P-mec

The rise of the machines: pharma equipment sector set for a surge in new technology implementation

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Summary

This P-MEC Report explores how the changing R&D pipeline of smaller volume drugs, coupled with advanced technologies that remove many of the scale up challenges (e.g. continuous processing and single-use) are not only transforming industry attrition rates, but vastly changing the types of machinery used in pharma manufacturing. Running alongside this pipeline evolution are newer approaches to reduce steps in pharma manufacturing and make production greener and leaner, as well as lower the overall cost of pharmaceutical manufacturing. We are at crucial point in pharma manufacturing as push (newer technologies) and pull drivers (changing pipelines and demand for lower cost drugs) combine to reimagine how drugs will be manufactured in the future. This is the beginning of the age of smart pharma manufacturing, as the industry takes centre stage in advancing medicine.

What is driving growth in pharma machinery

This year, machinery at CPhI Worldwide 2019 comes into extra special focus as P-MEC will be the only European event dedicated to pharmaceutical equipment. But with rapid changes being undertaken across the wider industry, it is also a crucial time to look at the underlying conditions that are driving growth and altering the types of equipment being purchased.

> *"the machinery sector has become a central inflection point of how new therapies are developed"*

The machinery used in the pharma industry has until recently gone 'under the radar' so to speak, with a majority of the excitement focussed on novel therapies and approaches. But with a changing pipeline, the rise of biologics and continuous processing, the machinery sector has become a central inflection point of how new therapies are developed. One key driver is the long-standing goal to lower overall costs, particularly relevant for high volume generics; Additionally, new types of therapies coming through the pipeline with many receiving orphan drug designations are driving development in the industry. In fact, of the 59 drug approvals by the FDA in 2018, well over half were for drugs targeting rare diseases[1]. But even amongst the approvals of drugs intended for larger patient cohorts, many were created using single-use systems and or involving increasingly complex chemistries, which is fundamentally altering the standard in pharma equipment and manufacturing. For example, all of the high potents entering the drug development pipeline require specialist containment equipment, as do the cytotoxic payloads of ADCs, which can be particularly toxic even in very small quantities. This affects the entire production cycle from API development and clinical supply through to commercialisation and even encapsulation – e.g. manufacturers will need capsule filling machines capable of OEB 5 containment[2].

But more generally, we are seeing a drive towards personalised medicine and individualised dosage forms in the industry. As a result, manufacturers' need filling and equipment systems that are more flexible. Adding to these needs for flexibility is the rise of outsourcing. CDMOs, in particular, require equipment that can switch easily between the demands of clients – including switching between dosage delivery vehicles like syringes, vials and cartridges. In fact, Consultancy firm Results Healthcare calculated the outsourcing sector now accounts for 25% of the market and it is expected to continue rising[3].

Another area where we have seen considerable development is the move away from the traditional batch – the reasons for which are one, the aforementioned smaller volumes of product, but also, the challenge of speeding up development. For example, single use systems in biologics and continuous processing in solid dose both come with the advantage of removing many of the challenges associated with scale-up. Ultimately, this means several months can be potentially be shaved off development timelines, enabling innovations to progress to patients more quickly. Concurrently, another driver for this trend has been the rise of PAT (process analytical technologies) and Quality by Design (QbD) both of which have seen a well-documented push by the FDA. The accepted view is that these technologies help manufacturers move away from the trial and error methodologies of many older batch production methods and seek far greater control of all process parameters. The FDA was, of course, also under the direction until April 2019 of Scott Gottlieb – with CDER benefiting from Janet Woodcock's decade long stewardship – who have together been instrumental implementing regulations that help potentially to bring new process technologies to market. The resultant effect has been to bring the industry more actively into the discussion and encourage the typically risk-adverse pharma to invest in newer, more productive manufacturing technologies – and these efforts to reform the industry should not be underestimated. Ultimately, they will have knock on implications for both ingredient's makers and even global generic manufactures over the coming decade, as well as innovators.

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Continuous processing

It is still up for debate what role continuous processing will play in the future of the industry, with the economies of scale required for continuous API production in many cases not there for truly continuous production. Yet despite this, we expect to see an increase in continuous rigs and flow chemistry will deliver many benefits – especially in the manufacture of compounds where large batches are potentially dangerous. Flow reactions generate smaller amounts of hazardous compounds and are also able to run at high temperatures and pressures, with faster reactions. Another benefit is the enhanced control and quality, by minimizing the likelihood of side reactions, which are common in large batch reactors, and reducing the likelihood of the presence of impurities. This is, of course, without even mentioning the advantages of reduced plant size.

Eli Lilly and Company is widely acknowledged as a leader with its continuous manufacturing line in Kinsale, Ireland. They are using a three-step continuous process to synthesize prexasertib (an investigational new drug), which is currently being used for clinical trial supply[4].

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Yet in finished dosage, continuous manufacturing could have an even more prominent role to play. The success seen with Vertex’s cystic fibrosis drug Orkambi (lumacaftor/ivacaftor) and Janssen’s HIV treatment Prezista (darunavir) are potentially just the breaking of the wave in things to come. The FDA is also accelerating the pace of adoption and in October 2018 finalised guidance on how manufacturers can participate in the agency’s continuous manufacturing programme. But despite these trends, adoption has remained surprisingly slow so far.

Emil Ciurczak, CPhI Annual Report expert forewarns, *“big pharma that declines to invest will be left behind, especially as development timelines could be sped up by 6-months to one year with CM (no scale-up).” He predicts that “with the convergence of more advanced equipment, competitive pressures, a wider pool of trained scientists and the backing of regulators we will see exponential growth of continuous manufacturing over the next five years”[5].*

Many progressive big pharma companies are now reinvesting profits to bring down costs. This potentially means its

products, once off patent, can compete with generics (and again this has obvious implications for generics manufacturers in older legacy sites).

In the longer term, continuous manufacturing could have considerable benefits in the generics industry where volumes are high. Yet despite this, the initial cost of investment is widely acknowledged as a barrier too large to overcome. The lifespan of generics is another obstacle (innovative drugs get around a decade of unopposed production), as is the regulatory hurdles – i.e. adoption of a continuous manufacturing process will be difficult in cases where the originator drug was approved using batch production techniques (it would slow regulatory acceptance significantly). The final challenge is that generic manufacturers usually run multiple products on single manufacturing line, meaning all of these products would have to be suitable for continuous manufacturing, and undoubtedly there would be some down time between switching over between products. Thus, widespread global adoption of the technology will first have to start with the pharma innovators themselves before proliferating at generics companies.

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However, one encouraging recent change is the PDA’s recommendations to alter how the global industry incorporates Post Approval Changes (PAC)s. Regulatory PAC worldwide are still very complex and inconsistent, with varying types of classification, differing submission requirements, and highly variable implementation timelines – which in the extremes can be as long as 5-years[6].

3D Printing – the next step

One of the most radical ideas to come to the fore in pharmaceutical manufacturing in the last few years was the concept of 3D printing of dosage forms for individual patient regimens. 3D printing is a relatively new development in the pharma world, with research coming to light first in June 2016, by Andreas Marcstrom and Klas Marteleur of GE Healthcare Life Sciences' Research and Development in Uppsala, Sweden[7]. While some researchers and physicians were already using 3D technologies to help plan surgeries, Marcstrom and Marteleur saw the potential to bring these concepts to every facet of healthcare. In 2017, GE Healthcare's first Innovative Design and Advanced Manufacturing Technology Center in Europe officially opened. The new centre brought together research and development teams; it uses the latest technologies, including 3D printing and robotics, to simplify production processes for GE Healthcare and its customers, helping them accelerate the launch of innovative products for the healthcare industry.

The connected machine

We are at the start of an age of digital machines and 'connected manufacturing' – manufacturing 4.0 if you will – whereby data is extracted instantly from cycle and adjustments in the process made in real-time. This has obvious benefits in being able to identify problems and reduce down time, but it will also help expedite process R&D and speed drugs through the development cycle. Similarly, the internet of things (IoT) is defined as "a system of interrelated computing devices, mechanical and digital machines, or people that are provided with unique identifiers (UIDs) and the ability to transfer data over a network without requiring human-to-human or human-to-computer interactions[8]." The IoT is rapidly changing the way manufacturers operate, introducing an opportunity to achieve new heights of operational innovation and excellence. IoT-enabled systems specifically could be used to help manufacturers benefit from reduction in waste through manual labour, materials, time, and energy, follow government compliance, meet optimum product lifecycle times and achieve tighter margins. Some other emerging technologies include artificial intelligence (AI), and machine learning. Despite the fact much of the industry's interest on AI applications has understandably centred on its use of aiding the discovery of

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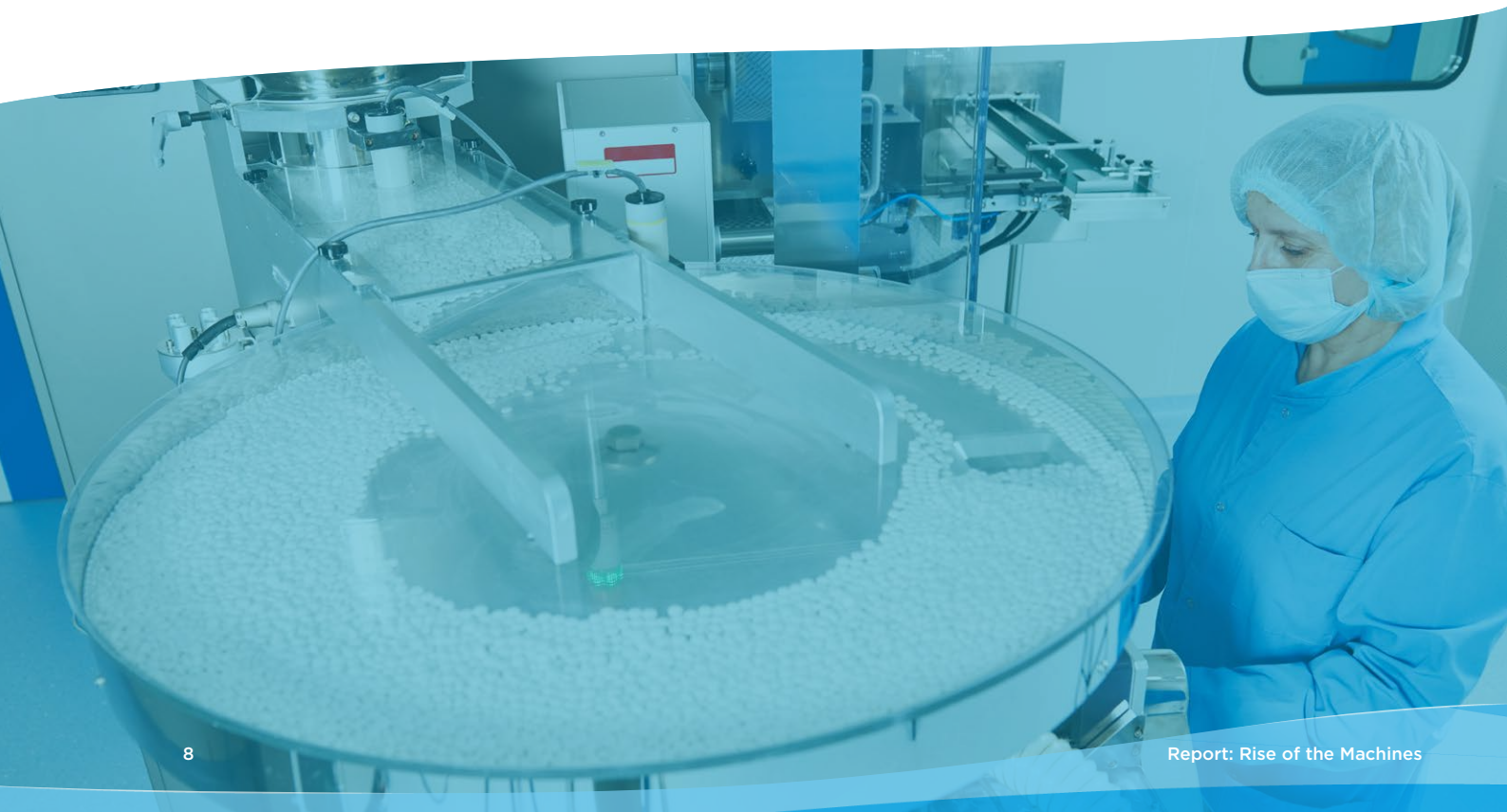
new drug targets, what has been under research thus far, is how AI could improve manufacturing processes. For example, machine learning can be used to make competitional models to explore how different manufacturing and process technologies could impact yields and purities. Alternatively, it could also be used to help in the development stage, whereby pharma manufacturers or CDMOs can use computational models to explore the likely impact of different dosage forms, and or scale up.

> *"pharmaceutical manufacturers are introducing technologies that can overcome many of the former limitations of older manufacturing processes"*

In fact, machine learning is being used more and more in the world of pharmaceutical manufacturing. McKinsey estimates that big data and machine learning in pharma and medicine could generate a value of up to $100bn annually, based on improved decision making, optimized innovation, improved efficiency of research and clinical trials, and new tools creation for physicians, consumers, insurers, and regulators[9].

Global pharma organizations could see great success and benefits from integrating these new technologies, such as optimising the workflow and manufacturing processes, complying with strict standards and regulation, enabling root cause analysis and alerts for better product quality and performance[10]. Advances in technology have played an instrumental role in helping companies attain new levels of automation, digitization, and data integration, a movement that has been labelled as Industry 4.0. This can be differentiated from Industry 3.0, which involved the automation of single machines and processes.



Green Chemistry

Yet these new manufacturing trends are not limited to only new chemical entities (NCE), as the pharma industry is still notorious for using many inefficient processes and lags far behind the yields and ee (enantiomeric excess) values seen in the chemical sector. As a result, we are increasingly seeing manufacturing leaders exploring technical solutions that can help increase quality, while reducing the number of process steps, and generating larger yields.

In particular in the production of APIs, it is well known that many of the older generics used inefficient manufacturing processes and thus resulted in lower volumes of API produced in comparison to ingredients utilized. This challenge is further compounded by the age of manufacturing facilities worldwide, with many facilities requiring significant machinery overhauls to implement some of the newer, more efficient processes especially for small-batch products. The challenge generic products face is the inability to significantly alter the manufacturing process beyond the originator API process for fear of seeing delays in their ANDA (Abbreviated New Drug Application).

> *"Within the past few years, the pharma and bio development and manufacturing sectors have experienced a shift from scaling up to scaling out"*

Until very recently – i.e. for majority of the last 30-years – what we have seen in the industry is a trend to lower costs by simply moving production to more cost-efficient manufacturing regions, notably India and China. However, the culmination of several factors in recent years is seeing a dramatic shift occurring – i.e. lowering cost through more efficient manufacturing – starting in the west and now moving east, as US and European manufacturers face the highest cost incentives to reform production processes. The collective forces of an increased need to use QbD and PAT; a desire to prepare manufacturing equipment for the next wave of pharmaceutical products; the necessity to upgrade existing legacy technologies; a growing awareness of the environmental impact of pharmaceutical production; alongside regulatory drivers from the FDA and EMA to pursue newer types of manufacturing processes, is leading a crescendo that considerably changes the outlook of generic manufacturers, API producers, and pharma companies globally. Thrillingly, pharmaceutical manufacturers have recognized this and are introducing technologies that can overcome many of the former limitations of older manufacturing processes. Ultimately, the single biggest driver of the change, as with any industry, is are required changes supported by viable business economics.

Biologics and disposable systems

Within the past few years, the pharma and bio development and manufacturing sectors have experienced a shift from scaling up to scaling out. Up until recently, the industry standard was scaling up because of a high demand for large batches of blockbuster products. However, recent innovation and improvements to single-use technologies and cell culture productivity, combined with the market's demand for smaller, more personalized batch sizes, have made scaling out becoming the preferred option, especially as we see less of the large-volume MAbs coming through the pipeline. In terms of bioreactors, scaling out means that bioreactors continue the same small volume, while manufacturers instead increase the number of bioreactors used in the manufacturing process. Thus, providing several cost and flexibility advantages for scaling out instead of scaling up. Specifically, in just one example, Thermo Fisher Scientific's single-use bioprocess containers (BPCs) are designed to improve the efficiency of multitude of processes such as facility operations and warehouse disposal, as well as quality operations and control and technical support. The crucial element to this approach is complete control of manufacturing - processes require ideal conditions, especially in the bioreactors, so the cells will produce the desired active substances in sufficient amounts with high quality.

Another example, of an approach to reduce the overhead of manufacturing in biopharma is from Octane Biotech. Last year acquired by Lonza, the company has been developing the Cocoon, an automated, scalable cell therapy manufacturing platform. The Cocoon contains a single-use cassette, with an input and an output side, and internalizes the entire end-to-end manufacturing of cell therapies including Mesenchymal stem cells (MSC) and Chimeric Antigen Receptor T cells (CAR-T cells).

More generally, the ease of disposal is a huge benefit of single-use bioprocessing products over the conventional products. Because they are disposable they do not require the conventional sanitization process, thereby increasing the efficiency of overall production. In addition, the use of a single-use bioreactor nearly eliminates any possibility of batch-to-batch contamination. Yet automation is a further development in the field of bioprocessing, and there is a lot of untapped potential in utilising the huge amounts of data generated by automated systems.

Conclusion

When looked at collectively, what is apparent across all segments of the pharmaceutical machinery sector, is that there is now marked economic drivers in the industry to reinvest in advanced equipment. Perspectives on new technology are shifting from 'in an ideal world we would' to 'we must have these to grow'. In a sector that has often been dependent on legacy systems and undertaking manufacturing in 'the same way as before' for fear of encountering any potential regulatory hurdles, this is a seismic shift.

"Perspectives on new technology are shifting from 'in an ideal world we would' to 'we must have these to grow'"

We are entering a critical point where the entire industry is looking to reinvest, driven by acceptance of the changing drug pipeline, and the need to come in line with regulations that go beyond the trial and error of batch production, and focus on real time process controls and analysis. Encouragingly, the advanced equipment – from mass spectrometers to closed casualisation, single use, and continuous rigs – is, and has for some time, been available in the industry. As methods improve pharma manufacturing productivity, the future will see an increased use of real-time monitoring, as encouraged by ICH Guidance's and Guidelines (Q8, Q9, Q10, and Q11) and use quality risk-based (QRM) methodologies and to implement faster and more modern sensors and controls (PAT/QbD). In fact, innovations in process analytical technologies (PAT) have significantly improved the ability of drug manufacturers to more tightly control process parameters and minimize the effect of Critical Quality Attributes (CQA). Spectroscopic methods (Raman and infrared) and chromatographic separation with faster technologies such as ultra-performance liquid chromatography (UPLC) or ultra-high pressure LC (UHPLC) are proliferating alongside flow-nuclear magnetic resonance (NMR). However, the big challenge that continues to remain is how to build these into commercial production for real-time analysis.

Flexibility in equipment design will also be integral to its lifespan usage, especially with the changing range of products coming to market (and produced for smaller patient cohorts). Alongside manufacturing, new delivery systems and dosages, also means new packaging and labelling equipment. In fact, the ability to process syringes, vials and cartridges from a single manufacturing platform will be essential to cater for the diverse product and pipeline requirements. In generics, very big things are expected of the new Post Approval Changes,

where it is believed that manufacturers blessed with massive incentives (and without the complex regulatory risks) will seek more efficient manufacturing for products.

Beyond the immediate response to lower costs and implement newer equipment that can speed development of new drugs, what we do not yet appreciate is the impact the digital technologies can have on the industry. Taking just the example of using connected machines (IoT), to reduce the need for pharma customers to audit in person contract manufactures or ingredient suppliers, the natural evolution of PAT and real time monitoring or the impact AI can bring in reducing down time and increasing process efficiency.

Like many innovations, the short-term impacts may be smaller (and cost initially more – think continuous processing) than expected, but the longer-term implications are likely to be far larger than we could imagine.

Pharma machinery just got smart and the smart money is investing ahead of the curve – innovators that take on new tech today, will gain an invaluable lead on the profits of tomorrow.

> Being second to market with new technology will not remain the *de rigueur* approach in pharma over the next decade. Pharma companies will instead use machinery innovations to create new USPs and commercial advantages.

References

1. http://www.pmlive.com/pharma_news/orphan_drugs_dominate_fdas_record-breaking_year_1273631
2. http://files.pharmtech.com/alfresco_images/pharma/2018/10/11/4f224c9b-e7eb-4ee7-8be6-d5c904c04770/PharmTech_Europe_March2017.pdf
3. https://www.aiche.org/resources/publications/cep/2018/december/pharmaceutical-manufacturing-current-trends-and-whats-next
4. https://www.contractpharma.com/issues/2018-09-01/view_features/continuous-pharmaceutical-manufacturing/
5. CPhI 2018 Annual Report.
6. https://www.pharmaceuticalonline.com/doc/pda-position-paper-a-call-for-reform-in-global-post-approval-change-processes-0001
7. http://newsroom.gehealthcare.com/3d-printing-meets-biopharma-engineers-turned-vision-printer-center-improve/
8. https://www.contractpharma.com/issues/2019-03-01/view_features/manufacturing-equipment-technology-trends
9. https://emerj.com/ai-sector-overviews/machine-learning-in-pharma-medicine/
10. https://www.manufacturingchemist.com/news/article_page/IoT_Industry_40_and_the_pharmaceutical_manufacturing_sector/123678

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