but up till now there is no news of such changes."

CPhI Question: When will the capacity crunch start to bite in China – with the pipeline growing much faster than facility growth of CDMOs (what will be the implication of this)

"Many developers are building in-house facilities. Many CDMOs say they are competing with developers' preference for an in-house facility. So we do not think there will be significant capacity crunch in China. Technical expertise in GMP grade bioprocessing and quality control may be more serious issues."

CPhI Question: If contract vaccine production is approved by NMPA this/next year how will that change the CDMO market (who will be the winners)

"If that is the case, the bigger CDMO such as WuXi Biologics will be the winners."

CPhI Question: Looking five years ahead (2025) how many CDMOs do we think will have moved up to tier one status with FDA/EMA approvals? (perhaps driven by China based innovators that want to tap into EU and USA in addition to domestic population)

"Maybe around 3-5"

CPhI Question: What do you foresee as the structure of the market in 2025 in terms of tiers of companies/ strategies: i.e. will the majority of this growth be served by meeting domestic innovator needs or will we see global contract providers see strong growth as well? (e.g. 65% of WuXi turnover is international)

"Growth will mostly be served by meeting the demands of domestic innovator. WuXi has significant global business, but the company also served global clients with global expansion. Commercial scale bioprocessing outsourced to China would be more mainstream in 2025 than it is now but still not a popular option by 2025."

CPhI Question: When/if will we start to see advanced therapy CDMOs in China – will this be the next step for companies like Lonza, WuXi Biologics and BI etc?

"There are already Chinese CDMOs working in this direction, such as Genescript. The current market size is not big; we project that only after cell therapy becomes more mainstream in US, the market size for cell therapy CDMOs will increase significantly."

CPhI insights

Part 2.

Digital adoption, patient centricity and global generic adoption by 2025

informa markets

PANEL MEMBER
Bikash Chatterjee, Chief Executive Officer, Pharmatech Associates

The Pharma Industry Becomes Patient Centric

Introduction

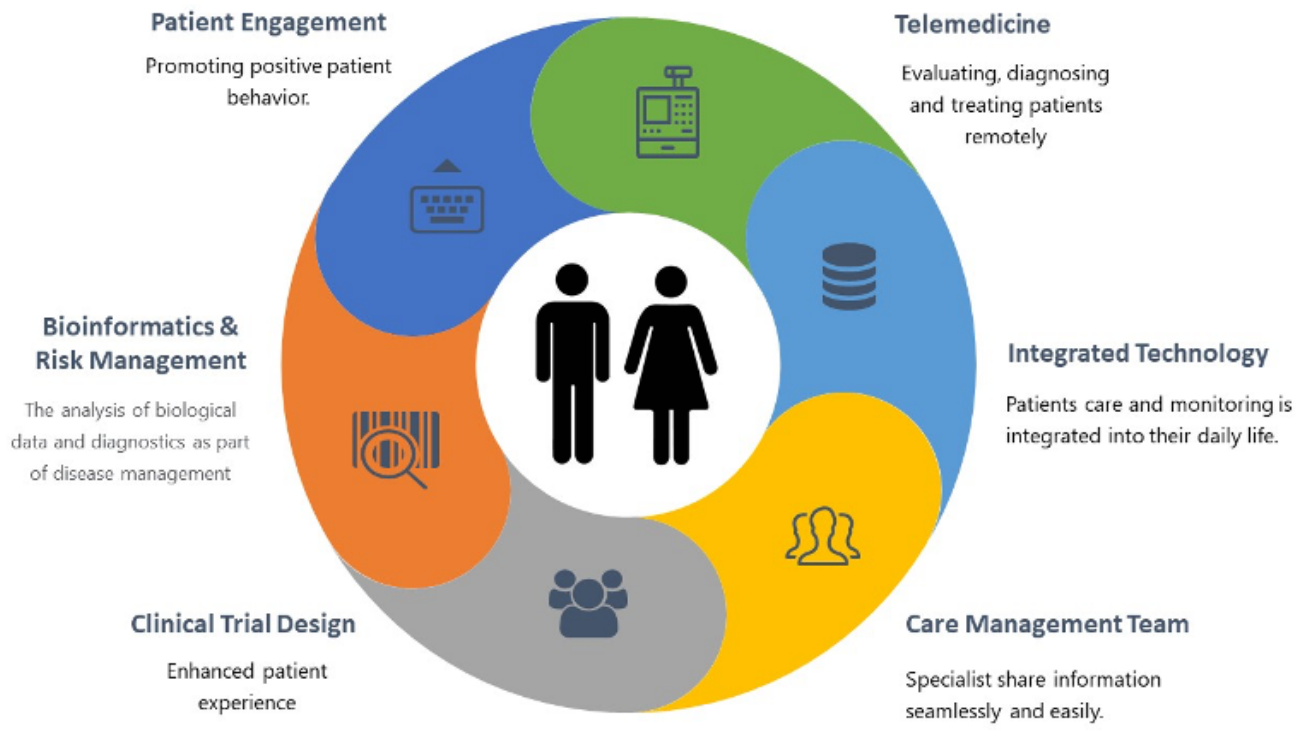
The healthcare market continues to grow, driven by rising populations, lifestyle changes and the socio-economic factors associated with a maturing emerging market, yet healthcare delivery models have not kept pace with evolving patient attitudes and expectations. Healthcare over the next decade will change radically, accelerated in part by the challenges presented by COVID-19 and in part by a patient population that wants more than just low cost drugs from the pharma industry. Pharma has always touted that the patient's concerns are at the core of its mission and vision. Upon closer inspection one can ask, who is the real customer for the pharmaceutical industry, the patient or the doctor? The pharmaceutical industry's marketing and sales strategy has always focused on the physician's experience, often to the detriment of patients. Today's patient is very different from the patient of the last 50 years. They have more knowledge, choice, and options to handle their own care and treatment. If the industry and physicians do not understand the journey of a patient in their care, they are likely to disappoint. In today's digital age, where seamless, personalized experiences are the norm, healthcare must begin to address the concept of patient-centricity and the expectations of an informed patient who pays for his treatment and expects value added care.

Building a Patient Centric Model

Many characteristics of the overall value-chain must be addressed to move to a patient centric business model. Figure 1 captures six factors that will be a component of the future healthcare marketplace:

These six components comprise a wholesale transformation on how the industry views the patient from not only a marketing perspective but also in terms of impact on profitability and growth. Looking closer:

Figure 1. Patient Centric Healthcare Model



Patient Engagement

Patient engagement subsumes several characteristics within the disease treatment paradigm. The simplest is compliance. As the industry addresses an increasing number of rare and orphan diseases, treatment often requires adherence to a strict regimen. Historically, the physician was often left in the dark regarding patent compliance. Today, however, digital health care solutions allow physicians to evaluate a patient's compliance and use that data to modulate their treatment strategy. The FDA has approved digital therapeutics, such as mobile applications for substance abuse, fertility, AFIB and birth control, etc., which not only allow a physician to evaluate their patient's compliance but also, in many cases, to evaluate their physical response to the treatment.

Patient engagement strategies range from allowing a patient to make their own appointment on-line, to setting up a portal to address symptoms and concerns of patients being treated, to making historical patient data available to the patient on their phone or tablet. Post-hospitalization care is one area where a strong patient engagement strategy can profoundly impact a patient's overall care experience and potential recovery. Once a patient leaves a hospital, they face the challenges of navigating and managing their treatment without the 24/7 support of healthcare professionals. As such, a comprehensive patient engagement strategy must transcend the four walls of the hospital to meet patients where they are in their care journey.

Implicit in these conduits for communication is a wealth of data that can provide insight and opportunity, not only for the healthcare practitioner, but for pharmaceutical companies looking to better address disease states.

Integrated Technology and Personal Devices

One area of the overall drug development lifecycle that has greatly benefited from technology has been clinical trial management. Each phase of clinical trial has a specific purpose as the drug moves towards demonstrating

safety and efficacy. Classically, patients were treated more like subjects in a grand experiment with characteristics appropriate to scientific study than patients whose contributions to drug discovery were essential and valuable. Clinicians often used highly technical language and procedures, with data passing straight from investigators to drug companies, affording little understanding to patients. This has changed greatly over the last decade as clinical trials have moved away from in-clinic or office visits to electronic data gathering solutions that allow a patient to participate in clinical trials at their convenience. This can have profound impact on a patient's experience and, potentially, on their response to therapy as the need for the number of in-office or in-clinic visits is drastically reduced.

Smartphones and smartwatches have had an important impact on the industry's ability to manage and gather trustworthy data efficiently and effectively. As the size and distribution of clinical studies have gotten larger the challenges in ensuring data integrity have gotten harder. In many cases, intelligent devices mitigate this challenge by autonomously gathering data and securely gathering data without physician or patient intervention. GlaxoSmithKline, for example, has developed an app to measure the severity and progression of arthritis, with a simple test that enables the tension and flexion in the wrist to be measured by holding the device. The app records data about whether they are flexing their wrist correctly, and researchers are able to distinguish between good and bad data from these tests. AliveCor2 has developed an intelligent wristband that works with the Apple watch that can take a 30-second EKG of a patient and securely transmit the data to the physician from anywhere. Remote monitoring through wearable monitoring technology reduces the likelihood of patient dropout from clinical studies, which will translate to more drugs coming to the market more quickly. Look to see home AI systems such as Amazon's Alexa and Google Home devices to integrate with systems that monitor and take care of patients undergoing treatment.

Telemedicine, COVID, and Collaboration

The promise of telemedicine or telehealth has been discussed for decades. While more than half of the world's population is online, there is an almost equal number of people who still do not have access to essential health services or direct access to a healthcare practitioner. Telemedicine is a pivotal, paradigm shifting technology that can transform healthcare to value-based care, by bringing care to more people and reducing the cost of a physician's consultation. It will foster better outcomes by pooling existing healthcare infrastructure while delivering care more quickly and efficiently across great distances. Finally, it will drive a more positive patient experience by providing consistent and higher quality of care to more patients.

While telemedicine has been slowly gaining traction, COVID-19 jumpstarted the adoption of telemedicine as in-patient examinations were restricted or forbidden by state mandate, as a way to control the spread of the virus. More importantly, COVID has promoted not only the use of telemedicine for patient treatment but also highlighted its ability to effectively promote collaboration amongst physicians and researchers in the treatment of the disease. Before COVID-19 shut down the United States, telehealth accounted for an estimated $3 billion1 with the largest vendors focused in the "virtual urgent care" segment: helping consumers get on-demand instant telehealth visits with physicians they have no relationship with. Prior to COVID approximately 11 percent of patients and practitioners were using some component of telehealth. During COVID that number has jumped to 76 percent. While the initial motivation in using telemedicine was the desire to avoid exposure to COVID-19, 76 percent are interested in using it going forward with 74 percent of individuals polled stating they were highly satisfied with their care1. Physicians and other health professionals utilized telehealth solutions to fill the gaps due to cancellations from in-office care. Telemedicine also resulted in greater apparent efficiencies translating to practitioners seeing 50% to 175% more patients via telehealth than they did before the pandemic. That is a win-win situation for both physicians and patients. The renewed emphasis on telemedicine has accelerated its likely integration in today's healthcare framework, as is underscored by Medicare and Medicaid Services approving more than 80 new service offerings.

However, there are challenges still to be addressed with telemedicine supplanting a major portion of regular physician care. One area that will have a profound impact on telemedicine's continued use, post- COVID-19, will be how insurance companies address the reimbursement model. Reimbursement models will need to evolve to reflect the value telemedicine can deliver. In the U.S., for example, reimbursements for telehealth and other virtual services such as remote patient monitoring and image evaluation are available for the treatment of Medicare patients through Centers for Medicare & Medicaid Services (CMS), but there is no universal recognized framework or standard. Pharma will have to adjust its marketing practices to accommodate less direct physician interaction, recognizing that the physician patient paradigm is changing in terms of treatment strategies and perhaps, be prepared to include the patient in its messaging and engagement to realize the full value from the reimbursement perspective of telemedicine.

Clinical Trial Design-Demonstrating Drug Efficacy and Safety

These market shifts are indicators of how access to information will impact the quality of healthcare for all people as well as driving business performance. The industry recognizes that improvements implemented across the entire value chain can also provide a wealth of information that can shrink time to market for new drug therapies, simplify the complexity and cost of clinical programs, and identify latent risks in new drug therapies before they manifest themselves. COVID-19 has reenergized the discussion regarding Real World Evidence (RWE) and distributed clinical trial designs as a surrogate for controlled clinical studies, fueled in part by the FDA Commissioner's desire to push the industry in this direction. RWE refers to evidence or data obtained from real world data (RWD). This concerns observational data obtained outside the context of randomized controlled trials (RCTs) and generated during routine clinical practice. The source data for RWD can be obtained in many ways. It can be derived from data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources including Electronic Health Records (EHR) or claims and billing activities. Some treatment therapies include patient registries, which can be very effective in demonstrating treatment effectiveness.

Clinical trial data management has evolved over the last 20 years. One major development that has greatly simplified the data acquisition and data management activities during clinical trials execution is the integration of electronic data management solutions. These solutions have greatly reduced the risk of data manipulation and adulteration that was prevalent during the early expansion of clinical studies to the emerging markets. In addition, it has greatly simplified the data acquisition and communication process for clinicians while paving the way for a broader implementation of digital data gathering and monitoring solutions we are seeing today. COVID-19 has exposed the challenges of using uncontrolled clinical data to derive a substantive proof of safety and efficacy, most notably with the early FDA approval under a EUA of Hydroxychloroquine (HCQ).

Defining Decentralization

Decentralized clinical trials, however, have the potential to speed and simplify the structure and execution of large-scale clinical studies. The industry sometimes uses the terms decentralized, remote, virtual and hybrid interchangeably, however the FDA has a very specific definition of decentralized clinical study designs. FDA considers decentralized trials as trials that employ decentralized technologies. These clinical trials use digital technologies for remote interactions with real participants. In contrast, virtual trials are preclinical trials conducted in silico or on models. Both examples use digital technology, but their application is different. Hybrid trials combine elements of traditional and centralized approaches where some patient consultations or tests may be performed

remotely and others in person at a trial site. Adopting a trial design depends on the trial's goals, the patient population and the available technology.

One impediment in the industry adopting these approaches has been the lack of a clear guidance by the FDA, but there is no doubt the benefits, both from a patient experience perspective and potential speed of execution warrants looking closer at these solutions. There should be some normalization once the FDA issues its guidance on decentralized trial design. The role of industry experts in measuring patient interaction with new digital technologies, whether it is an app, watch, video, web-based journal or other interactive digital solution will become a significant new area of development as the industry looks to leverage this new approach to clinical studies and ensure the trial data will not only gather the appropriate data but will do so without unconscious bias. Technology must make sense for the context in which it is used. Data integrity and traceability will be paramount in having confidence in data derived from these trial structures so FDA expectations such as 21 CFR Part 11 compliance for software and evidence of design controls to support device validation will be very important in arguing confidence in the data.

Bioinformatics and Risk Management

Bioinformatics is an interdisciplinary field that develops and applies computational methods to analyze large collections of biological data, such as genetic sequences, cell populations or protein samples, to make new predictions or discover new biology. The computational methods used include analytical methods, mathematical modeling, and simulation. The completion of the Human Genome Project in 2003 brought together bioinformaticians to analyze genomic data and inform further pharmacogenetic research. Next-Generation Sequencing (NGS), also known as high-throughput sequencing, is the catch-all term used to describe several different modern sequencing technologies. These technologies allow for sequencing of DNA and RNA much more quickly and cheaply than the previous techniques. NGS solutions have been approved as companion diagnostics, especially in the field of clinical oncology, to confirm that a patient has the genetic anomaly associated with specific disease states. Within the context of clinical trial enrollment the ability to confirm that a patient or clinical cohort is appropriate for evaluating the clinical endpoint of a study greatly improves the overall potential for determining efficacy and safety of that trial while adding another quantitative filter for clinical trial enrollment. Commercially, for patients, this translates to a higher probability of treatment effectiveness.

Care Management Team

Care management is the range of activities intended to improve patient care and reduce the need for medical services by helping patients and healthcare providers more effectively manage health conditions.

Health care organizations run the spectrum from those in the early stages of entering into risk-based contracts, where they will be held accountable for providing care to specific populations of patients, to organizations that have developed proprietary or home grown tools and systems that make scalability challenging. Electronic medical records are just the tip of the iceberg in establishing a positive patient care system. There are several important components to consider when designing Care Management solutions:

1. Patient Engagement: Informing patients about their care planning in order to facilitate interaction among all care team members. This could include application-based secure messaging, assessments, care planning

and associated activities, and education.

2. Care Coordination and Data Integration: This includes the ability to pull, analyze and share data from multiple Electronic Medical Records (EMR) and other data sources with care team providers, care team communication and collaboration on patient assessments along with care planning, and interventions.

3. Patient stratification and intake: Using data driven decision-making tools to identify high-risk, high-utilization patients. This solution would also supply care managers with prioritized work lists for interventions, greatly simplifying their work.

4. Performance measurement: Advanced reporting capabilities to show how the care team performed after analyzing and acting on the data provided.

An analytics-driven care management system that addresses the above issues will streamline workflows, prioritize daily tasks for care team members in a predictive way, and steer activity to the areas that will positively impact the most patient lives in the most efficient way.

Conclusion

Health systems creating a data-driven culture will require thoughtful planning and execution. Under pressure to improve care and reduce costs, implementation of the analytics infrastructure, best practices and deployment processes are critical to success. Making data part of the everyday decision-making process while building a data-driven culture will be the basis for moving toward the patient, not the caregiver as the ultimate customer. Pharma must be ready to evolve with this inevitable transformation, recognizing a clearly defined information management strategy will be key to realizing the benefits of the myriad pathways for data acquisition, aggregation, and analysis. The ultimate result is a more patient centric framework resulting in better, more effective drug therapies on the market, with faster, simpler, more cost-effective clinical trials and a much higher level of patient satisfaction with regard to their overall care and treatment.

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CPhI Question: How soon will patients be able to integrate digital healthcare apps and monitoring with in home AI systems? Perhaps being able to say 'alexa send today's healthcare diary to my physician, insurer, etc.' or 'alexa tell me my health goals for today'. Could this mean that ownership of health record may begin to transfer form physicians to patient as custodians?

This ability is already in place. In April 2019, Amazon unveiled their secure software solution toolkit that allows health care companies to build Alexa voice tools capable of securely transmitting private patient information—a move that opens the door to a broad array of uses in homes and hospitals. The patient will always own their own data, regardless of where and how it is generated. Privacy concerns will move to the forefront of the design considerations as data acquisition and monitoring moves outside the physician's office. The challenge with this evolution is ensuring the accuracy of the data provided and maintaining the validity of any diagnosis provided as the data acquisition framework integrates the patient.

CPhI Question: Might we see a situation in the near future where 50% of GP appointments are telemedicine driven – will this potentially save money on healthcare systems? Is an evolution of this potentially having people provide ongoing real time data?

As I mentioned in my article the challenge right now is updating reimbursement policies to reflect the value of the advantages and capabilities of telemedicine. The number of patients that can be seen via telemedicine is considerably higher than in office visits. So there is a framework in place for a gainful situation for both physicians and insurance carriers.

Regarding patients providing on-going data: This is exactly the direction the industry has gone. Pharmacovigilance is achieved via on-line registry, and patients' vital data is provided by smart devices and smartphone applications. This is a large component of the patient-centric transformation.

CPhI Question: Could regulators (nor necessarily medical ones) be the main barrier to having greater digital engagement and new level of cross-party sharing – e.g. how will EU laws around data privacy be adhered to alongside opening-up medical records etc?

There is no question privacy is a volatile topic amongst the major markets (U.S., EU, China) and approaches could not be more disparate. The U.S. has loosened privacy protection under the current administration. In the EU GDPR is a sweeping regulation already in effect, but enforcement has been hampered by both Brexit and COVID-19, with industry wondering whether the cost of compliance is worth the trouble. China's government requires access to all information being shared among all individuals in the country. Zero-trust networks are maturing with the U.S., among other governments, looking to deploy the architecture across government agencies. Deploying a similar structure for HIPAA compliant info is a very real possibility and would support privacy concerns from a cybersecurity and data integrity perspective, although the compliance requirements for specific regulations would still need to be addressed.

CPhI Question: Looking more widely could telehealth approaches be cost effective ways to open-up healthcare in emerging economies to more people?

This is where the emphasis has been for telemedicine from its onset. Applying this technology in the mainstream has only served to reinforce its viability because it is capable of bringing medical expertise to remote areas and poorer economic areas globally.

CPhI Question: Can you give a snapshot of what a hybrid/digital healthcare model should look like in 2025 in the EU and USA – how far along will we actually be in this (i.e. will look like) – will one market pull ahead in adoption?

By 2025, telemedicine and patient participation in routine health care will be the norm in the U.S. The EU will be close behind even if GDPR represents a significant compliance hurdle, as does the 2013 transparency legislation in the EU. Pharma will bring a more mature component of its R&D framework to analyze and harvest treatment information from telemedicine databases.

PANEL MEMBER
Aurelio Arias, Engagement Manager, Thought Leadership, IQVIA

Innovators are the future off-patent winners

Introduction

The off-patent industry has been under continuous pressure for the last decade. The fallout from COVID-19 will spur healthcare systems to reduce expenditure as they face a looming global recession. Innovative strategies, rarely seen in the off-patent industry, will allow manufacturers to provide medicines that offer greater value to both patients and payers.

Generics pricing and volume are pressured

Lower demand

Over the past five years, global prescription medicines volume growth has halved to 2%. This has not been driven by developed economies, but by a sharp deceleration in emerging ones as their populations shift demographically and economically. This is a worrying trend for an industry that derives the bulk of its volume from these emergent markets. As a consequence, generics companies have found it harder to rely on the steady upwards consumption of medicines.

Fragmented Industry

The number of players operating in this sector has seen a sharp rise in key markets such as Asia and the US. Over the past decade, BRIC (Brazil, Russia, India, China) countries have seen the number of companies double. In the US, the number of players has increased by a half; most of this change in the last few years. This rapid increase of players drives up competition, which leads to lower prices, which is good for buyers, but if left unchecked, can be problematic for supplying quality pharmaceuticals over the long-term.

Powerful buyers

In many regions, buyers are consolidating purchasing power, and this leaves little room for bargaining by the manufacturers. For example, 90% of all purchases in the US are controlled by only three wholesalers (AmerisourceBergen Corporation, Cardinal Health, Inc., and McKesson Corporation). China, expanding its volume-based purchasing policy, has successfully driven prices down in the largest Asian market and Europe continues to drive effective price-control measures.

Supply chain scrutiny

In the wake of serious adverse events such as the Sartans scandal of 2018, where it came to light that many bulk pharmaceuticals were contaminated by potentially carcinogenic nitrosamines, the FDA increased its scrutiny on imported medicines.

This, coupled with increased collaboration between FDA and EMA inspectors, means that the US and EU have intensified their focus on offshore manufacturers as evidenced by a rise in warning letters. The additional regulatory burden for small manufacturers will push them to look at other markets, potentially regional and domestic ones.

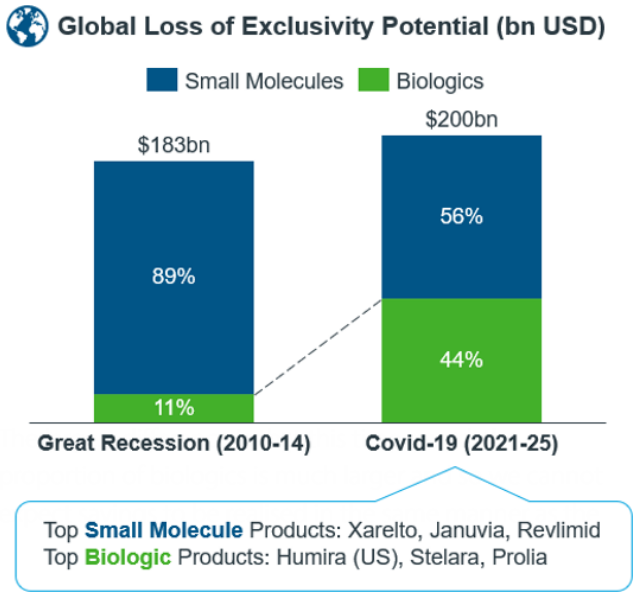
The COVID-19 pandemic drove supply chain fragility into the political sphere, the US and EU have been vocal on shifting manufacturing of intermediates from to their own jurisdictions through executive orders such as "Buy American" and the UK's "Project Defend". Whilst these initiatives are aimed at decreasing reliance on overseas suppliers, it is likely that unless specific policies are put in place to dictate a minimum onshore supply guarantee, the current economic unfeasibility will mean the status quo will remain. For a local supply of medicines, prices must rise, and healthcare systems must be prepared for this, especially as they deal with the fallout from the COVID-19 pandemic.

COVID-19 likely to shift prescribing and provisioning patterns

As the pandemic stabilises, healthcare systems turn their attention away from immediate treatment response to longer-term sustainability and debt servicing in the face of an impending global recession.

Over the next five years, the global savings from LOE could be similar to that faced after the great recession of 2007-08 (see figure 1).

Figure 1. Global Loss of Exclusivity Potential (bn USD)



previous recession. This is significant as recent experience shows us that biosimilar launch and uptake is still sluggish in many countries. It could mean that markets with higher biosimilar uptake rates will be able to unlock savings over those with slower uptake. Manufacturers should be aware that pro-biosimilar policies could be prioritised.

During the pandemic, recommendations to minimise physical attendance to clinics and hospitals drove healthcare professionals to modify the way they interacted with and treated patients. For example, interim guidance from NHS England suggested prescribing safer alternatives such as value added medicine Abraxane (albumin-bound paclitaxel) instead of plain taxanes and DOACs (direct oral anti-coagulants) instead of warfarin to minimise patient visits. The upshot is that a different class of medicine was preferred, one that brought patients from the hospital to the clinic and from the clinic to the home setting.

The influence on physician prescribing and patient preference is meaningful and it is yet to be seen to what extent these switches will persist. Feedback on remote interactions and reduced physical visits has been positive in many areas, and so it is likely that these processes will remain in place.

Areas of opportunity

Generics manufacturers wishing to expand into new opportunities will need to think outside their conventional business model and, as they so often excel at doing, borrow ideas from originators. This needs to begin from the top, leadership will need to reframe their thinking from cost optimisation to value creation. The following three areas offer compelling and scarcely explored opportunities.

1. Specialty generics

A subset of generics that has drawn interest in recent years because of a higher barrier to entry has been complex generics. Generally defined as generics that have a complex active ingredient, route of administration, formulation, or drug-device combination, complex generics at their core are a collection of medicines that are costly to develop.

Complex generics are tricky to categorise due to their many permutations, but they most likely overlap with Specialty generics, which we do actively classify. IQVIA defines Specialty as medicines that treat specific, complex diseases with four or more of the following attributes: initiated only by a specialist, administered by a practitioner, requires special handling, unique distribution, high cost, warrants intensive patient care, or requires reimbursement assistance. We can therefore, by proxy, gain insights into this sector

Specialty generics list price value growth is four times faster than non-specialty and this looks like it is set to continue as high specialty value from innovators trickle through to generics as their protection expires. Oncology medicines are largest and fastest growing, followed by antivirals. On the horizon, expect to see kinase and JAK inhibitors as sources of growth.

2. Digital Value Added Medicines

Value added medicines are at their core modified off-patent medicines to bring about positive societal and economic benefits to the healthcare system through repositioning, reformulation or combinations.

A natural advantage of value added medicines is that they encompass a broad range of technologies, giving interested parties a large degree of flexibility in choosing their optimal product strategies. This innovation spectrum ranges from continuous, stepwise improvements through to disruptive hi-tech solutions.

Digital services and therapeutics also play an active role in this space where partnerships between pharma and tech companies are the norm. They break the mould in the innovations spectrum by facilitating solutions in the virtual realm, thereby potentially increasing scale at a lower cost base.

The ultimate benefit of digital integration to a manufacturer would be to harvest patient-reported data and generate evidence to prove the value of their portfolio to payers and other stakeholders. Manufacturers should explore broader value propositions, beyond the drug, that are focused on user experience and heavily integrated in the personal and medical device ecosystem. This will both deliver a superior patient experience, closely aligned with better outcomes, and maximise the potential of gathering robust healthcare data.

The evolution of digital value added medicines will tend towards understanding patient behaviour with greater precision from the wealth of generated data. A further layer is to introduce gamification concepts to capitalise on network effects by forming communities of connected patients who can be incentivised to reinforce positive behaviours, such as adherence and wellness. Ultimately, preventing declining health will save downstream costs for the healthcare system and improve patient quality of life.

3. From Biosimilars to Biobetters

Before embarking on this next section, I'd like to make a point on nomenclature. There is no current consensus on the definition of a biobetter, but for this piece, I would like to define it as an "off-patent biologic that has been improved upon by a non-originator manufacturer".

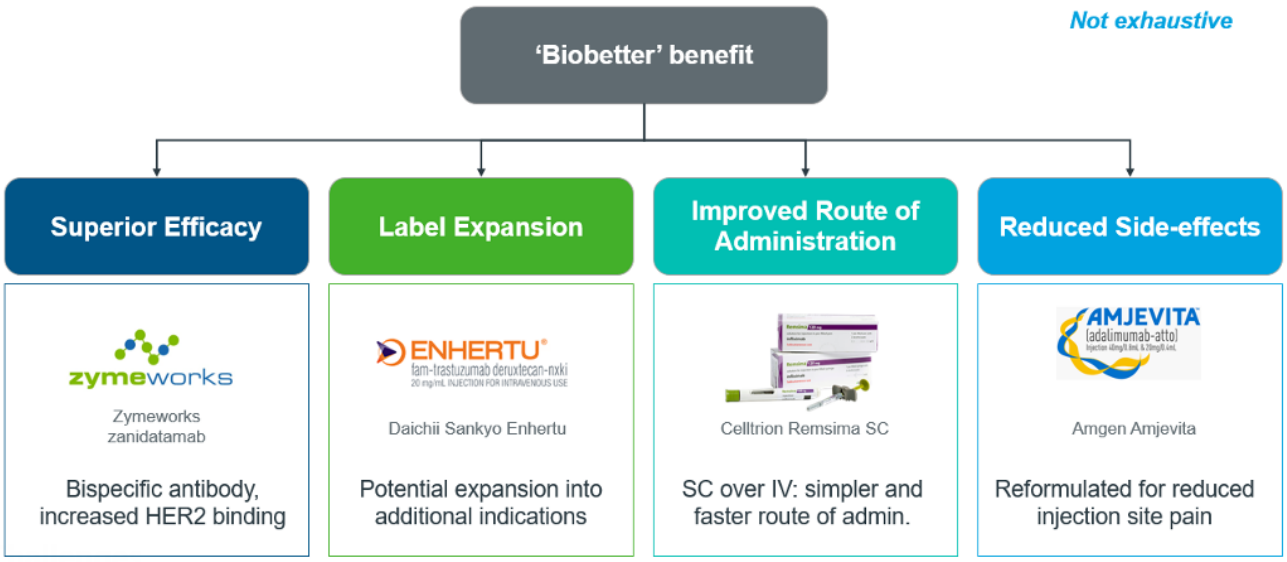
Biosimilar manufacturers face a rapidly evolving market where winners appear to be the trailblazers, achieving first-to-market benefits due to low competition. Many pipeline candidates are for older molecules aimed at non-EU/US markets as the return doesn't justify the cost of development. As future opportunities decrease in size, some companies are taking steps to differentiate their off-patent biologic offerings. The first breakthrough came as Amgen specifically referenced Humira's (adalimumab) improved formulation, aimed at lowering patient discomfort during administration, and used this to great commercial success of its biosimilar.

Celltrion pushed the envelope further. They have successfully developed a subcutaneous version of infliximab, where the originator only exists in an intravenous form. In doing so, they have increased the convenience to the patient and healthcare givers. During the COVID-19 pandemic, many physicians preferred subcutaneous modes of administration because in many cases it reduced the patient's attendance to a hospital. In addition, Celltrion have taken the unprecedented step of trialling novel oral antibody delivery technologies.

Off-patent biologics needn't only look for modifications in route of administration (see figure 2), other technologies blur the lines between copies and innovative molecules. Enhertu (trastuzumab deruxtecan) is a conjugation of two off-patent molecules, and there are more candidates in the pipe that display conjugation as their primary differentiator. Bispecific antibodies such as Zymework's zanidatamab which modifies the antibody arms to bind to distinct domains on the HER2 protein use old, proven molecules and mechanisms of action in novel ways.

Not all these can be classed as biosimilars, but there is certainly a case to be made that successful international biosimilar manufacturers will explore these avenues to make the most of expired biologics.

Figure 2. Biobetters can take many forms to provide additional patient benefit



Companies that are interested in developing the specialty generics, value added medicines or biobetters are faced with numerous challenges on bringing these products to market. Some of these include:

- Identifying commercial and regulatory opportunities.
- A lack of guidance which creates a good deal of uncertainty.
- Smaller patient pools for certain medicines.
- Increased regulatory scrutiny, leading to additional quality and safety evidence requirements.
- A need to bring these products to market rapidly to gain favourable pricing and in certain cases, limited exclusivity.

In order to address many of these issues, companies will have to engage regulators early, presenting a development and clinical roadmap which will often contain elements normally seen during innovative development.

Conclusion

Generics companies have long griped at the headwinds they are forced to navigate and are now faced with increased pressure from global healthcare markets to provide savings needed to cover the increased healthcare costs of the COVID-19 pandemic.

A number of generic manufacturers received a revenue boost from the increased volume of essential medicines consumed during the height of the pandemic. Although recognised as short-lived, many can turn this into an opportunity to use this growth spurt to accelerate value creation strategies within their company.

A crucial factor to the success of these novel ways of operating will be proving the additional value to stakeholders. This can be achieved by early engagement with patients and healthcare practitioners to identify unmet needs and close payer and regulator discussions to address any concerns. Engaging patient advocacy groups during product design phase will also play a large role in success, after all, they will be first to recognise the benefits of these innovations.

The leaders of tomorrow's off-patent industry will be manufacturers who begin to behave in the way innovators do. Investing in patient-centric product design, engaging stakeholders, generating real world evidence and partnering with MedTech start-ups are all activities they will need to be comfortable in performing. This will allow them to align their products closer to patient needs and in doing so, creating efficiencies in healthcare provision. An efficient healthcare system will not only lead to greater overall savings but also benefit a greater proportion of its patients.

CPhI Festival of Pharma Questions and Answers

CPhI Question: Will the monopoly the big three US wholesales have potentially be broken up to help gain greater efficiencies in medicine supply (i.e. could less wholesaler margins – which are often high – deliver more sustainable manufacturer profits and even simultaneously lower overall costs)?
"Ultimately it is in the purchasing groups' interest to ensure that an adequate level of competition is maintained across the molecules it procures. A drop in quality or supply due to price erosion is not positive for patients and may spark regulators to take action. I don't expect they will be broken up any time soon, there are many avenues to explore before this would become a reality, such as implementing purchasing policies that encourage multiple winners."

CPhI Question: Could some of the biggest generics companies be what we might now call innovators – i.e. as biologics come off patent, innovators who already have an advantage of complex development will turn to biobetters (of any definition) to retain large % of market share… if there is little price difference do we anticipate more patients (or payers) will stay with originators?

"Some of the largest generics and biosimilars companies are actively exploring innovative strategies as a source for continuing growth. Relying on volume increase alone cannot sustain their size. Behaving like innovators offers avenues to growth but they will find it challenging to gain reimbursement for their efforts if they struggle to communicate the additional value from their products to payers. Some originators show they are happy to compete on price with their referenced copies and but this still leaves room for an innovator to improve upon any originator product. If innovative off-patent products are to succeed, they should show value over the current standard of care, but need to carefully price accordingly so as to be acceptable to payers."

CPhI Question: which market might see the best cost savings by 2025 – i.e. who has more developed biosimilar encroachment?
"North-Western European countries, especially the Nordics, UK and Germany, have historically shown immediate entry and rapid uptake of biosimilars so they are well poised to generate the greatest savings by 2025. There are a couple of large biologics approaching expiry over

the next few years such as Eylea and Stelara. These will be focus areas for EU healthcare systems. The US however, will see the biggest saving of all when Humira exclusivity runs out in 2023. Currently there are around 8 biosimilar candidates lined up ready for launch in that year and this unprecedented level of competition will likely generate the highest savings."

CPhI Question: Will generic companies be forced to consolidate to achieve economies of scale – particularly for high volume, low complexity products?

"M&A activity increased around 2017/2018 as a reaction to generic companies wishing to focus their portfolios and shedding unprofitable assets so in a sense this consolidation has been happening already. Manufacturing of high volume, low complexity products will remain in the east unless US and EU policies are put in place to guarantee minimum local production. In the time being, western manufacturers will need to focus on complex, profitable molecules for new growth and asset divestment may continue if it helps them focus on core areas."

CPhI Question: In drugs coming off patent – will all future generics require a value-added element by 2025 to remain competitive? (i.e. will generics have two tier strategies by 2025: one with scale; and one with value added elements for newly genericised drugs)

"Not many companies will be able to successfully operate a two-tier strategy unless they have the sufficient resources. It is likely that we'll see an increasing number of specialist generics and biosimilars companies that focus predominantly on innovation. For example, Celltrion have explicitly stated that they will increase their focus on biobetters and have recently announced trials on an oral biologic. Generics in five years' time could indeed come in many forms but the regulatory and payer environment will have to recognise and support them along the way."

CPhI Question: still 56% of newly genericised drug by 2025 will be small molecules – what is the opportunity here for innovator verses generic company?

"Most of this value comes from Specialty medicines, those likely to be initiated by a specialist, require special handling, high cost etc - such as oncology and immunology. As they are small molecules, they will inevitably face rapid generic competition but given their nature, they may have a higher barrier to manufacture, handle or distribute. This represents an opportunity for companies able to navigate the added complexity. Innovators in this space should focus on reducing administration complexity and adding a digital layer to their therapeutic offering helping patients manage their therapy."

CPhI Question: do we anticipate that emerging markets by 2025 will have recovered and to start driving growth again (i.e. emerging markets 2025 onwards will again be main drivers)?

"With a looming global recession predicted as a fallout from COVID-19 on top of uncertainty on how long the pandemic itself may last, it is likely that healthcare systems will turn to increasing their use of plain generics as a way to generate savings. This coupled with a fall in out-of-pocket expenditures as wages are squeezed could mean that growth from branded generics, value added medicines and biobetters may be slower than normal. It is unclear whether emerging markets will have recovered by 2025, but if it is anything like the global recession of 2008, then it could mean they will continue to drive growth within five years, albeit at a slower rate."

CPhI insights

Part 3.

Mammalian biomanufacturing supply and demand predictions for 2024

informa markets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Supply and Demand Trends: Mammalian Biomanufacturing Industry Overview

Trends Overview 2020-2024

- Demand for biologics manufacturing by volume is projected to reach over 4,700kL, a 5-year growth rate of over 10% per year (just over 2,600kL in 2019).
  - If Alzheimer's drugs and PDL/PDL-1 checkpoint inhibitors are approved, demand could be much higher resulting in capacity shortages in a typical forecast. However, if approved, COVID 19 therapies and monoclonal antibody-based infection preventatives could cause significant pressure to large-scale manufacturing networks
- Global biologics manufacturing capacity will increase to 6,500kL by 2024 from nearly 4,700kL in 2019
  - CMO/hybrid companies increase their control of capacity from 33% in 2019 to 36% in 2024 and by 2023, Europe will have capacity equivalent to North America. Capacity in Asia continues to grow.
- Half of the typical products in late phase development (Phase 2, Phase 3) can be met by a single 2,000 or 5,000L bioreactor. However, COVID 19 therapies and monoclonal antibody-based COVID-19 infection preventatives will require large scale bioreactors.
- Overall, pandemic aside, capacity, should experience some loosening in short-term constraints but may tighten after 2024. With the majority of capacity remaining in-house, it may be difficult for companies with products in development, but without internal manufacturing, to access capacity at the right time and under the right terms. COVID 19 therapeutics and infection preventatives may place significant and unprecedented pressures on large scale manufacturing facilities.

Abstract

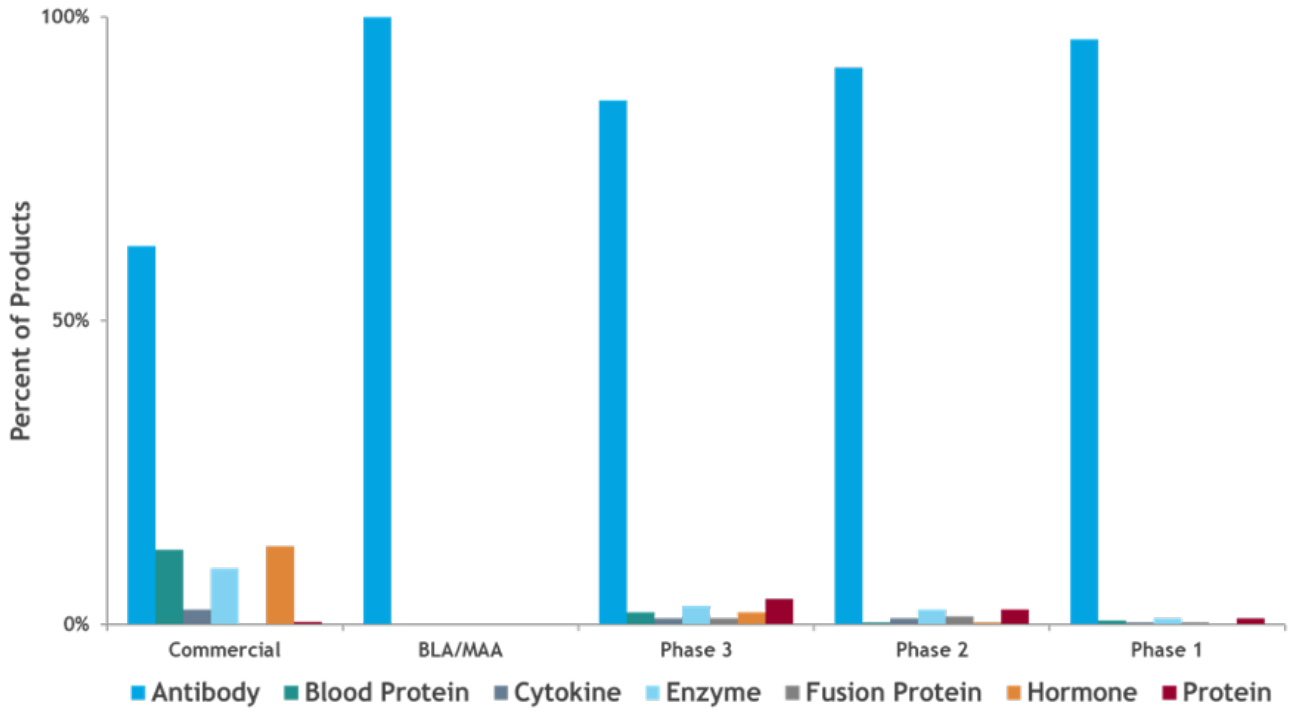
Biologic-based drugs are an increasingly important part of the portfolio growth strategies for pharmaceutical and biopharmaceutical companies. As the number of commercial products and pipeline candidates grow and will likely include COVID 19 therapies and infection preventatives, key issues facing the industry include the current and future state of biomanufacturing capacity, the availability of that capacity, and technologies impacting upstream and downstream bioprocessing. BPTG provides a high-level overview of the current state of the supply of and demand for mammalian-based biopharmaceuticals, forecasting where the industry is heading and how manufacturers are keeping pace.

Article

Since the approval of the first recombinant therapeutic antibody, OKT3, in 1986, mammalian-based biopharmaceutical products have become a larger percentage of overall pharmaceutical company revenue. In 2019, the sales of the top five selling recombinant proteins (Humira, Keytruda, Eylea, Opdivo, Avastin), all antibody-based products, totaled just over $52B. The compound annual growth rate for antibody product revenue, which include naked monoclonal antibodies, Fc-fusion proteins, antibody fragments, bispecific antibodies, antibody conjugates, and other antibody related products, was approximately 20% from 2004 to 2014. However, this growth has slowed to the mid-teens in the recent years due to the maturation of many products and emerging alternative therapeutic modalities. Also, it is difficult to sustain such growth rates as the overall market size increases.

To provide context around this growing segment of the pharmaceutical market, BPTG's proprietary bioTRAK® database of biopharmaceutical products and manufacturing capacity estimates that there are nearly 1,600 biopharmaceutical products in some stage of clinical development in the United States or Europe. The majority of these products, approximately 85%, are produced in mammalian cell culture systems. We evaluate the distribution of mammalian products by product type and phase of development to further refine the biopharmaceutical manufacturing market. Figure 1 shows the distribution of product types, including antibody products, blood proteins, cytokines, enzymes, fusion proteins, hormones and other recombinant proteins, by phase of development. Antibody products are the dominant commercially marketed product type at nearly 60% and are the largest product type for all phases of development, with the early stage pipeline consisting 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.

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



Whether commercially approved or in development, each of these products needs access to mammalian production capacity. For current commercially approved biopharmaceutical products, the future demand is estimated from each product's reported annual sales data, along with estimates of each product's future growth rates. Our future product growth estimations take into consideration a product's age, as sales growth typically slows as a product matures, while newly approved products often do not reach full market penetration for several years.

The projected treatment population size is estimated based on price per mg and sales. Combining the population with the yearly per patient dosing, we forecast the kilogram quantities required to meet demand of each product for the next 5 years. These kilogram quantity forecasts can be converted to liter quantities for each product using cell line expression level and overall purification yield estimates. These estimates are based on industry benchmarks at the time the product was being developed and the maturity of the company developing the process. For example, the commercial process for a product launched more than ten years ago will likely have a lower expression level assigned in our forecast algorithm than a product currently in clinical development. For products in development, future commercial demand is estimated based on the market penetration of currently approved products or proxy products with similar indications. Additionally, for products in development, we employ a phase-based commercialization probability assumption when calculating future demand.

Figure 2 shows the projected kilogram quantities of product needed to meet annual commercial and clinical demand for all product types produced using mammalian production systems. In 2019, nearly 30 metric tons of product were required. As more products enter the pipeline and products in development receive commercial approval each year, the overall kilogram requirements needed to meet product demand increase from nearly 30 metric tons in 2019 to nearly 60 metric tons in 2024. Demand for corona virus disease (COVID 19) related products are not included within the typical forecast which is shown below.

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

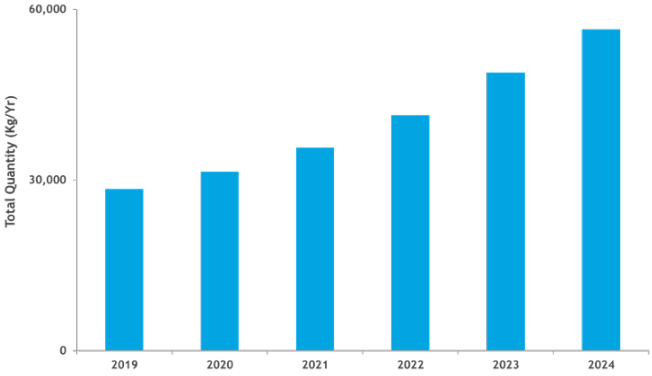
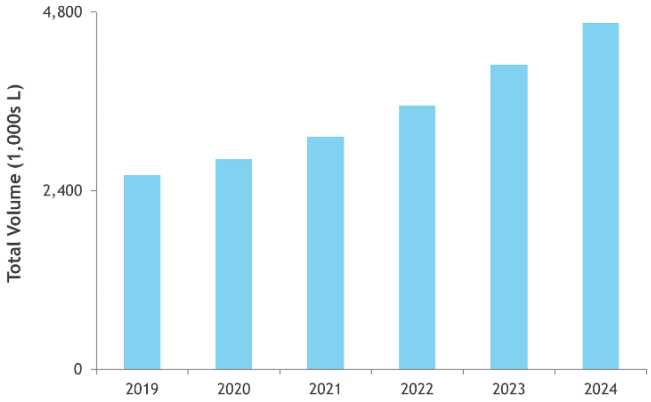


Figure 3 shows the projected volumetric capacity needed to meet annual commercial and clinical demand for all product types produced using mammalian production systems. In 2019, the annual volumetric requirements were just over 2,600kL, while in 2024, the volumetric requirement is projected to be nearly 4,700kL, a 5-year growth rate of 12%. Volumetric demand for COVID-19 related products are not included within the typical forecast which is shown below.

Figure 3: Estimated Volumetric Capacity Needed to Meet Product Demand



As with any forecasting model, our assumptions for a typical year are based on the mostly probable scenarios and include estimations for biopharmaceuticals which are being developed for certain large patient population indications such as Alzheimer's disease or broad cancer treatments like PDL/PDL-1 checkpoint inhibitors. Should several of these large-demand products obtain regulatory

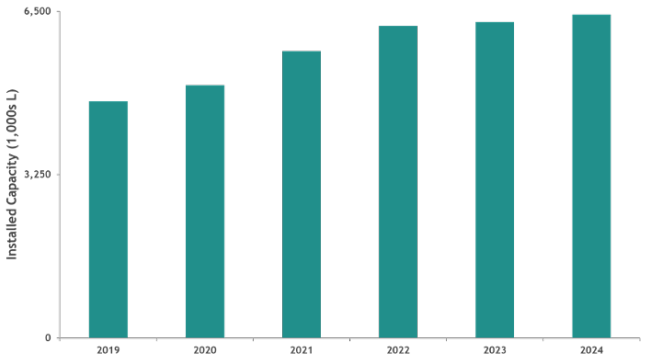
approval and adequate reimbursement by healthcare oversight organizations (i.e. US Pharmacy Benefit Managers, the UK's National Institute for Healthcare and Excellence (NICE)) or become part of a managed entry agreement between a company and public payer of a social or national health insurance system, a significant increase in demand for manufacturing capacity could occur potentially leading to a serious capacity shortage.

In addition to the products being developed for typical indications, this year we face an additional challenge of incorporating demand for recombinant proteins being developed to combat the corona virus disease (COVID 19) pandemic. We have begun to track novel and repurposed products being developed to treat active cases of severe COVID 19 related symptoms. Additionally, we are tracking several novel antibody-based products projected to be used as potential COVID 19 infection preventatives, although there remains a debate over just how significant a role any antibody treatment might play in preventing COVID 19 infection.

Conversely, there are other manufacturing trends which could result in a decrease in demand for some biopharmaceutical manufacturing capacity. Among these are the industry's increased focus on orphan indications, a shift from full length naked antibodies to alternative antibody formats and more potent products (e.g., antibody drug conjugates (ADCs) or bispecific antibodies) which would require lower doses. Given the projected increase in volumetric demand over the next 5 years, the industry is cognizant of the inherent volatility of production capacity forecasts. There is always a degree of uncertainty in balancing the demand and supply equation due to production problems, market demand fluctuations over time, regulatory and reimbursement issues, and competitive factors.

To understand how the industry is positioned to meet these product demands, we estimated the 2019 mammalian cell culture supply to be approximately 4,700kL and predict it to grow to nearly 6,500kL by 2024, 5-year growth rate of 6.4% per year (Figure 4). However, not all capacity is equally available throughout the industry. In 2019, Product companies, i.e., companies focused on product development, control nearly 70% of the installed mammalian cell culture capacity, while Hybrid companies, i.e., companies that are developing products, but also sell or make available any excess manufacturing capacity, and CMOs control significantly less capacity. The distribution of capacity changes slightly in 2024, with Product companies controlling nearly 65% of the installed capacity, while CMO capacity increases 3% and Hybrid companies remain stable.

Figure 4: Mammalian Manufacturing Capacity



While Product companies control the majority of cell culture capacity, the distribution of this capacity is highly concentrated within ten companies, as shown in Table 1. Capacity for companies not ranked in the top ten is distributed among nearly 130 companies in 2020, and nearly 135 companies in 2024. Currently, over 60% of the capacity is controlled by ten companies; in 2024, this changes to less than 60%. Based on substantial capacity investments, WuXi Biologics and Celltrion will displace Bristol Myers Squibb and Regeneron Pharmaceuticals from the top ten.

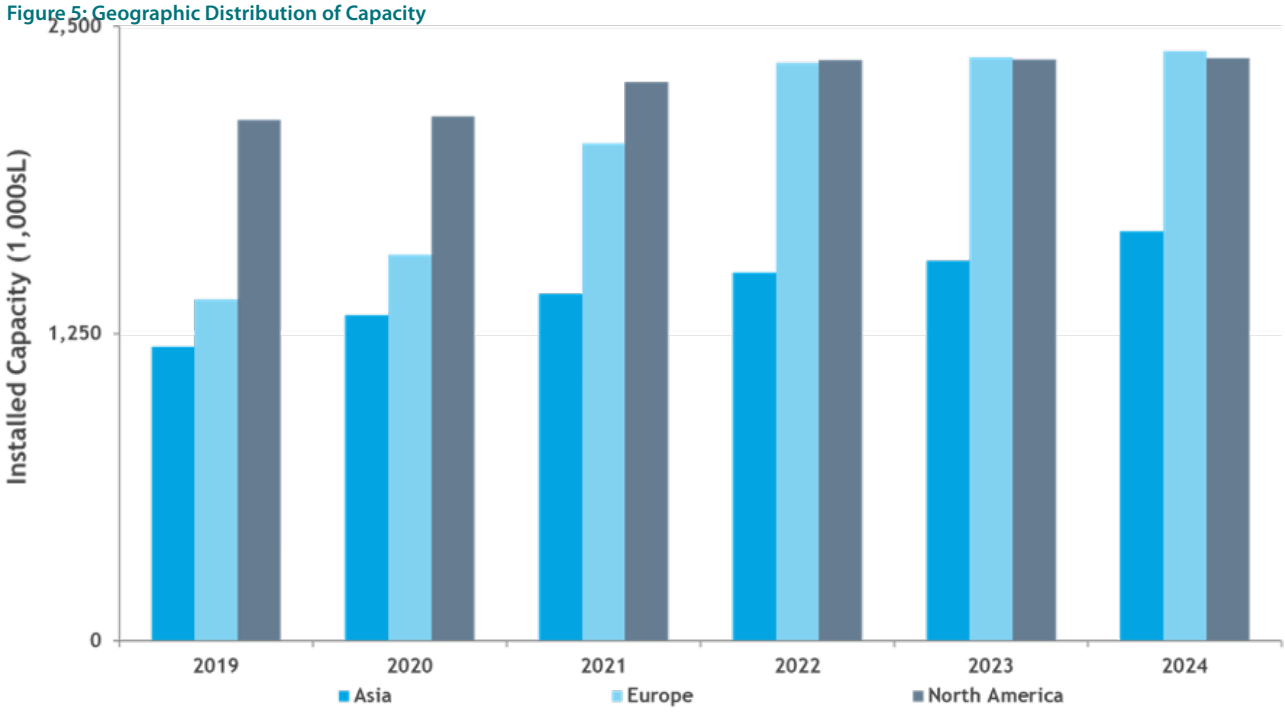
Table 1: Control of Manufacturing Capacity

2020 Rank	2024 Rank	Company	Company Type
1	1	F. Hoffmann-La Roche	Product
2	4	Samsung Biologics	CMO
3	2	Lonza Group	CMO
4	3	Boehringer Ingelheim	Hybrid
5	8	Johnson & Johnson	Product
6	-	Bristol Myers Squibb	Product
7	9	Amgen	Product
8	7	Sanofi	Product
9	-	Regeneron Pharmaceuticals	Product
10	10	Novartis	Hybrid
-	5	WuXi Biologics	CMO
-	6	Celltrion	Product

Figure 5 shows the geographic distribution of the manufacturing facilities. In 2019, nearly half of all mammalian capacity is located in North America, followed by Europe and Asia. Over the past five years there has

been modest capacity growth in North America and Europe, with significantly greater growth in Asia. By 2024, with significant growth rates projected in Asia (~7%) and Europe (nearly 12%), North America and Europe will have equivalent capacity. The capacity growth in these areas, particularly in Korea and Singapore as well as Ireland, are likely due to government incentives and tax advantages, among other factors.

Figure 5: Geographic Distribution of Capacity



As described earlier, different products require different capacity. For example, the 2019-kilogram demand for the top five selling antibody products totaled approximately 4.4 metric tons. The demand for the more than 100 remaining marketed antibody products combined was approximately 20 metric tons (an average of ~200 kg each, the median 48 kg). For products still in development, in a best-case commercial scenario where market success and maximum market penetration are assumed, projected demand for approximately 60% of these products in development is expected to be less than 100 kg per product per year. Only 8% of the products, such as those for Alzheimer's Disease, Parkinson's Disease, Diabetes, and possibly some coronary heart disease or atherosclerosis products, are projected to require over 750 kg per year. For COVID 19 products, if we conservatively estimate half of the patient population of severe COVID 19 related symptoms and half of those qualifying for potential COVID 19 preventative treatments receive a gram or multi-gram dose per patient, respectively, the kg demand for these products could require approximately 30 metric tons.

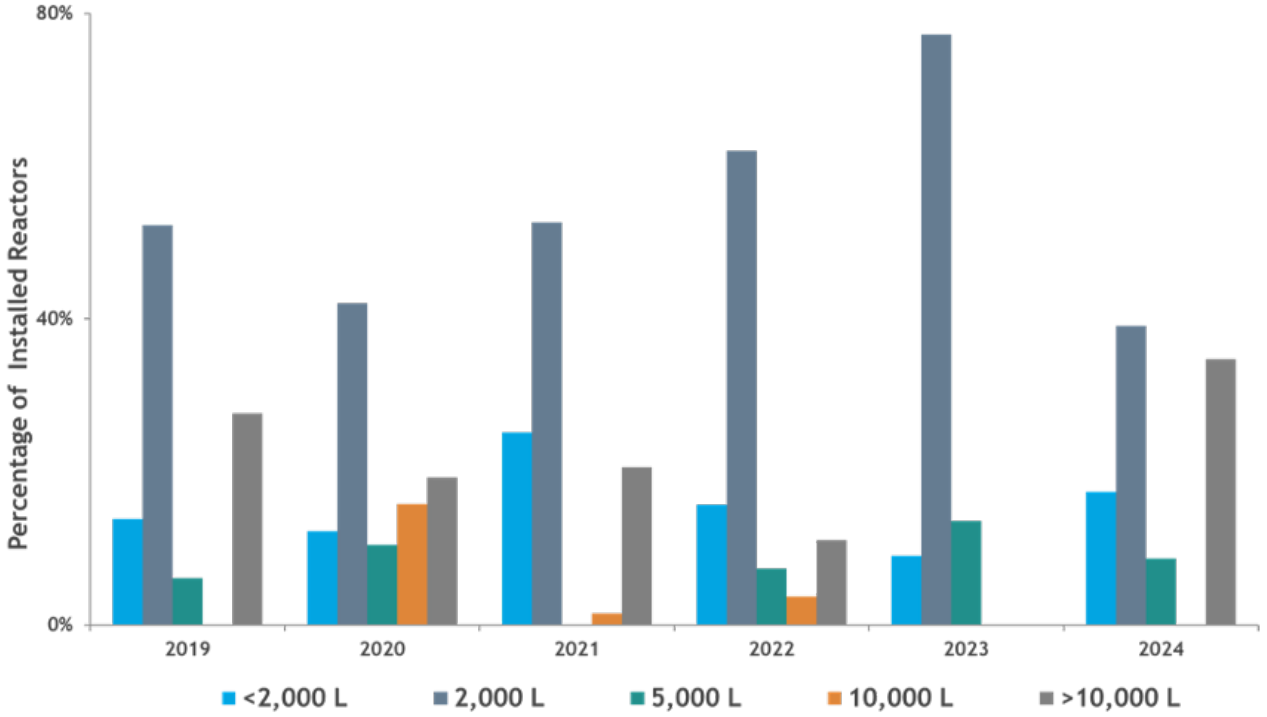
A closer review of future projected commercial manufacturing demands for products in Phase 2 and Phase 3 clinical development reveals half of the products can likely be met with a single 2,000 or 5,000L bioreactor assuming 18 batches per year per bioreactor with a 90% success rate for batch manufacturing (Table 2). However, this does not mean that large scale capacity is no longer needed. Our model predicts that the remaining half of products will need bioreactor capacity of 10,000L and greater to meet the forecasted demand. Increasing the number of bioreactors increases the manufacturing capacity and not surprisingly causes a shift in the percentage of products whose development can likely be met. As an example, a single 2,000L bioreactor is capable of manufacturing 39% of the products in Phase 2 and Phase 3 while a trio of bioreactors at this scale would be capable of manufacturing over half (54%) of the products in development. COVID 19 products will undoubtedly require multiple require large scale bioreactors to meet even a modest demand.

Table 2: Percentage of Product Demand Met by Bioreactor Scale

No. Bioreactors	2,000L Bioreactor	5,000L Bioreactor	10,000L Bioreactor	>10,000L Bioreactor
1	40%	13%	11%	36%
2	48%	16%	11%	25%
3	56%	15%	10%	19%

If we analyze the cumulative number and scale of bioreactors coming on line between 2019 and 2024 at the <2,000, 2,000, 5,000, 10,000 and >10,000L scale (Figure 6), it is evident that more than half of the bioreactors projected to come on line are 2,000L. Nearly 20% of the bioreactors are at a scale of 10,000 or greater. While manufacturers understand the capacity demand scenarios and are installing capacity to meet these anticipated demands, it is certain that the potential demand for COVID 19 treatments will add significant pressure to manufacturing networks with large scale capacity.

Figure 6: Percentage and Scale of Future Bioreactors



Overall, the biopharmaceutical industry will continue to have strong growth for the foreseeable future, and antibody products will be the dominant driver of this growth. Installed capacity is currently able to meet the typical manufacturing demand for these products, but control and location of capacity can affect accessibility. The majority of capacity is product based, rather than CMO based, which could make it difficult for companies without capacity to access it at the right time and under the right terms.

While capacity will increase over the next five years, demand for capacity, pandemic aside, will increase at a slightly faster rate allowing for some short-term loosening of capacity constraints, but after 2024, capacity tightening may occur. In recent years, we have noted that the industry was experiencing some capacity constraints at the clinical scales due to very high clinical demand and the industry has responded in kind with a wave of facility expansions. The type and scale of capacity being installed will also be important as the demand for half of products in mid-to-late stage development can be met with 5,000L of capacity or less; while the remaining half of products will need larger capacity to meet future demand. However, with the current pandemic, COVID 19 therapeutics and preventatives will require significant large-scale capacity if approved. With new bioreactor installations reflecting a pre-pandemic demand profile, we are focused on watching how the industry is responding and rising to the challenge to meet the typical and additional demands for capacity as it is critically important to ensure current and future products are available to patients.

CPhI insights

Part 4.

Contract services forecasts: vaccines, mega- and small- cap pharma demand

informa markets

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More Mega Cap Drugs Mean Less Work for CMOs, But Small Cap Pharma Boosts Clinical Manufacturing Outsourcing

Introduction

The percentage of approved new drug applications (NDAs) sponsored by mega cap companies was high in 2019, which caused a relatively low manufacturing outsourcing rate. But contracts for clinical-stage drugs are making up for marketed drugs, as smaller sponsors outsource their pipelines and pharma turns to CMOs to accelerate COVID-19 treatments.

There were fewer approved NDAs in 2019 than in 2018, as the FDA approved 16% fewer innovator therapies than in the previous year. This is partially due to the January 2019 US government shutdown, which caused the FDA to suspend reviews.

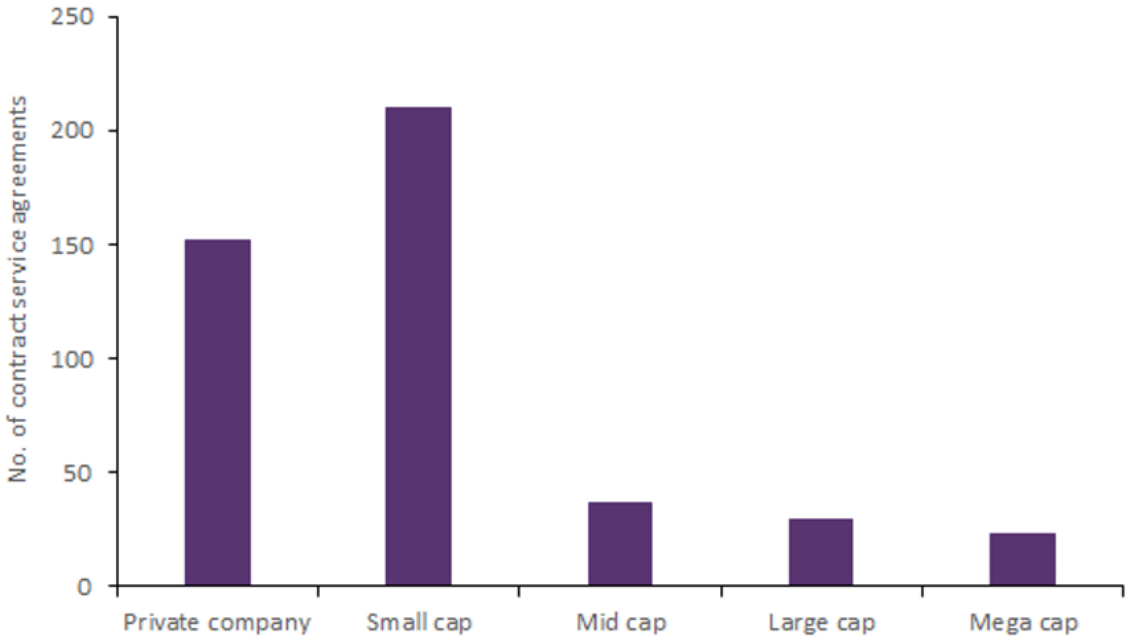
For the NME products approved in 2019, outsourcing relationships for dose manufacturing were spread among a limited number of CMOs. Pharma giants Patheon (owned by Thermo Fisher Scientific) and Catalent topped the list with nine and seven contracts, respectively. Across all contract manufacturing agreements between January 2018 and March 2020, the largest number of contract manufacturing agreements were signed by CMOs Catalent, Lonza, and Patheon. These figures are based on disclosed contract manufacturing agreements from public sources, but it is important to note that not every manufacturing relationship is publicly disclosed. A large number of agreements are concentrated among a small number of CMOs because they have established a reputation for high quality and a wide range of capabilities with the few companies that have the money to afford them.

High Market Caps Spell Low Outsourcing Rates

In keeping with the lower overall approval rates, fewer NDAs were dose manufactured by contractors in 2019, much lower than the 2014–2018 average. The number of NDA approvals was particularly high for mega cap companies in 2019. This trend is potentially detrimental to CMOs, given that their clients are more likely to be smaller companies that are unable to invest in their own facilities or enhance their own capabilities.

Small cap companies offer CMOs the highest probability of business. Between 2010 and 2019, 79% of NMEs and 67% of non-NME NDAs that were sponsored by small cap pharma companies had their dose form manufacturing outsourced. NME approvals from small cap sponsors in 2019 had their dose manufacture outsourced for 89% of products, showing a strong dependence on dose CMOs. The number of contract service agreements increased for pipeline (discovery, preclinical, or clinical stage) drugs during 2018–2019 and small cap sponsors provided a substantial number of those agreements.

Figure 1: Contract Service Agreements by Sponsor Market Cap, 2018–2020



Source: GlobalData Pharmaceutical Intelligence Center Deals Database (Accessed April 15, 2020) © 2020 GlobalData Plc.

Note: small cap = market capitalization of less than $2B; mid cap = market capitalization of $2–10B; large cap = market capitalization of $10–100B; mega cap = market capitalization of more than $100B

Figure 1 shows that the likelihood of a publicly owned pharma company outsourcing its manufacturing is inversely proportional to its market cap size. Small cap companies have traditionally outsourced their drugs' production more than other companies due to a lack of funds necessary to build or acquire manufacturing facilities. Mega cap companies often have a larger portfolio of marketed and pipeline drugs than their smaller counterparts, but are more likely to invest in their own internal manufacturing capabilities. Mega and large cap companies often use contractors to manufacture multiple pipeline products at a clinical scale, providing CMOs with opportunities.

COVID-19 Raises CMO Costs but Brings Manufacturing Opportunities

IIn the short term, the COVID-19 pandemic is changing the types of drugs being approved by the FDA and the environment that CMOs operate in, given the industry's focus on developing treatments and vaccines for COVID-19. From June to August 2020, the industry has reported 24 COVID-19 vaccine-related contract service agreements (GlobalData, 2020b). Once effective COVID -19 vaccines or antivirals are approved and distributed globally, non-COVID related pipeline drugs and market approvals will eventually return to previous levels.

The pandemic has also affected clinical trials, with the greatest proportion of disrupted trials being in oncology (GlobalData,

2020d). Pharma companies have also been impacted, with pharmaceutical professionals stating that employee safety and supply chain disruption are their top COVID-19-related concerns (GlobalData, 2020c).

A number of small pharma companies took Paycheck Protection Program (PPP) loans from the US government, which is an indicator that the current crisis may affect how much funding business CMOs can secure, especially from regular small cap sponsors (GlobalData, 2020f).

The FDA has had to reassign staff to support the increased workload caused by COVID-19-related new drug filings. Since the pandemic began, the FDA has focused on COVID-related drug approvals. GlobalData expects to see fewer market approvals than were expected and therefore fewer contract service agreement activity for non-infectious disease drugs in the short-term due to the changes caused by the pandemic. The drug pipeline for COVID-19 has led to many clinical manufacturing projects for CMOs this year, as pharma companies try to accelerate these drugs into being approved.

Advanced Technologies Drive CMO Demand

Increasingly complex and niche products requiring special technologies increase the need for CMOs, especially for small cap companies that lack the ability to develop their own manufacturing capabilities or the expertise to cope with changing demands.

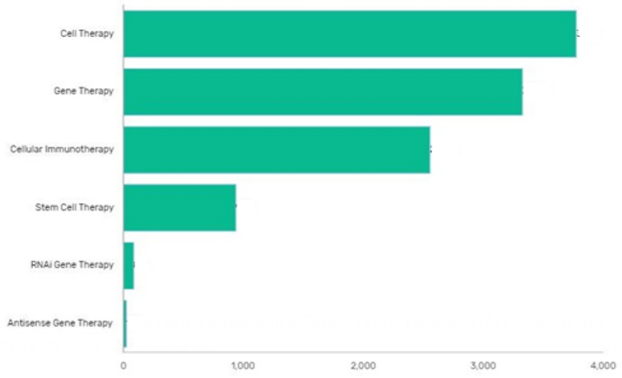
The outsourcing propensity of NME approvals requiring solubility enhancements was relatively high during 2017–2019, and most molecules in development have solubility challenges. The number of marketed products requiring solubility enhancement is likely to increase over time. CDMOs with the greatest range of solubility enhancement tools can expect a great deal of opportunity over the next few years from innovative small molecule drug contracts.

Recently, much interest has also been shown in gene and cell therapies. Accordingly, the top CMOs for NMEs are preparing for the future by investing in complex technologies. Thermo Fisher Scientific opened a $90M viral vector manufacturing site in Lexington, Massachusetts in December 2019, and acquired Brammer Bio (Patheon Viral Vector Services) for $1.7B in the same year, thus significantly enhancing its advanced biologic capabilities.

Catalent has also improved its biologic manufacturing capability through its February 2020 acquisition of MaSTherCell Global for $315M and its May 2019 acquisition of Paragon Bioservices for $1.2B. Additionally, Catalent acquired Bristol-Myers Squibb's oral solid, biologics, and sterile product manufacturing and packaging facility in Anagni, Italy in January 2020.

Figure 2 shows that there are a large number of cell and gene therapies in development. These products will form a future wave of marketed therapies requiring larger scale manufacturing. Bottlenecks, especially in viral vector manufacturing and slow processing, will limit the wide-scale commercial manufacture of advanced therapy medicinal products. This capacity crunch will lead to significant demand for related services. CMOs should be investing in cell and gene therapy manufacturing now to meet future demand, although only the largest CMOs will be able to afford to gain these capabilities.

Figure 2: Advanced Therapy Medicinal Products in the Pipeline



Note: Pipeline drugs are in Discovery, Preclinical, IND/CTA Filed, Phase 0, Phase I, Phase II, Phase III, and Pre-Registration stages.

FDA approvals requiring special handling have generally increased over the last few years. This trend bodes well for CMOs, as the regulations for associated facilities can be onerous and out of reach for small and mid-sized companies. As molecules become more complex, future production will require enhanced technologies for the expression, development, and manufacture of these molecules..

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Flurry of Outsourcing Deals as Bio/ Pharma Views Manufacturing as Greatest COVID-19 Vaccine Hurdle

Introduction

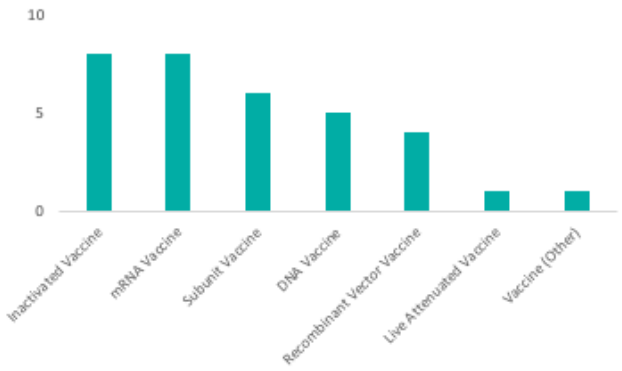
As the pharma industry scrambles to develop one or more viable COVID-19 vaccines, the greatest hurdle to immunizing the world's population is the manufacture of billions of doses in parallel. The time pressure to end the pandemic means that we must prepare for commercial-scale manufacturing now, even though the vaccine candidates use many different, incompatible production platforms and there is no clear winner yet.

In response to this challenge, vaccine developers are signing an unusual number of outsourcing agreements with contract manufacturing organizations (CMOs) and other service providers. In 2018 and 2019, oncology drugs were the most popular therapy for contract manufacturing agreements, but this has flipped to infectious disease in 2020 as a result of the pandemic. Meanwhile, governments and NGOs recognise the scale of the manufacturing challenge and are spending billions to fund scale-up of production, even before a vaccine has hit the market.

There are 380 vaccines in development for COVID-19, of which 32 are in Phase II or Phase III clinical development. Only one has regulatory approval: Russia's home-grown Gam-COVID-Vac recombinant vector vaccine is approved in Russia.

The majority of these late-stage candidates are inactivated vaccines, or use messenger RNA (mRNA) or DNA technology. To date, no mRNA vaccines have been approved; bio/pharma company Moderna and a collaboration between BioNTech and Pfizer are furthest in development with this platform. In theory, these vaccines can be manufactured more quickly than traditional platforms.

Figure 1: Highest Development COVID-19 Vaccines by Molecule Type
Source: GlobalData Pharma Intelligence Center Drugs Database © GlobalData Plc.
Notes: Includes vaccines whose highest phase is Phase II or Phase III development, or marketed as of October 1 2020.



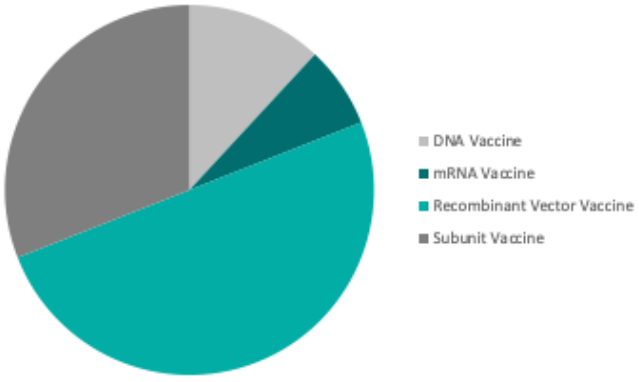
Unprecedented Outsourcing

COVID-19 vaccine developers are signing contract service agreements at an unprecedented rate for a novel indication. Consequently, infectious disease drugs have already overtaken perpetual leader oncology as the year's top therapy area for contract manufacturing service agreements.

Pharma companies have publicly revealed 42 contract manufacturing service agreements for 26 unique pipeline COVID-19 vaccines, according to the GlobalData Pharma Intelligence Center.

Both small Biotechs with early-stage vaccine candidates and larger companies with late-stage products rely on outsourcing to contract manufacturing organizations (CMOs). The smaller companies lack manufacturing capabilities, so have no choice but to use external suppliers, and even the largest companies require extra resources to produce the billions of doses needed should their candidate be approved. Vaccine sponsors as large as AstraZeneca and Johnson & Johnson are using CMOs for their pipeline vaccines.

Figure 2: COVID-19 Vaccine Contract Manufacturing Service Agreements by Molecule Type



Source: GlobalData Pharma Intelligence Center © GlobalData Plc.

Most contract manufacturing service agreements are for recombinant vector vaccines, followed by subunit vaccines. This is despite the fact mRNA vaccines dominate the top COVID-19 vaccines. There are few mRNA outsourcing agreements relative to the number of mRNA candidates because of the novelty of this unproven technology. Few CMOs have the capability to produce active pharmaceutical ingredients (APIs) for mRNA vaccines, not least because they are unique and patented. For dose manufacturing of COVID-19 mRNA vaccines, sponsor companies are opting to partner with manufacturers rather than outsource to CMOs.

Vaccine developers are choosing CMOs close to home for their COVID-19 vaccine manufacturing: the US, UK, and Germany are the most popular supplier locations. These supply chains contrast with the general trend within the pharma industry to outsource production to China and India, especially for low-cost, high-volume orders and generics.

Figure 3: COVID-19 Vaccine Candidate Contract Manufacturing Service Agreements by Facility Geography

Source: GlobalData Pharma Intelligence Center © GlobalData Plc.

The vaccine candidate with the most manufacturing agreements is AstraZeneca's AZD-1222, a recombinant vector vaccine in Phase III development. Trials of the vaccine were suspended worldwide in September due to a suspected adverse event in one patient but have now resumed in the UK. The drug has manufacturing agreements with 12 service providers including major players Catalent, Emergent BioSolutions, and Novasep, as well as pharma company Merck KGaA which is performing excess capacity manufacturing.

The CMOs benefiting most from COVID-19 vaccine development so far are Emergent BioSolutions and Catalent, which each have four manufacturing deals, including with AstraZeneca and Johnson & Johnson, but the real winners will emerge when the major markets grant regulatory approval.

Large pharma companies are also investing in captive capacity. Pfizer plans to manufacture millions of doses

of BNT162, the COVID-19 vaccine it is developing with BioNTech "at risk" by the end of 2020, and hundreds of millions of doses in 2021. The vaccine will be made at Pfizer's sites in Massachusetts, Missouri, and Michigan. Pfizer is pushing many of its internally manufactured drugs out to CMOs to free up space.

Billions of Dollars for Billions of Doses

Several governmental schemes are attempting to advance vaccine development and manufacturing through advance funding.

In the US, "Operation Warp Speed" is a $10B initiative funded by the federal government with significant military involvement to support the production of 300 million COVID-19 vaccine doses by early 2021. Nine candidates have been chosen to date.

Operation Warp Speed's timeline for the production of such a high number of vaccine doses with candidates only in Phase I or Phase II trials is very optimistic, given that vaccine developments have required a minimum of five years in the past. The initiative picked seasoned vaccine developers, which is a logical approach, however it did not explain the criteria behind its choices. Most candidates are not manufactured using traditional approaches, like inactivated or subunit vaccines. Instead, two vaccines use mRNA technology.

On August 5, the federal government announced $1 billion in funding for Johnson & Johnson's (Janssen) vaccine candidate. On August 11, the government granted up to $1.5 billion for Moderna's candidate.

Over in Europe, the European Commission has launched a €2.7B ($3.22B) Emergency Support Instrument (ESI); one of its tasks is to fund manufacturing costs through advance purchase agreements with individual vaccine companies on behalf of EU countries. In return for the right to buy a specified number of vaccine doses in a given timeframe and at a given price, part of the upfront costs faced by vaccine producers will be financed from the ESI. The ESI has been more reticent than Warp Speed about its picks, but signed its first agreement on August 14 to purchase 300-400 million doses of AstraZeneca's vaccine. It is also in talks with Sanofi-GSK and Johnson & Johnson.

The UK has rejected the EU's scheme and has signed separate deals with GlaxoSmithKline, Sanofi Pasteur, BioNTech/Pfizer, and Valneva. Japan is planning to order 521 million vaccine doses by 2021 (for a population a quarter of that size) and has struck deals with AstraZeneca, Pfizer/BioNTech, and Shionogi, which is developing a discovery-stage unnamed vaccine.

Separately, the World Health Organization (WHO), the GAVI vaccines alliance, and the Coalition for Epidemic Preparedness Innovations (CEPI) are running COVAX, a procurement scheme for high-, middle-, and low-income countries. So far, 156 countries including the EU and Japan have signed up, but the US and China have not joined the alliance. Higher income countries will pay upfront by October 9 to reserve their doses; these funds will pay for manufacturing scale-up. Nine candidate vaccines are currently being supported by CEPI with the aim of at least three viable vaccines. COVAX next plans to start signing formal agreements with vaccine manufacturers and sponsors to secure 2bn doses by the end of 2021.

Table 1: US Operation Warp Speed and EU Emergency Support Instrument COVID-19 Vaccine Candidates

Drug Name	Company Name	Development Stage	Molecule Type	Operation Warp Speed/ EU Emergency Support Instrument (ESI) Choices
AZD-1222	AstraZeneca Plc	Phase III	Recombinant Vector Vaccine	Warp Speed; ESI
BNT-162b1	BioNTech SE	Phase III	mRNA Vaccine	Warp Speed
BNT-162b2	BioNTech SE	Phase III	mRNA Vaccine	Warp Speed; Under Discussion for ESI
mRNA-1273	Moderna Inc	Phase III	mRNA Vaccine	Warp Speed; Under Discussion for ESI
BNT-162a1	BioNTech SE	Phase II	mRNA Vaccine	Warp Speed
BNT-162c2	BioNTech SE	Phase II	mRNA Vaccine	Warp Speed
COVID-19 vaccine	Sanofi	Phase II	Subunit Vaccine	Warp Speed; Under Discussion for ESI
INO-4800	Inovio Pharmaceuticals Inc	Phase I	DNA Vaccine	Warp Speed
JNJ-78436735	Johnson & Johnson	Phase II	Recombinant Vector Vaccine	Warp Speed; Under Discussion for ESI
NVX-CoV2373	Novavax Inc	Phase II	Subunit Vaccine	Warp Speed
CV-07050101	Curevac AG	Phase I	mRNA Vaccine	Under Discussion for ESI
COVID-19 vaccine	ImmunityBio Inc	IND/CTA Filed	Recombinant Vector Vaccine	Warp Speed
COVID-19 vaccine	Vaxart Inc	IND/CTA Filed	Recombinant Vector Vaccine	Warp Speed

Source: GlobalData Pharma Intelligence Center

CPhI insights

Part 5.

Potential macro supply chain geo-realignments post COVID

informa markets

PANEL MEMBER
Girish Malhotra, President at EPCOT International

A road map for driving pharmaceutical manufacturing back to the USA by 2025

Introduction

There is a saying that thundering clouds seldom rain. Does this apply to pharmaceutical manufacturing coming back to USA, especially for the generic and essential drugs is anyone's wild guess? But it seems that this proverb could become a fact.

In this perspective, an attempt is made to outline what has happened in the last ten years of drug shortages, high prices and the ongoing rumble of 'bring manufacturing home'. Perspective presented in my own and devoid of any financial relationship with any profit or non-profit making entity.

History:

The faint, but increasing rumble of the last few years to bring manufacturing home and improve affordability has picked up again with the arrival of COVID-19.

A Presidential executive order was issued on August 6, 2020. Per this Executive Order, the FDA is now tasked with enlightening us on a pathway and plans to remedy the drug shortage and bring pharma manufacturing home to the US. Yet this design forces me to recap on the futile efforts that have been made by earlier US administrations [2] and the FDA [3, 4, 5], which have not resulted in any meaningful change. The regulator has been proposing, for some time now, that the use of advanced technologies [6] will also reduce shortages. But companies should be the ones selecting and evaluating technology rather than a regulatory body, which has no commercial experience.

Thus, the possibility of something meaningful coming from the August 2020 Executive Order [1], if we use results of earlier attempts as a benchmark [2, 3, 4, 5], are going to be minimal to none.

The primary underlying reason for shortages and high prices are PROFITS. Yes, profits are a necessity for any company to be in business. But my conjecture is that the pharmacy benefit managers [7] (PBMs) have total control of US drug supply chain and they prevent any meaningful competition. Remarkably – perhaps outrageously – as a result of their massive turnovers they make up four of the top ten Fortune 500 companies [8]. To give an idea of what we are dealing with. A company as large, influential and groundbreaking in its supply chain innovation as Amazon has tried and failed to break the PBM juggernaut - twice.

Their 1999 investment in drugstore.com failed to disrupt the prescription drug business [9], and Amazon's second attempt buying PillPack [10] has not yet made a visible impact.

PBMs negotiate buying and selling prices to maximize their profits. They are uninterested in a manufacturers or seller's profits, instead PBMs push the manufacturers to sell at the lowest price. If the manufacturers cannot make their desirable profit they don't make the product and shortages result. This suggests, at least to me, patients exist in the PBM supply chain just as a medium to make profit.

Another puzzle is "Formulary Lists" (11). They complicate the landscape. Why are they needed and what value do they have especially when FDA has approved a drug and checked its efficacy? Drugs should be available to the patient and if it is higher priced, then competition will readdress their availability. So the addition of drug on the Formulary list to me suggests it is effectively used by the PBMs as a bargaining tool to drive their purchasing price down and improve their own profits. Once this happens there are no checks and balances on the selling price. Since US population pays a co-pay amount, it is fascinating that no one in US prescriptively – excuse the pun – knows the real price of drugs.

What would it take to bring pharma manufacturing home?

Reviewing the timelines outlined in the recent Executive Order [1] very high and precise expectations are laid out. However, my own perspective is that FDA does not have enough experienced manpower to assess manufacturing, technologies needed, supply chain, economics, process development, design and commercial needs. Unless a very capable team with proven expertise is assembled, their feet are held to the fire and a concerted effort is made, it is possible the Essential Drug Shortage conversation may be repeated again after two or five years. This team could work under FDA's umbrella, but vested interest influence has to be avoided. The reason for this is that after multiple attempts the United States has made no visible progress [2, 3, 4, 5, 6], and no one wants to take responsibility for drug shortages, quality or high prices [11].

My conjecture is that PBMs do not want manufacturing to come home, as profits remain a major stumbling block. If drugs are manufactured in US, PBMs and supply chain conglomerates will have to raise their prices to retain profits. This means the patient's prices will go up, making drugs unaffordable. To counter this price hike, there will be legislative pressure and a tug of war will ensue, which could result in higher shortages, quite contrary to the very goal of reducing shortages.

Landscape:

The WTO and TRIPS agreements (13) in 2006 essentially changed the landscape completely. It is well known that most of the active pharmaceutical ingredients (API) and their formulations are now produced outside USA. China and India produce the majority of the APIs used for the generic drugs used in US. In addition, most the raw materials that are needed for the API manufacturing have also moved overseas. Companies from China and India capitalized and fulfilled the developed country pharma needs. PBMs profited from low-priced drugs supplies. These facts are not only important, but critical. We in the United States have ignored and failed even with repeated warning signs and suggested proposals to pay attention [14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24].

Obstacles that need to be overcome:

Like with any task that needs to be improved, one has to understand the landscape and obstacle creators. On the US pharma landscape PBMs (pharmacy benefit managers) are the middlemen between drug manufacturer and the pharmacies [7]. In US, except for about 8.5%, the population (employer or government provided and individual) is covered by some kind of healthcare insurance. About ~92% of the population is covered by mutually subsidized healthcare system and no one knows the exact price of drugs. But we do know that prices in the United States are substantially higher than rest of the world (15) and are continually rising [25, 26] – but despite this we see ongoing shortages. COVID-19 amongst its waves of effects has exposed vulnerabilities of the US drug supply chain. A Presidential Executive order is asking now to remedy the situation, but the question that needs addressing is: "do the people entrusted with the job cohesively understand and are capable of doing what all is needed".

My conjecture is that FDA personnel do not have the expertise to identify the candidates, the right manufacturing technologies, processing equipment, sites, process economics, environmental compliance, raw material supply chain. They are regulations experts. Thus, the expectations of the Executive Order [1] will most likely not be met. Another obstacle will be compliance with FDA's cGMP regulations and its arcane outdated rules and regulations that are over ten years old. Maybe it is an opportunity to update the filing and review processes which could reduce approval process and ensue competition (23, 24).

Challenges:

It is expected that by bringing pharma manufacturing home generic drug prices will be lower and reduce/ eliminate shortages. On the contrary PBMs in order to retain their profits will need to raise their selling prices. This is due to higher US operating costs. But this could be countered with better methods and technologies, yet even in this case the likelihood of lower costs being passed on to patients is low. Most likely shortages and prices will go up and this will be counter the very purpose of the Executive order.

An argument could be also made that US should produce the raw materials for the API and excipients and it is a valid argument. However, the economies of scale, for companies in the United States, do not exist to be able to really rely on domestic market sales. Thus, dependence on imported raw materials like imported APIs and excipients will be still be there, it has after all rightly or wrongly moved overseas for a reason.

The good news about financial incentives [23], improved generic drug applications submission, and faster approval process [27] is that they would bring pharmaceutical manufacturing home. But for streamlining and implementation it could take as much as five years or more. And, the US is at a strategic disadvantage. Many of the vested interest groups and that includes PBMs, legislators, regulators, pharma lobbyists – which includes pharma companies and consultants – could or will attempt to impede the process of bringing pharma manufacturing (API and/or finished dosage form) home. If any of the pharma manufacturing has been brought home by 2023-2024 or earlier, it will be a significant achievement, but all or more of the following has to happen first.

Task force team:

A team that has proven expertise of chemistry, process engineering, economics, supply chain, regulations (environment and drug manufacturing) and construction of green field or revamping brown field operations is needed. Basically, we need to explore creating plants (existing or grass root) from scratch with efficiencies as

their core drivers with NO interference from the vested interests.

- Products have to be defined and their processes tested in laboratory. Process simplification might require selection of appropriate equipment. Parameters and methods that will produce quality products from the get and all the time will have to be tested, approved and used.
- Raw materials that will be used have to be sourced and tested. Buyer/supplier relationships will have to established.
- Sites and the equipment will have to be modified if necessary and tested.
- FDA, once it has approved the manufacturing methods, processes and product quality, needs to minimize its interference.

Landscape Change:

For the pharmaceutical manufacturing to come back to USA, the current landscape has to be revised and overhauled. The following needs to be considered.

- US Congress and the Legislator has to create four or five pharmaceutical manufacturing hubs (call it economic hubs) evenly distributed around the country where the pharma companies will have financial tax incentives for a limited time (e.g. ten years) to produce the drugs needed by the US population. API and formulation excipients will be US produced [24]. These companies cannot be subsidiary of any foreign entity.
- Companies located in these pharmaceutical hubs would be able to sell and distribute the drugs directly to patients [14]. Current PBMs can participate in the drug distribution but their selling prices would be available to patients so they can make a choice.
- FDA regulations and approval processes will have to be revamped [28,29] so that the necessary approvals instead of the current generic drug approval time of 36-48 months from filing date has to be done in 90 days. This will be give companies participating in the manufacturing hubs incentive to get to the market quickly and brew competition on quality and price. Such a revamp will reduce regulatory costs. There will be very high resistance from many vested groups for such change.
- Since the drugs are approved by the FDA, every approved drug has to be available to patients. Thus, the need for different formularies has to evaluated. They could be considered hinderance to free competition.
- Companies instead of receiving 483 citations for cGMP variances would be barred from producing and selling less than quality drug for four years [20]. Currently PBMs and their supply chain partners have never been held accountable for the less than quality drugs that get distributed. They have to be held accountable [20].
- FDA and equipment vendors and manufacturers should refrain from suggesting which technology and how to use them. It should be the responsibility of the manufacturing company to select the best and most economic technology for the product. FDA as stated above also has to revamp its processes so that manufacturing companies have incentive to use the best technologies and manufacturing processes as long as the drug performance is not compromised.
- Establishment of a governing body that is independent of the FDA, which samples drugs sold in the US market and tests them for quality. They will have the oversight for continued manufacturing if companies meet established product quality. Companies would be publicly recognized for continued product quality.
- Along with the above any company exporting pharmaceuticals into the United States will have to comply with US environmental, health and safety or equivalent standards. Laws similar [30] to US laws could be set under World Trade Organization or a similar trade body.

All of the above calls for a re-configuration of the current landscape. There will be significant resistance but the right team will make the plan to "Make drugs in USA" very feasible and plausible. It is national security and strategic need. Task at hand is not easy. If it was, we would not be discussing this. This can be achieved in the next five years if a concerted effort and plans are established.

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PANEL MEMBERs
Manni Kantipudi, CEO at GVK Bio
Ramesh Subramanian, Chief Commercial Officer at GVK Bio

Is 2020 India's inflection point to build global leadership in outsourcing of innovative medicines?

Introduction

The pharmaceutical industry has adapted extremely well so far to the challenges of COVID-19, with the supply chains showing a great deal of resiliency in spite of global lockdowns and the ensuing logistical challenges. What the pandemic has done, however, is highlight the desire for greater geographic diversity in the global supply chain, to reduce risk and reliance on few countries for a majority of ingredients, discovery and chemistry services, and/or development and manufacturing. Looking at holistically these macro changes will potentially see a 'redrawing' of supply chains with a number of countries benefitting. As a global pharmaceutical hub, India is synonymous with generics manufacturing and vaccines – an obviously immediate boom area – but is potentially at seismic moment as its reputational and scale in development and chemistry services accelerates. In these review of recent developments for Indian pharma CPhI India sat down Manni Kantipudi, CEO at GVK Bio and Ramesh Subramanian, Chief Commercial Officer at GVK Bio. Together, they look at India's historical provenance, current opportunities and how COVID-19 might accelerate growth in the country for high value CRO and CDMO development services to both western pharma and biotech innovators.

MK = Manni Kantipudi
RS = Ramesh Subramanian

Q) Could you give us an overview of the Indian pharma industry as a whole?

MK: We can split the Indian pharma industry into four (broad) main categories. The first key area is in the manufacturing of products, including generics, APIs and formulations – and this market is around $30bn dollars. Then there are vaccines, which India is a big player in globally with – in fact, the Serum Institute of India remains the world's largest producer by volume of does. Then you have medical devices, where India is starting to realise, they should invest in this space and become more self-reliant. And finally, you have pharmaceutical services - this

is category is where we (GVK Bio) fall under. Currently the Indian pharma industry is worth around $45bn, and we expect this to be worth $70bn by 2025, which in itself shows fairly sizable growth. Breaking this down into volumes we see about 60% of vaccine units in the world are made in India, and about a third of generics prescribed in the US are made in India. In fact, more than 110 countries in the world receive medicines from India. One area we will see the country as whole to try and improve its output is in medical devices where we still import some 86%, and additionally there was a huge reliance on other countries for PPE during the pandemic.

In response the government has now taken on a number of initiatives to become self-reliant on the provision of medical devices. Additionally, with the large generics industry here, there has been a realisation that with 80% of ingredients imported that this needed to be addressed also, and now we have seen considerable Government incentives to buy domestic APIs, and build new ingredients sites here in India.

Q) It is fair to say it is currently an exciting time for Indian pharma right now, in spite of the pandemic?

MK: I think so. It seems like the industry is growing, and very well set for continued growth. If you look at the Indian pharma stock market index for example, you can see that pharma has done extremely well in the last three months. Lots of the anti-retroviral and anti-bacterial drugs are being made in India and naturally there has been a big increase in demand. If you look at 2020 first quarter results here – which for India is April-June – you are seeing notably improvements with excellent revenue increases.

Q) The global pharma supply chain has remained relatively robust in the face of the pandemic. And we know that a lot of manufacturing work was still being done in India throughout the pandemic. Could you give us an overview of this, including any initiatives that have been put in place?

MK: Just like any other country we were initially in lockdown, but the government quickly identified the pharmaceutical industry as an essential service. The industry responded in kind and the country has manufactured throughout the pandemic, not just for India but patients around the world. There were logistical challenges at the start of the pandemic, but much of the country's output is pretty much back to normal levels. I hear there are still some challenges with supplying into Africa, but supply chains into North America and Europe has continued to see tremendous resilience.

Q) The pandemic has particularly helped recover the reputation of pharma in the public eye and it has really come front and centre in the last few month. Could you discuss the impact of the pandemic and other macroeconomic changes we have seen in the last few years are having on the global supply chain. Similarly, what this may mean for companies in India?

RS: In the sense that there is now more public awareness regarding the good work that we do, the pandemic has certainly been positive for the industry as a whole. In terms of the macro-economic context and what this now means, let me start with some background. There has been great biotech funding in the last few years. From 2005 – 2009, biotech funding was on average $25bn per year, but from 2016 – 2020, the funding level have risen to $53bn. Where we had 2000 companies from 2008 with what we call an active pipeline, right now we have 4300, over

double the level from 2008. Similarly, in terms IPOs that came from biotechs this year, many were oversubscribed. Ultimately, this means the outsourcing of chemistry services, development and commercial production is rising in parallel.

But this growth in interest is now being augmented by wider macroeconomic shifts that Indian pharma has benefitted from, particularly the services industry. The growing tensions and subsequent trade war between the US and China has increased the desire for geo-diversity within the supply chain. Additionally, the cost structure in India and China has also diverged – China has become more expensive to outsource to. Alongside this China's pharma economy is shifting towards one that is driven by innovation as well as services, so there are many companies actively discovering and developing their own therapies there now. Meanwhile, India has maintained its more singular focus on building its pharma services. So taking this all into account, we are seeing companies – particularly those in the West – looking to diversify their supply chains, and India will definitely benefit from this. What the pandemic has done however is accelerate these global changes. On the discovery side of things there has been an immediate impact, because the need for geo-diversity has been immediate. From our experience at GVK Bio, many of our partners have shut down due to COVID and were therefore completely dependent on partners like us to continue working, providing them with compounds and with the data. We have been developing compounds on a weekly basis and getting them back to our customers. However, on the development and manufacturing side of things, the impact has been more muted, because lead times for manufacturing are a lot higher, either 4 – 6 months or 6 – 8 months long. But the want for diversification is still there and companies are waiting for the pandemic to settle down before looking to diversify. This side of pharma is also more regulated, and a lack of client audits, which are not presently possible due to travel restrictions, have temporarily slowed this shift. But we fully expect the manufacturing side of things to follow the discovery side in terms of geo-diversification over the curse of this year and its huge opportunity for pharma manufacturing in India.

Q) And what about the role between big pharma and biotechs? If the number of companies with innovative pipelines has roughly doubled in the past 10 – 15 years, then surely that implies there will be a growing need for outsourcing in the future?

RS: This is certainly the case. If we look at the statistics again, 24% of approvals in 2014 were from biotechs. But it is estimated that this percentage will increase to 47% by 2022. The biotech pipeline is also significant: 5000 compounds in preclinical stage were coming from biotechs in 2009, but right now there are 8500 from biotechs. So it is clear to see that biotechs are becoming increasingly important in our pharma ecosystem, and there has and will be huge funding in both discovery and late phase development. Venture capitalists are becoming more comfortable with virtual biotechs, where all the discovery and development work is outsourced and done externally. But it should be mentioned that the needs of biotechs are different to those of big pharma. They are young, they don't necessarily have the money to invest in their own IP etc. At GVK Bio we have put in certain processes and systems in place to fulfil the needs of biotechs. The Indian pharma services sector has certainly seen a lot of growth coming from biotechs in recent years and we expect this is increase quickly as the biotechs themselves compete for the best providers to help them develop products.

Q) What about the need for everybody to have supply chain security, whether that be having a second facility or even the same company having facilities in different geographic locations. How is that going to play out for CROs and CDMOs in the future and how might this affect the Indian pharma services sector?

MK: I think innovators globally are rethinking their approach and reliance on one particular supplier and even one particular geography. The pandemic has given everyone time to rethink what is the safest strategy. Consequently, supply chain lines will be redrawn, there will be more happening in the US and in Europe, but there will be companies that are price-sensitive and would still like to outsource to Asia. And, if I go back and reference what has already been said, I think India will benefit greatly due to the macro shifts we have seen. The large pool of resources now available, the good political relations India has with the west, and the fact that as an English-speaking country there are no communication barriers there. So globally India is increasingly competitive and we can do the same quality of work, for an often reduced price and even more rapid timelines.

Q) Finally, where do you think Indian pharma will head in the next 2-3 years?

MK: We expect the well-established Indian generics industry to continue to grow steadily, that is a very much a given. But we are now at an inflection point in 2020, where India might start to play a much, much bigger role in the innovative outsourcing sector. At GVK Bio we have been doing the right things – making the right investments and managing our growth. We have seen a lot of customer interest in our company and as travel restrictions ease, we expect customers to start visiting our facilities to qualify them. But we won't be alone in this and India will see a rapid resurgence in interest. I think our time is coming and the next few years the country will become well established as a global pharmaceutical outsourcing hub well beyond just generics with increased innovative development. It won't happen overnight; a lot of things have to fall in place. But the tailwinds are in the right direction, the government support is absolutely there in the form of initiatives and tax incentives. Most significantly, the confidence is building amongst customers that India is now on path towards becoming a globally focussed, outsourcing industry that advances NCEs and biologics as well as generics.

CPhI insights

Part 6.

Building a sustainable future for pharma

informa markets

PANEL MEMBER
Gregor Anderson, Managing Director at Pharmacentric Solutions

The biggest driver of sustainability change is the increasing collaboration between pharma companies and its suppliers

How is the relationship between pharma and suppliers changing?

Arguably the biggest driver right now is the increasing collaboration we are seeing between pharma companies and suppliers. For starters, sustainability is now on the agenda of every pharma company – they are continuing to take on corporate responsibility initiatives, setting their own sustainability targets and collecting the relevant data to ensure they are meeting these targets. I think that suppliers were previously guessing what pharma companies were looking for in their sustainability planning– the cooperation was a bit disjointed between the two parties, partly because sustainability was not at the top of every company's agenda. But now we are seeing a much greater understanding between pharma companies and suppliers – who are now seen as integral in the strive towards sustainability – and we expect this to expedite the development of more sustainable solutions in packaging and devices.

What significant innovations/improvements are likely to improve pharma's green credentials in 2021? What would the market look like in 2025?

I think that over the next 5 years, Europe will be the leading market in terms of environmental standards and will look to manage waste the most. There are lots of different initiatives coming through. The UK has initiatives coming through on the use of recyclable materials and polymers for single use products that contain a minimum percentage of recycled material to try and encourage their use and discourage using non-recyclable materials and virgin materials when necessary. Unfortunately, many of these recycling schemes have not been budgeted for, so governments will be looking at potential tax revenue streams. France are also trying to remove PVC from packaging, and I'm sure there will be a premium for that. However, I think the US still remains a bit of an unknown quantity, because the national and state level of governing is different, and the level of commitment to

sustainability may not be as well-aligned. What we may see is the consumer look to drive some changes to improve sustainability, with states such as California pushing on with sustainability and recycling initiatives once the immediate priorities of the current global pandemic have been overcome. Another thing to note is that the use of blister packaging in emerging markets is increasing. This is because the medicines need to be protected from the harsher environment found in these countries. Consequently, we'll start to see these nations planning recycling schemes to try counteract waste further ahead in the future, the West will drive more immediate change and emerging markets will follow.

What would the recycling of devices and packaging look like in '21 and '25? Will it be centralised programmes from big companies or will we move towards more standardised materials we can put in bin?

I think that the industry will slowly but surely start to move towards the use of more standardised, recyclable materials in packaging. For example, PVC is commonly used in many types of packaging, notably blisters, but it is not easily recyclable. France have announced that they will stop using PVC in packaging, but the issue there is that it is an excellent, well proven packaging material, and at present is hard to replace with a recyclable material that has the same r properties (including: ease of forming, sealing, and use by patients). It is used in the packaging of historic medicines and patients know how to use the packs already. And despite significant investment in alternative materials, you have to ask, what will be done with all the existing packaging containing PVC? I think that PVC packaging should be kept for the historic medicines that we are familiar with, but pharma companies and material manufacturers should collaborate to develop new, more sustainable packaging for new products coming to market. This could be a lengthy development process, possibly exceeding 2025, simply because it is difficult to break out of the current material and processing infrastructure (that includes stability, transit, extractable and leachable testing etc), , but there is real potential for change there.

Do you think we'll see increased collaboration in recycling– e.g. countries agreeing to certain standards?

We will have to if we are serious about becoming more sustainable. Pharma is such a global industry and I expect there to be a growing sense of harmonisation between the major pharma economies with regards to recycling and sustainability schemes. Because if global pharma markets all agree on adhering to the same 'greener' guidelines and rules, such as say, aiming to become completely PVC-free by 2030, then I feel the markets will be more inclined to try and achieve those targets. It would look bad on those countries who haven't been making a clear effort to adhere to targets that were agreed upon globally. We are seeing a gradual harmonisation of regulatory standards with regards to drug manufacturing between the west and the east, and the ultimate aim there is to accelerate drug approvals worldwide, allowing for medicines to get to all markets faster. So I don't see why we cannot see a similar sense of collaboration and harmonisation with regards to sustainability and recycling, in order for global pharma to become more sustainable more quickly.

How will interoperability of devices affect the market? Could this stifle innovation?

It's not really there yet and we have not really seen much success for connected devices. One of the main challenges is that the people that have the lowest adherence – and they are the ones we are really targeting improvements at – tend to be the ones that won't favour a connected device. Adherence in the elderly is a far bigger problem than the young, but it's asking a lot to have a 70+-year-old using a connected device with a Bluetooth smart phone. But it must be said that some of the elderly population are in fact quite savvy with new technology. So this is where I think you will get a mixture of the newer, digital means of reminding patients to take their medicines, and as well more 'old-school' reminder packaging. In fact, we are currently seeing a lot more medicines being pre-packed and delivered to patients who are currently shielding. The question is, is who will be driving this initiative? I believe the national health providers and insurers will, as they are the ones to benefit most from patients taking their medicines properly. Emerging markets may also eventually adopt the use of connected devices to improve patient adherence, as mobile phones are a lot more widely used than they were say 10 years ago. Solutions will have to be affordable though and accessible

The one product that is out there now in the US that is very interesting is Teva's Digihaler, but it is again expensive and unfortunately it is not easily recyclable (it has a sealed in battery). I am sure lots of pharma companies will be monitoring its progress and seeing how it performs – to see if it's a false dawn or if this is something that might enter the mainstream of devices in the future

In the absence of governments agreeing standards, do you think pharma companies could agree standards amongst themselves

Ultimately that has to be the solution, as individually it's not enough just for the companies, even the biggest of pharma, to work alone. If in the future when developing new products – as obviously no one is going to go back and reverse engineer approved products – they agree to working with maybe a more limited number of materials or standardised materials, that will make a big difference. As would maybe partnering amongst industry on recycling schemes, e.g. for batteries, as the economies of scale would obviously lower the costs of implementing schemes.

How do you see the use of different types of packaging changing by 2025? (i.e. increased or decreased blister packages, bottles, primary, secondary, will we see a convergence back towards blister packaging, how will this change between Europe and the US)

On the positives; new schemes with pharmacies and national health services could be a game changer – once people are start returning to some sort of normality again in big numbers. Coupled with the increase and permanent adoption of telemedicine. We could therefore see better recycling (in pharmacy), but also much adherence. If this was the case, we will have the best of both worlds in the longer term – dual eco benefits of bringing patients in and increase contact at home. This could make a massive difference and be a lasting legacy from COVID-19.

That said, I don't think blister packaging will be going away any time soon. With this type of packaging the emphasis is really on protecting the medicines from degradation. And this is even more so true in emerging markets, where their climates are typically harsher for medicines. What I do think we will see however is more focus on extending the shelf life of medicines in order to decrease the chance of medicines expiring before it reaches the patient. You will be surprised by how much medicine is disposed of due to expiration. I think this is where we will see a bit more

research, looking at extending the shelf life of medicines through re-engineering blister packaging materials,. If we look at bottles, there is definitely a real opportunity to improve sustainability by increasing their usage. They are extremely easy to recycle because they are typically made of a monomer (and caps are easy to separate). Where the problem lies is that the pharma companies or health providers/insurers will have to get them back from patients, as well as make sure that there is no leftover medicine in the bottles. I think this is where increasing patient adherence will help, and as well looking into ways to incentivise patients to return their bottles or recycle them directly.

Is COVID going to aid or hinder green processes and environmental adoptions in the future?

A lot has been moved to the forefront in pharma in response to COVID-19 – namely the development of treatments and vaccines, PPE etc – and as a result things like sustainability have taken a back seat. All you have to do is look at the amount of waste we are producing with regards to PPE to see that there will not be any significant, positive changes in 2020 with regards to sustainability. Looking at the bigger picture, there was initially a lot of noise at the start of the pandemic about the environmental advantages that came out of lockdown, such as reduced carbon emissions through transport and manufacturing. But these levels are now returning to normal?. It is understandable because obviously the priority right now is to continue to manufacture medicines. I think after the pandemic, once we return to some level of normality, sustainability will come back on the agenda. We will be looking at improving efficiency of processes and be more conscious of the amount of materials we use in packaging and devices, and whether these are recyclable or not. Big pharma are still producing packaging, which is either going into landfill or it is incinerated, and typically not recycled. But health providers such as the NHS and health insurers do have sustainability targets, so we will likely start to see increasing levels of collaboration between big pharma and health providers/health insurers after the pandemic to ensure that all these stakeholders meet their sustainability targets.

About CPhI

CPhI drives growth and innovation at every step of the global pharmaceutical supply chain from drug discovery to finished dosage. Through exhibitions, conferences and online communities, CPhI brings together more than 100,000 pharmaceutical professionals each year to network, identify business opportunities and expand the global market. CPhI hosts events in Europe, China, India, Japan, Southeast Asia, Russia, Istanbul and Korea co-located with ICSE for contract services, P-MEC for machinery, equipment & technology, InnoPack for pharmaceutical packaging and BioPh for biopharma. CPhI provides an online buyer & supplier directory at CPhI-Online.com.
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