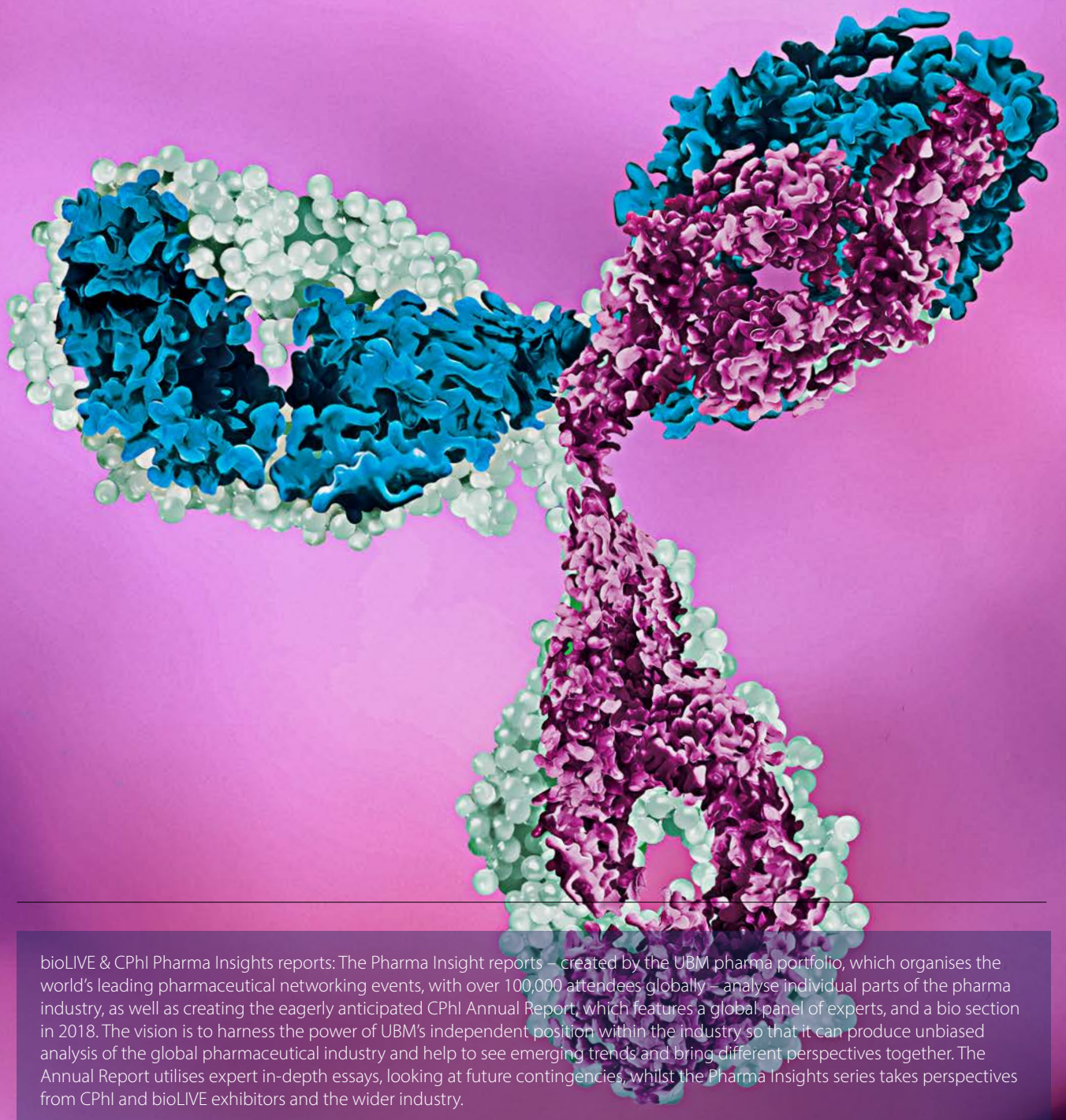
bio LIVE

UBM

Opposites attract

Blurring the lines between small and large molecule manufacturing



bioLIVE & CPhI Pharma Insights reports: The Pharma Insight reports – created by the UBM pharma portfolio, which organises the world's leading pharmaceutical networking events, with over 100,000 attendees globally – analyse individual parts of the pharma industry, as well as creating the eagerly anticipated CPhI Annual Report, which features a global panel of experts, and a bio section in 2018. The vision is to harness the power of UBM's independent position within the industry so that it can produce unbiased analysis of the global pharmaceutical industry and help to see emerging trends and bring different perspectives together. The Annual Report utilises expert in-depth essays, looking at future contingencies, whilst the Pharma Insights series takes perspectives from CPhI and bioLIVE exhibitors and the wider industry.

To get more information on bioLIVE, please visit www.bio.live

The biopharmaceutical industry has grown impressively in recent years, with its global compound growth rate (CAGR) estimated to reach 8.5% between 2018-2023, outstripping traditional New Chemical Entity sectors[1]. Emerging novel drugs show huge therapeutic potential, such as antibody-drug conjugates (ADCs), checkpoint inhibitors and viral gene therapy. But as the industry grows, it may face potential issues securing an expanded supply chain.

Until recently the bio industry's primary focus was to simply get their products to clinic as quickly as possible, with little incentive to focus on product and supply chain efficiency. However, now that the industry is experiencing greater demand and product volumes are increasing – coupled with generics and healthcare reforms – there is an increased desire to explore how overall cost of production can be lowered. It's a mirror image of the small molecule industries maturation some 10 or 20 years earlier. As a result innovators and bio-generic companies are exploring not only how to speed products to market, but also, how they might lower costs in the commercial phase (for which a majority of processes are set earlier in the development cycle).

This whitepaper assesses the current state of the large molecule sector, and how it may be able to learn from the small molecule industry in terms of its supply chain support infrastructure, as well as its acquisition of staff and the adoption of PAT. We also look at what the large molecule industry can offer the small molecule industry in terms of novel technologies currently adopted in biologics. Included here are expert insights across both industries, evaluating just some of the potential benefits that could be enjoyed through further collaboration.

Large biopharma firms now have a greater number of drugs in the pipeline, and with an increased global prevalence of biosimilars, the supply chain will come under increasing pressure. But the industry is still in its relative infancy, and some of the key factors that may allow companies to meet these demands are not yet fully matured.

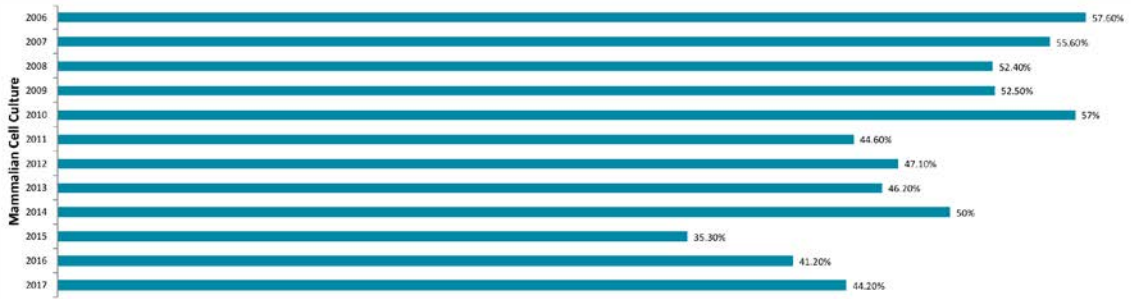
For example, the large molecule industry, according to some experts, has reported issues in terms of a fully supported infrastructure, with an increased need for supplier directories, talent recruitment, and appropriate support and consultancy services.

Additionally, as biologics developers now are more comfortable using outsourcing providers, we are seeing a gradual shift away from performing all production activities in-house. In 2010, according to BioPlan Associates, 57% of biopharma did all of their mammalian bioprocessing in-house, whereas in 2017, only 44.2% undertook all work themselves[2]. This is due in part to many Contract Development and Manufacturing Organisations (CDMOs) developing and investing in the skills and technologies required to make biologic drugs.

Looking ahead, the emerging drug pipeline of advanced and newer drug classes should further fuel outsourcing. BioPlan CEO Eric Langer explained this issue with bioLIVE, putting the best opportunities into context, with newer areas likely to see sizable growth – especially as drug developers become more diverse (i.e. smaller biotechs innovating and not just big pharma with many in-house resources): *"There is going to be a continuing need for uniquely skilled and competent CDMOs in niche, high-value areas. There will be an expanding need for*

1 https://www.mordorintelligence.com/industry-reports/global-biopharmaceuticals-market-industry
2 https://www.pharmoutsourcing.com/Featured-Articles/342564-Outsourcing-Trends-in-Biopharmaceutical-Manufacturing/

Percentage mammalian production undertaken in-house by year



Source: 14th Annual Report and Survey of Biopharmaceutical Manufacturing, BioPlan Associates, Inc. April 2017 www.bioplanassociates.com

competent contract manufacturers as these novel therapies move through the pipeline."

In fact, already, despite the pipeline's infancy, we have seen significant moves by several CDMOs to build facilities for the emerging cell and gene therapies. Paragon, Brammer Bio, Fujifilm, Cobra Bio, WuXi Advanced Therapies and Lonza are amongst a host of earlier adopters – the latter in fact opened the world's largest dedicated cell and gene therapy facility in April[3].

Langer believes that cell therapies could present a key opportunity for CDMOs because the technologies and methods used to make such products are still developing. "Even though there are hundreds of pipeline cell therapy products, and many in clinical trials, the industry continues to evolve. We still have a number of technical and operational issues to be resolved and we do not know what the situation will be in five years' time. For example, whether cell therapy platforms will be mostly based on autologous or allogeneic manufacturing technologies."

For example, the novel CAR-T cell drug Kymriah (tisagenlecleucel), manufactured by Novartis, has recently been approved by the US FDA for a second indication of relapsed or refractory large B-cell lymphoma, after it had previously been approved for acute lymphoblastic leukaemia. However, the main drawback to this potentially ground-breaking drug is its cost, with Kymriah costing around $373,000 – which is still $100,00 less than for its original therapeutic approval. How the industry adopts to bringing more of these diverse therapies into commercial production is key to their viability.

Keith Thompson, CEO of Cell and Gene Therapy Catapult (CGTC), a UK centre set up to help biotechs test their new therapy candidates (without building GMP facilities) said: *"The huge variety observed in cell and gene therapy products translates to a plethora of manufacturing processes trialled, with a diverse range of technologies and scales being explored and developed. This is expected to put a significant strain on current GMP manufacturing infrastructure as not all facilities can accommodate the range of processes"*

Analyst perspective: Fiona Barry, Editor, PharmSource – a GlobalData product

"We expect to see a shift towards outsourcing more cell therapy manufacturing in the near future with the coming wave of cell therapy approvals.

Although there are fewer CMOs in the cell therapy space at the moment than in small molecule pharma or the biologics space, it's clear that cell therapy manufacturing volumes will rise in the next five years as these products move from the clinic, where production is manageable in a lab by PhDs often using repurposed blood banking equipment, to the commercial stage. The industry is going to need to overhaul manufacturing methods and automate to keep up.

This could be an opportunity for CMOs to invest in technology and capacity to help protect cell therapy companies from inefficiency and mistiming capacity building, avoiding the problems Dendreon ran into with Provenge.

In terms of other trends, if you look at the FY 2017 results from public CMOs, there were strong signs of growth in the biologics sector -- Samsung and WuXi had aggregate revenues over $600M, mostly stemming from US customers. Small molecule APIs had a less exciting year but the results were still solid -- all the major participants grew, and the smaller players PCAS and Bachem showed double-digit growth. The finished dose sector saw mostly low growth."

There are clearly parallels with how outsourcing in the small molecule space has contributed to increased manufacturing efficiencies and reducing overall costs. In fact, many solid dose CDMOs now sell their services on enabling technologies for 'difficult to manufacture' compounds. Over the next few years we will likely see a 'technological arms race' amongst outsourcing providers to help increase efficiencies, lower costs and decrease clinical timelines in bio. To take just one example, reducing the cost of protein A

3 https://www.fiercepharma.com/manufacturing/cdmo-giant-lonza-debuts-world-s-biggest-gene-and-cell-therapy-manufacturing-plant

capture step in biomanufacturing is a clear area for potential efficiency improvement.

Another aspect that may increase the amount of work in biologics is the growing complexity of biological products. Biotech firms, especially smaller ones, may have an innovative product or idea, but lack the expertise and technology required to develop, or commercialize it.

The product classes themselves are also becoming increasingly intertwined, as many advanced therapies now contain a small molecules payload, such as in ADCs; whilst in stem cell therapies, molecules are sometimes used to trigger a therapeutic response. That is without even considering the fact that small molecules themselves are growing increasingly large, and peptides are now routinely synthesized rather than fermented. Oligonucleotides are in many ways a new class altogether – not fitting into the definitions of small or large molecule.

As a result, we are seeing an increasing level of limited collaborations across both small and large in recent years - most notably in antibody-drug-conjugates. Many in the industry now believe there are transferrable skills and lessons that can be shared between the two, particularly in areas such as staff, processing and scale-up, as well as regulation.

To produce this whitepaper, we spoke with a number of experts from both small and large molecule fields. One surprising finding was that many of our experts identified API producers as potentially having the most relevant and transferable skills sets. It was argued their experiences are most similar to what a biopharma company is replicating in everyday use. For example, API synthesis is performed in solution, with materials, molecules and reactants emerging over time. Thus, the instruments used for chemical and physical measurements for API production may only need minor alterations to be useful in fermentations. Continuous chromatography, which is beginning to become more common in API work, could also be used in bioprocesses.

Beyond APIs there are potential benefits in exploring overall manufacturing methodologies. Whilst large molecule companies have only recently begun to generate their own optimisation data, the small molecule industry has been around for 50 years, streamlining its supply chain to establish the best practices. Even if their production modes are distinct, there are certainly experiences of the small molecule industry that could pave the way for biopharma's own supply chain to flourish. It is now imperative that these two sister industries share knowledge where there are mutual problems.

Addressing this issue directly, the 15th Annual Survey on Biopharmaceutical Manufacturing Production and Capacity, conducted by BioPlan Associates, asked several questions about the potential integration. The data[4] was collected from 120 industry experts in an attempt to try and pinpoint the exact areas where there could be useful crossover.

The result of the study has shown that the most prominent areas where respondents' believe they could learn from small molecule firms' were:

- Process control: (33%)
- Quality Management (30%)
- Training operators and technicians (29%)

Mike Ultee, Principal, Ulteemit BioConsulting, commenting on these findings, added: "these top three areas are not particularly surprising since they address current good manufacturing process (GMP) practices, which are consistent across both the large and small molecule industries."

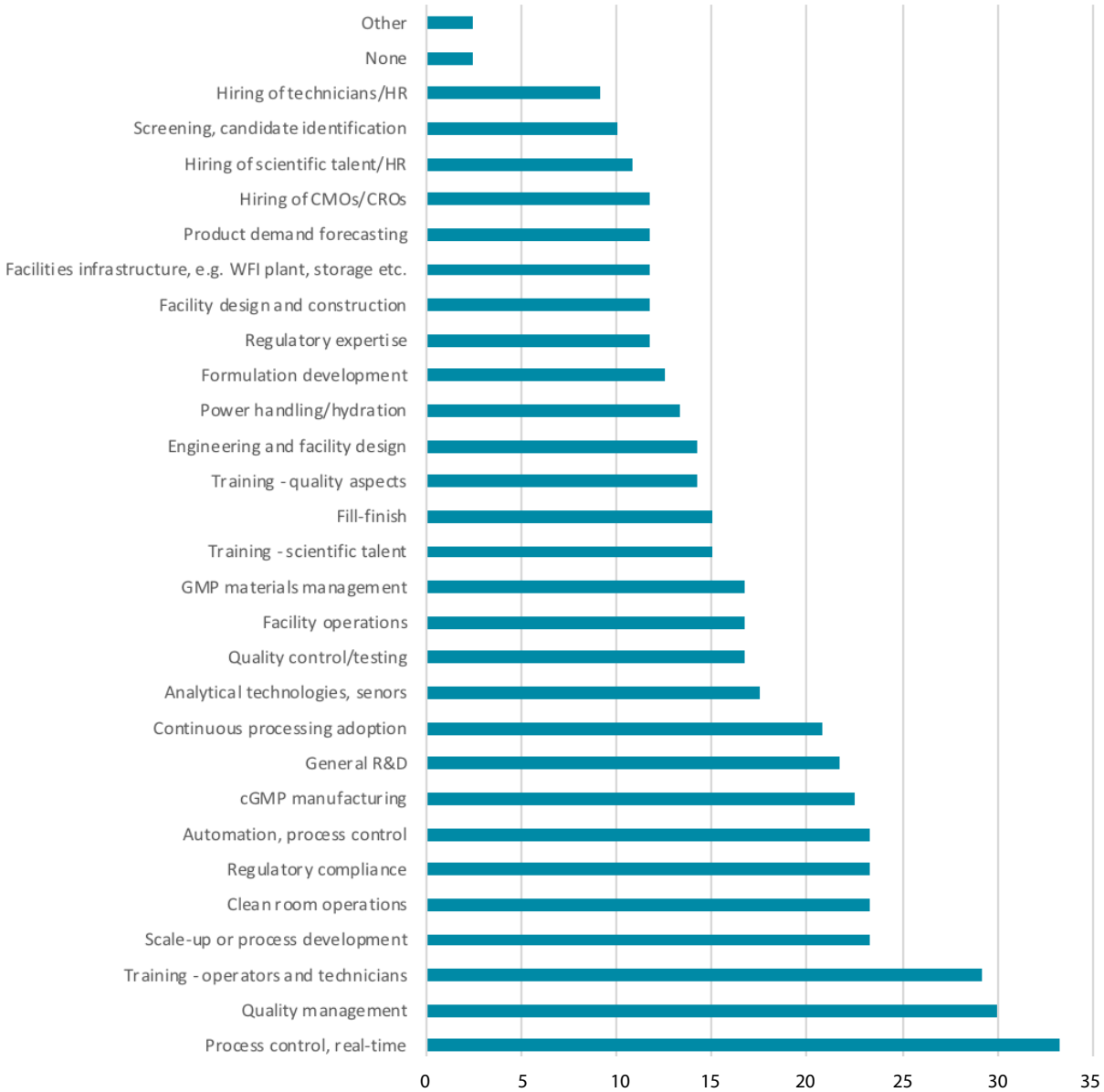
Although the positive response data from biopharmaceutical manufacturers may not appear to be very high, this could be 'due to a lack of familiarity with the level of expertise of technology available to them', – commented CPhI Annual Report Expert Emil Ciurczak of Doramaxx Consulting – 'rather than a firm understanding of the sector and a discounting of its relevance.' He believes that if the question were to be reversed – i.e. asking small molecule experts about the areas where their technology could be of use to the large molecule industry – that the positive responses would be much higher. For example, using Raman or NIRS for incoming raw materials, NIR for residual moisture in lyophilization, NIR or Raman to double-check identity of clinical supplies before sending them to clinics, and, comparing fermentation to API synthesis, monitoring a reaction with NIRS or Raman. Even if final release is by compendial methods, knowing when to sample would be simpler with spectroscopic help.

4 Preliminary data as of March 2018, however the final data is unlikely to show much statistical variation.

Other areas of potential crossover identified in BioPlan's survey include 'scale-up or process development', 'clean room operations', 'regulatory compliance', and 'automation/ process control', where just under a quarter of respondents believed that large molecule manufacturing could benefit from small molecule expertise. This indicates that a collaboration between the two industries could lead to greater production levels, with better quality and at a lower cost. The full data can be found below:

Large molecule manufacturers could also benefit in the future from the use of continuous bioprocessing. Although continuous methodologies have entered the small molecule space and are currently *de rigueur*, biologics has not

In which of the following areas could large molecule manufacturing benefit from small molecule pharma manufacturing expertise? (n=120)



adopted it to the same degree. Experts pointed to the fact that continuous bioprocessing is more difficult due to fermentation processes being one of the key requirements, which are restrictive for time, temperature and other factors. This means the drug formation rate may be limited and not allow for a continuous flow. There are some initial steps being made to adopt this technology, with Pall Life Sciences announcing last year that they would equip a Swiss training facility with resources to teach continuous methods to biomanufacturers. CPhI small molecule expert Girish Malhotra stated that in order to move towards continuous bioprocessing, *"manufacturers will need experienced fermentation masters, chemists and chemical engineers who understand finances, process development, and process simplification values. In order to develop continuous fermentation processes, active production time has to be minimised, much reduced from the current times of hours and days".*

Another area that needs to be addressed for large molecule manufacturers is staffing. There is a widely-acknowledged shortage of specialised biomanufacturing experts, and the concern is that as the industry grows and demand increases, the staff shortage will continue to compound. This may be attributed to the fact that the industry has only recently expanded, and the facilities to educate and train staff have not been able to keep up. It also appears that there is a pattern – that it is more likely that biopharma companies will hire staff with small molecule expertise for certain job roles.

The second question in the BioPlan Associates survey asked: 'what are the most prominent areas that staff were hired with small molecule pharma expertise?' Of the 112 responses, 1 in 4 answered 'scale up', 'process development' or 'engineering & facility design'. These were followed by general R&D, and regulatory compliance. Ultee added: *"'Scale up' reflects basic engineering principles, which are comparable amongst both small and large, and along with 'process development' is a highly-specialised area. The high ranking of these specialised areas may be due to the scarcity in these areas of expertise."*

To address this issue, there are new initiatives with The National Institute for Bioprocessing Research and Training (NIBRT) – an internationally recognised centre for training students to work in the biopharmaceutical industry – a notable example. Speaking in an interview with bioLIVE, Mary Lynne Bercik of the NIBRT discussed the staffing issue: *"Current (bio) employees were too overwhelmed to train new talent, making it hard for new employees to bed in. Successful launches made it seem feasible to push through normal limit, R&D had done what they were asked, creating a successful pipeline. Now it was up to commercial to take it across the finish line, from both a materials and COGS perspective. However, it has become obvious that the lack of skilled workers was beginning to hurt the process."*

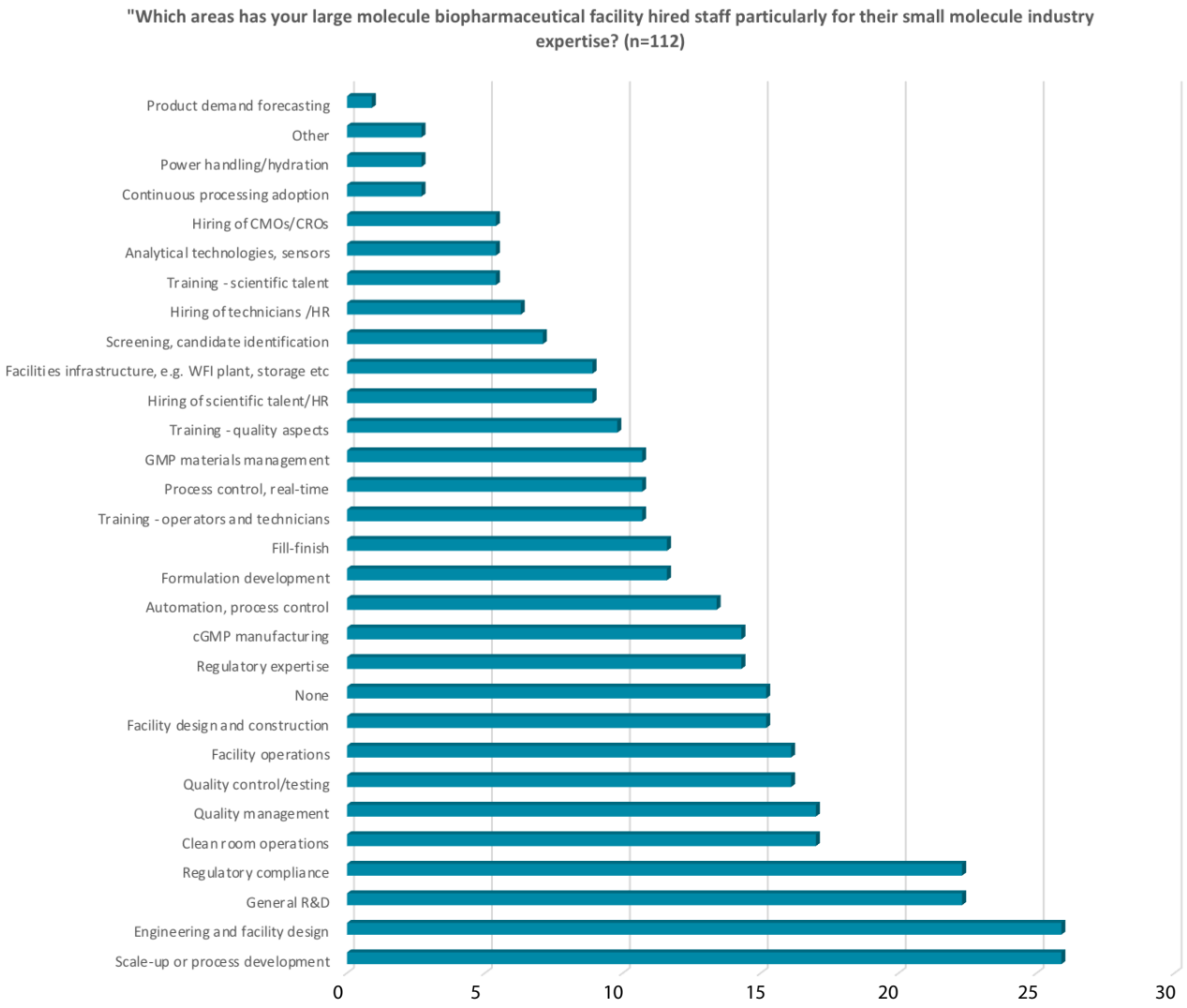
But there are efforts to respond to this issue. NIBRT, for example, has partnered with the Jefferson Institute to open a new biopharmaceutical training facility in the US. It will open in Spring 2019 just outside of Philadelphia, and bring increased access to world-class training.

Clearly, to address the shortages in bio, more small molecules expertise should be sought, especially in areas like PAT (Process Analytical Technology) implementation, where there are directly transferable skills. In fact, there is overall still something of a shortage of bio professionals fully familiar with PAT guidance.

CPhI Expert Emil Ciurczak goes on to explain: *"asking one of the bio-scientists to assess technology entirely outside their frames of reference was bound to meet with more resistance than was present in the early days of small molecules' introduction to the PAT Guidance. Indeed, the USFDA plainly stated that the Guidances' and ICH Q8, 9, and 10 were designed for small molecules. Therefore, there is a time gap in familiarity with these technologies, algorithms etc".*

However, Ciurczak believes that this situation will be mitigated in the large companies with both research and development activities across small and large molecules. And it is perhaps from this example that pure play biologics companies should begin integrating some knowledge from their small molecule colleagues for implementation of QbD and PAT. He added, *"the management of larger companies are more likely to see the time, cost-savings, and quality increases associated with PAT/QbD when looking at the Biotech branch of their corporations. A "pure" biologics company, by comparison, will not have direct experience with PAT and seldom do small molecule personnel switch careers to work in Biopharma companies."*

Whilst there is a lot that the large molecule industry can learn from its small molecule counterpart, there is still plenty to gain on the small molecule side of a collaboration



between the two. As small molecule pharma manufacturers have established their best practices over the past 50 years, the industry tends to be risk averse and does not easily adopt new technologies; even though technologies such as continuous processing could lower costs over time.

CPhI expert and president of EPCOT International, Girish Malhotra had this to say on continuous processing – a hot topic in both industries: *"It is remarkable that even with the process and equipment technologies being available to formulate continuously, the pharmaceutical industry has shrugged from using such processes. Continuous processes, provided there is product volume need, will improve profits and could make drugs affordable to many more than the current demand."*

Biopharma as an industry has been more adept at adopting new methods – such as single use technologies, which reduce the need for scale up, as well as complicated weighing and dispense steps, and cleaning validation. If these two industries could learn from one another's strengths they will have the capability to manage and even streamline the complex supply chains and development timelines in order to meet greater demand and reduce the overall costs.

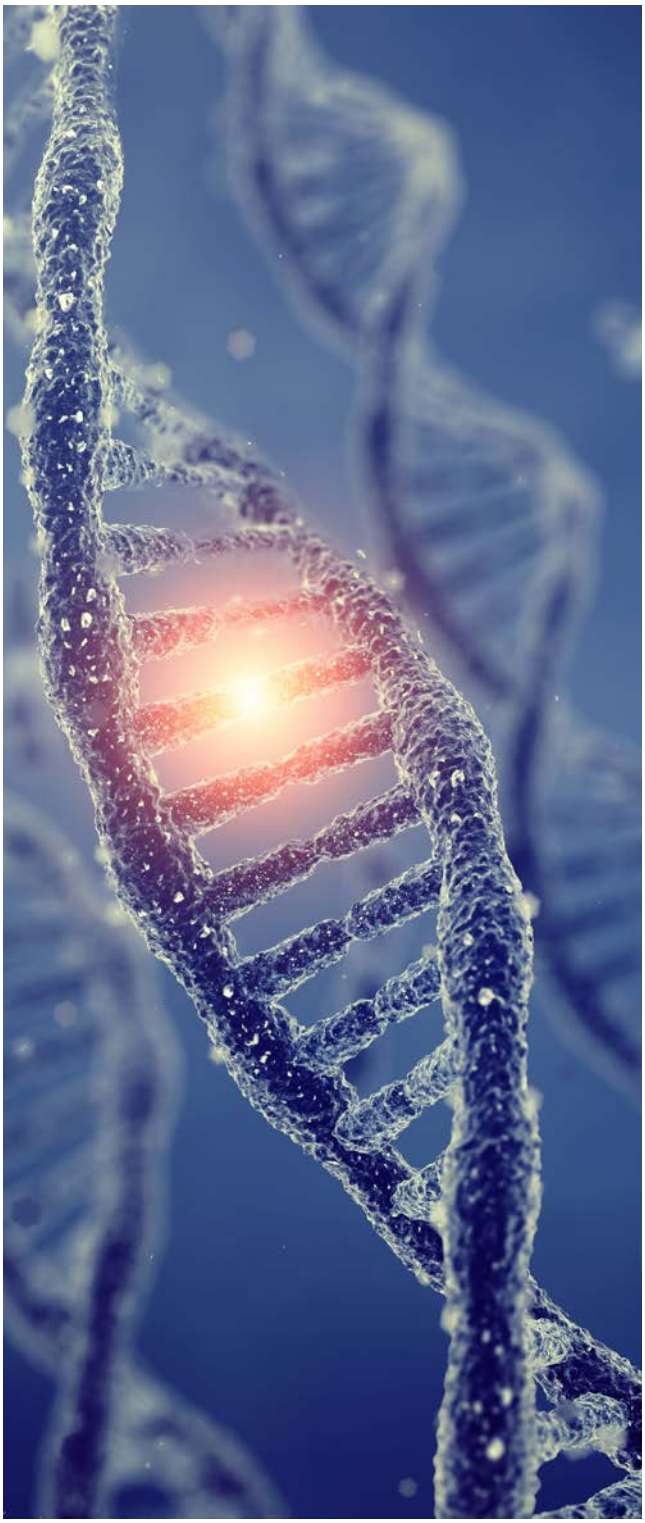
It is clear that, even though we are only at the inception of this trend, we are gradually moving towards a new era where pharmaceutical and biopharmaceutical manufacturing are no longer viewed as distinct entities – with workforces, regulatory pathways and new technologies working more closely together. In particular, the biopharma supply chain is becoming increasingly complicated, and managing these intricacies will be key to maintaining the industry's growth. Biopharma industry experts agree there

are clear opportunities to learn from small molecule firms in refining their supply chain as well as finding new staff. However, what is interesting, is that in the small molecules space experts argue they may in fact have even more knowledge to pass on to the counterparts in bio. Finally, with novel processes and methodologies now being tested in bio, the small molecule space should explore how these newer approaches are being introduced into a highly-regulated space.

In terms of contract manufacturing, the fastest growth is now coming from bio CDMOs, with newer companies introducing contact cell and gene therapy services over the next 5-years – thus, supply chain learnings and skills from small molecule experts should be in increasingly high demand. Another approach to differentiate and achieve growth for smaller bio CDMOs is novel technologies that accelerate production and lower costs. Already we have seen big pharma partnering with a number of smaller biotechs for anything from AI technologies to 3D micro-organoid modelling and bio process improvements – the latter is where there will likely be a new 'arms race' for the best technologies amongst outsourcing providers. Big pharma will also seek to mirror its approach in the small molecule industry, and mitigate supply chain risk, by seeking to partner with several CDMOs in both development and commercialisation of its most profitable new targets.

To help address these issues, bioLIVE in October (9-11) will run sessions across the expanding supply chain including 'building a sustainable bio workforce', 'continuous manufacturing', 'cell and gene therapies', 'single-use systems for extractables and leachables' and the increasing role of newer market entrants like China.

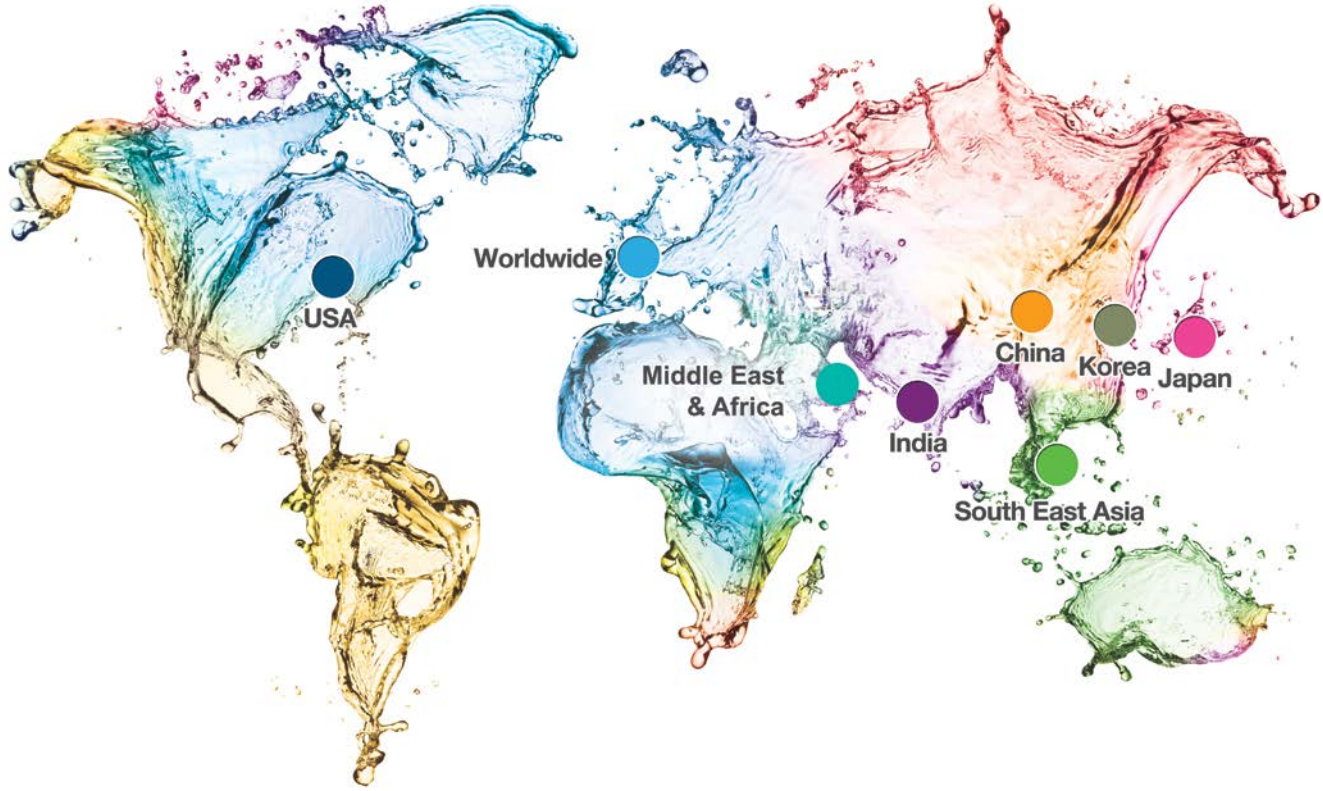
To conclude, the white paper suggests there are clearly short term supply chain efficiencies to be learned from the small molecules sector, coupled with PAT and scale-up process improvements from the API space. But the willingness to take a long-term view and incorporate modern technologies – that may come with short term regulatory hurdles – is clearly something that bio is embracing much faster than its older compatriot.



About bioLIVE

bioLIVE is a 3-day exhibition and content platform for the fast growing biopharma industry, hosting over 45 hours of content. The event focuses specifically on bio manufacturing and processing, connecting biotechs, big pharma and service providers across the value chain. By running adjacent to CPhI Worldwide and its 45,000 attendees, bioLIVE enables business partners from across the entire pharma market to meet – all under one roof – creating a unique platform for both industries to learn from each other.

For more information visit: **www.bio.live**



CPhI Global Events

CPhI China	20-22 June 2018
CPhI Korea	28-30 August 2018
CPhI Middle East & Africa	3-5 September 2018
CPhI Worldwide & bioLIVE	9-11 October 2018
CPhI India	12-14 December 2018
Pharmapack Europe	6-7 February 2019
CPhI Southeast Asia	12-14 March 2019
CPhI Japan	18-20 March 2019
CPhI North America	30 April - 2 May 2019
CPhI Conferences	year round