Achieve Pharma 4.0 with Emerging Technologies

Transforming the Science of Making Therapeutics

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Keywords: pharma 4.0, pharmaceutical, continuous manufacturing, drug manufacturing, digital transformation

Introduction

Over the last two decades the drug making process has continued to increase in complexity as a result of globalization, supplier specialization and the pressure to drive cost savings due to reimbursement pressures. Pharma 4.0™ is a framework for adapting digital strategies to the unique contexts of pharmaceutical manufacturing; including increased connectivity, improved productivity, simplified compliance, and the gathering of design history and production information to respond to problems as they emerge.[1] This term is coined by the International Society for Pharmaceutical Engineers to envision a digitally mature pharmaceutical industry, and it's operating model incorporates organization and processes, resources, information systems and culture.

In Pharma 4.0, viewed as the next transformation of the pharmaceutical industry, thought-leaders from regulatory agencies will continue to mandate better traceability of data and improved quality oversight of the complex processes and supplier networks. Manufacturers will need to address these pressures in addition to continuing to accelerate their new therapeutic pipelines. Doing so will likely require new or more advanced technologies that can fulfill unmet analytical needs, ranging from new instrumentation, innovations in automation and continued advancement in informatics, including leveraging artificial intelligence (AI) to displace current data analysis and interpretation approaches. Consequently, Pharma 4.0 is expected to completely change pharmaceutical manufacturing—making it faster and more efficient to ultimately provide safe, more accessible therapeutics.

As the SARS-CoV-2 virus started to spread around the world in late 2019, many market segments, including the pharmaceutical industry, saw the need to accelerate transformational initiatives to improve their speed, efficiency and overall agility. The resulting pandemic further accelerated plans institutions had to invest in connected laboratory instrument strategies so they could extend remote data sharing, with even broader benefits ahead.

For example, the transition to Pharma 4.0 is expected to incorporate orthogonal and new technologies and techniques that will increase confidence in product safety and quality, while streamlining product release testing to reduce human error and testing time. Some of today's technologies have the necessary capabilities and, therefore, more of these devices will be included in pharmaceutical manufacturing. As Richard Ladd, pharmaceutical expert at Laddavis Consulting

in the UK, said in a panel discussion, "I think the big area is the ability to integrate what we currently have."[2]

Such integration grows increasingly necessary because manufacturers need to get the most out of technology for numerous reasons, including changes in the medicines being developed. "New and more complicated products need emerging technologies to be able to properly ensure their quality," explains Jared Auclair, Director of the Biopharmaceutical Analysis Training Laboratory at Northeastern University in Boston. Plus, advanced methods, such as continuous processing, push the need for technologies that can ensure product quality, reduce human intervention and allow real-time release testing.

To achieve all of Pharma 4.0's benefits, the industry must incorporate three key elements: digitally-enabled laboratories, automation and distributed quality control (QC). Evolving from today's analytical platforms, these advances will provide sophisticated methods of measuring, including the future use of sensors for in-line testing, and valuable capabilities, such as real-time quality tracking, streamlined QC and release protocols.

Most of these steps ahead also require more data, and improved analysis and informatics. This information will allow pharmaceutical companies to better understand the science that underlies every step in developing and manufacturing a drug.

In this whitepaper, we'll discuss aspects of today's pharmaceutical manufacturing that need improvement, some of the technologies and techniques that can fulfill these needs, and briefly review several ongoing examples of industrial innovation.

Areas Needing Innovation

In addition to developing new technologies, suppliers must continue to improve existing ones. In today's reaction monitoring during manufacturing, scientists often use various analytical techniques—including gas or liquid chromatography (GC and LC, respectively), as well as ion chromatography. However, the trend is turning toward using mass spectrometry (MS) based workflows to streamline testing approaches that significantly improve data confidence and operational efficiency, which will eventually be replaced in this application by sensors. These transitions might not always be seamless, however, because of the time and cost associated with moving to MS and as many sensors remain to be developed. Through collaborations between academics, industry and vendors, advanced forms of MS and sophisticated sensor technology will be created.

The approaches to monitoring are also changing, such as performing analytical measurements in-line with bioprocessing. However, the adoption of these methods raises challenges that must be overcome. Beyond the sensitivity limitations, in-line methods could also risk contamination at the interface of the production line and monitoring technology. In short, the analytical devices need to work effectively within the bioprocessing line, and the overall method must meet regulatory approval.

As Auclair describes this challenge: "We do have to have that marrying of data, people and regulatory acceptance." Still, more needs to be done. As described in From Data Integrity Regulations to Pharma 4.0: "Regulators are openly promoting change and improvements within drug manufacturer operations with a focus on making the data more transparent and expect pharmaceutical organizations to take more responsibility and demonstrate digital and quality maturity."

In many cases, reaching that maturity will include introducing automation to enhance reproducibility and reduce manual labor, which will allow laboratory personnel to place more attention on higher-value tasks. With automated technology, says Pauline Rudd, a visiting investigator at A*Star Bioprocessing in Singapore, "You can rely on the data being the same every single time."

Almost all technology in Pharma 4.0 is likely to be smaller, faster and smarter. This applies to a wide range of devices, such as a portable analyzer that a scientist can take to the laboratory or the manufacturing line. Instead of broad-application instruments, Pharma 4.0's technology consists of dedicated devices that are customized for specific manufacturing processes.

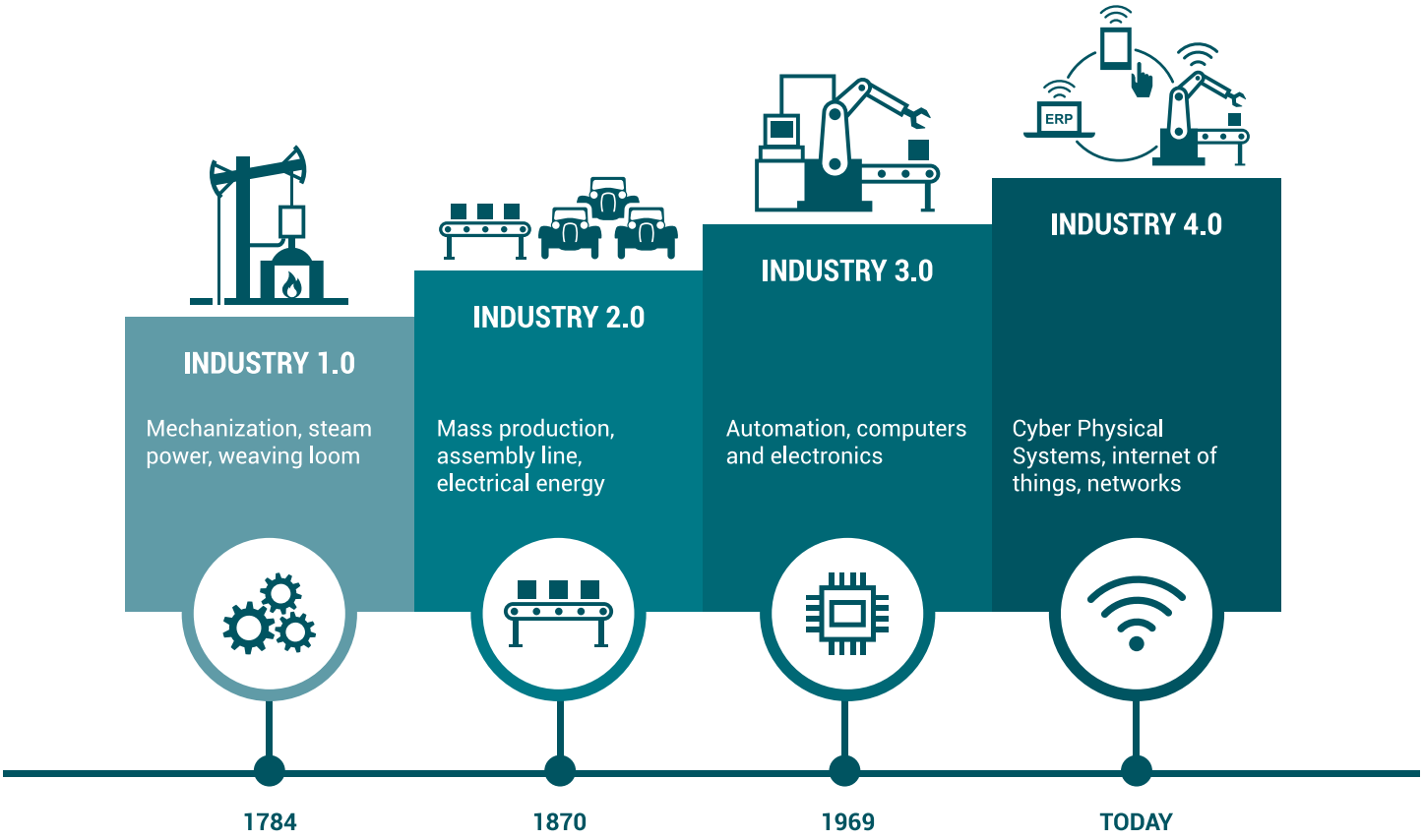


Figure 1. Industrial evolution from Industry 1.0 to Industry 4.0.

Challenges for small, large and biosimilars

Today's pharmaceutical landscape includes drugs in three general classes: small molecules, like aspirin; large biological molecules, such as monoclonal antibodies; and biosimilars, which closely resemble a specific large biological molecule. Different challenges come with each of these categories, and the following describes a few of them.

At Janssen Pharmaceuticals in Belgium, scientists use a collection of analytical technologies in manufacturing small-molecule medicines. Janssen scientists analyze raw materials with hand-held Raman spectrometers and use near-infrared (NIR) spectroscopy—and sometimes Raman—for in-line monitoring. If a production line includes granulation, Raman is used to monitor particle size and water content. Overall, Peter Van Broeck, Scientific Director, small molecules pharmaceutical development at Janssen, envisions a future where the incorporation of data from sensors in process models can control the manufacturing of a small-molecule drug.

With large molecules, scientists desire more in-line monitoring. If something is going wrong in a batch, a manufacturer wants to know as soon as possible to stop the process and limit the loss. "There are all kinds of new technologies in the LC/MS space that are coming along that should help us innovate in the in-line process," Auclair states. Nonetheless, more improvements are needed. Although modern MS platforms are much smaller than the room-size space they took 30 years ago, drug manufacturers want them smaller. As Auclair explains: "I can't stick a huge mass spec right next to a single-use bioreactor." In some cases, the MS footprint just exceeds the available space.

To address footprint needs from research to QC, the Thermo Scientific™ Orbitrap Exploris™ mass spectrometers are significantly smaller than other MS platforms. As Alexander Makarov[i], Director, Global Research, LSMS at Thermo Fisher Scientific, says, "Years of design know-how allowed us to achieve a more compact footprint yet deliver leading performance to address the variety of new challenges drug manufacturers face."

[i] Inventor of the Orbitrap technology

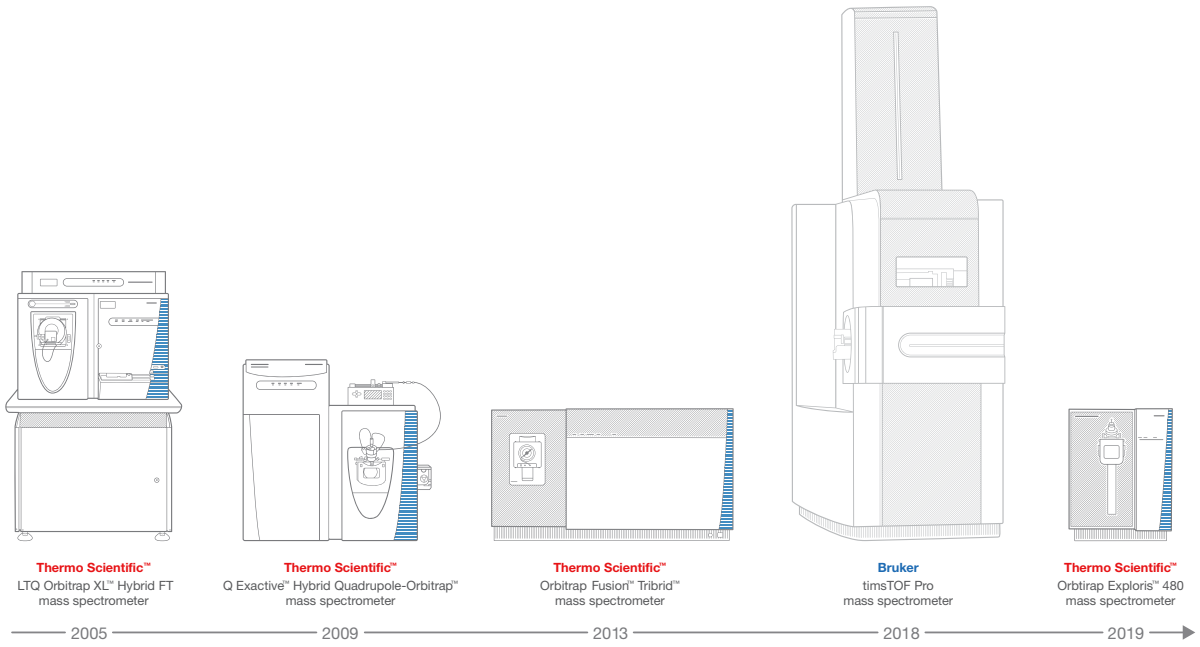


Figure 2. Since the commercial launch of the first Orbitrap based High Resolution Accurate Mass LCMS system in 2005, Thermo Fisher continues to reduce its footprint while increasing performance to meet the growing needs of various market segments, unlike most other mass spectrometry vendors.

In making biosimilars, high-throughput analysis is needed to measure many attributes, which are required for comparison with the original biologic. Sridevi Khambhampaty, Vice President, biosimilar product development at Intas Biopharma in India, sees such analysis being most helpful early in a drug's lifecycle, where in-line monitoring can be applied to many attributes during research and development to improve the process as much as possible before scaling up to commercial levels.

Combining analytics and informatics

For Pharma 4.0, all areas of the pharmaceutical industry must make better use of data, but that starts with the right kind of data. According to Saw Yen Ow, Associate Director of analytical biochemistry at CSL Limited in Australia, "The data generated by analytics must be fundamentally clean and well-defined so that it can be ingested and retrospectively modeled."

Before collecting any data, however, a scientist should pair the technology with the question. In glycosylation analysis, for instance, Rudd says, "If all you want to do is profiling, you can do that very rapidly with almost any technology." Detailed analysis will require other approaches, as shown in Figure 3.

After collecting the data, scientists need more advanced analysis, which could include artificial intelligence (AI). Most AI or machine language (ML)-based tools rely on large datasets, but some forms are being developed to work with the amounts of data available in pharmaceutical manufacturing.

Although pharmaceutical companies keep collecting more data, they want to use it more thoughtfully. In the past, companies took a brute-force approach of trying to analyze every piece of data. Instead, Ow recommends reducing the amount of data that is analyzed and simplifying the number of dimensions. Solving this challenge will depend on manufacturers working closely with biocomputing experts.

Thermo Fisher Scientific's digital solutions can help companies get more out of data. For example, a laboratory information management system (LIMS) can control devices, automate workflows, and manage both experimental and operational data. Scientists can also add data efficiency by replacing paper with an electronic lab notebook (ELN), which can be integrated with a LIMS. The overall data handling can be simplified with a scientific data management system (SDMS) that can work in combination with ELNs and a LIMS. Incorporating these tools can be easier through a collaboration, where a good partner sets expectations, educates, brings scientific expertise and creates easy scaling. Such a collaboration can produce fit-for-purpose solutions. Luckily, some of the desired combinations of technology already exist, as described in "The Lab of the Future is Here."

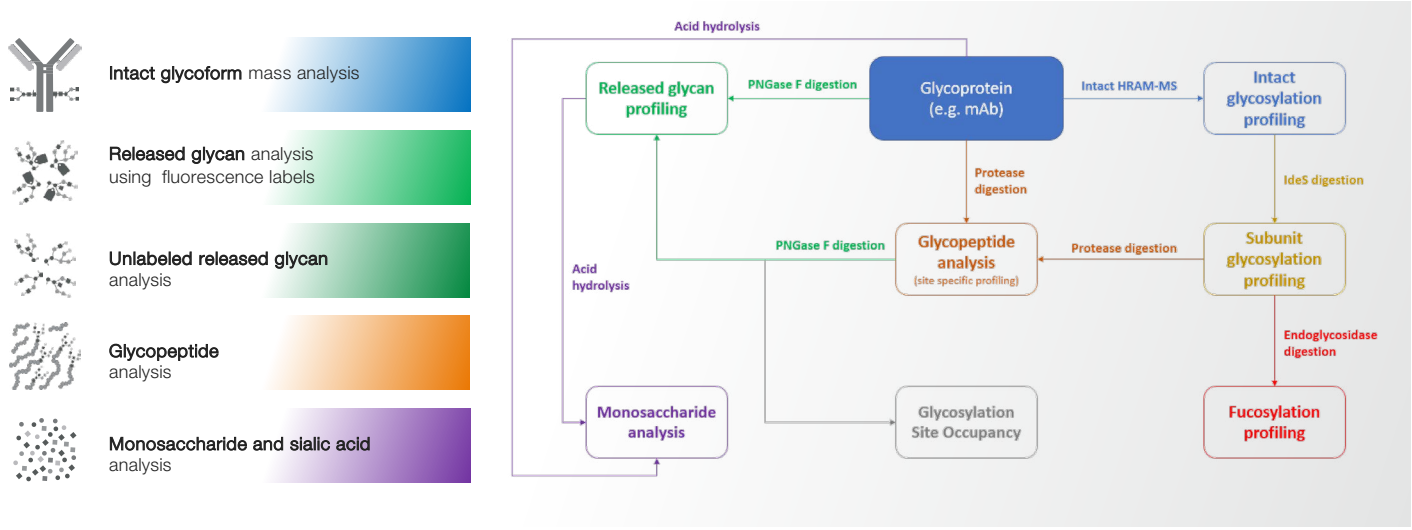


Figure 3. The type of glycan analysis determines the required technique, such as monosaccharide analysis via acid hydrolysis or glycopeptide analysis via protease digestion.

Such collaborations might also reduce the need for some regulatory requirements, such as dissolution (also known as release) testing. This test determines the time required for a pill to go into a solution. Rather than performing off-line testing, Van Broeck and his Jansen colleagues hope to combine NIR technology and modeling to develop in-line dissolution testing.

Other manufacturers foresee even further integration of analytics in processes. Intas Biopharma is developing a lab information system that integrates a database into their processes. "What happens in R&D is that truckloads of experiments are done, but very little of that data eventually gets used," says Khambhampaty. "But we'd like to use this development data to expedite our next product development." That requires building the R&D data into a database in a structured manner so the scientists can "actually gain some intelligence out of it," Khambhampaty further explains. "Otherwise, the R&D development cycle for products just seems to repeat itself, without us ever getting smarter about it and doing it faster."

Gaining better control

Improving the manufacturing process is fundamental to Pharma 4.0, and this section reviews three ongoing examples.

CSL Limited is combining custom analytics to better understand process control and gain the knowledge to ultimately make adjustments to improve it. The company uses this technology in its biomanufacturing facility in Switzerland. In 2020, Thermo Fisher Scientific and CSL Limited collaborated to create improved flexibility and higher volumes in manufacturing biologic-based therapies. CSL Chief Operating Officer Paul McKenzie noted: "As part of the strategic review, we are in the process of transforming our end-to-end supply chain with a view to ensuring the company's global manufacturing network is operating at a best-in-class level. This includes balancing internal investment with access to capabilities and capacities that are available with an experienced partner."[3]

In another collaboration, scientists from Thermo Fisher Scientific and the National Institute for Bioprocessing Research and Training (NIBRT) are exploring several approaches to acquire more knowledge about manufacturing processes and then use that information to stimulate innovations. As one example, these scientists are developing at-line process analytical technology using the multi-attribute method (MAM) for QC. MAM provides peptide mapping through data from high-resolution MS. In this method, peptides in a sample get separated with LC and analyzed with high-resolution accurate mass (HRAM) MS. The resulting information—including data on post-translational modifications, glycosylation and other features—can be used in part of an overall effort to use quality-by-design in continuous manufacturing and real-time release of drug lots—two important elements of Pharma 4.0.

Various forms of digital technology could also improve manufacturing. As an example, A*Star Bioprocessing is integrating analytics and software, such as a digital twin, to monitor its manufacturing process. A digital twin consists of a virtual model of a physical process and the related devices.

thermo scientific



Figure 4: Digital twin technology is enabling the paradigm shift from batch to continuous manufacturing a reality.

So, digital-twin technology can monitor a biomanufacturing process, and the resulting information can be used to make real-time adjustments to prevent problems in product quality. "The bits are all there, it's just finessing them or getting the hardware to link up in a way that's practical to the systems," Rudd says. "It's an engineering problem, really."

Conclusion

As shown, Pharma 4.0 depends on a range of existing and new technologies that will improve manufacturing of small and large molecules, as well as biosimilars. To reach the needed improvements in technology, "there should be a really good collaboration between suppliers, academics, industry and also, of course, the regulatory agencies," Van Broeck said.

Similar collaborations will also be required to integrate advances in data management and analysis with existing and new technology. With that integration, a biotechnology or pharmaceutical company will gain advantages in producing high-quality products and doing so with improved reproducibility, increased speed and, perhaps, reduced cost.

Ultimately, Pharma 4.0 promises better knowledge of existing processing and faster timelines to developing new processes, but that depends on teamwork. The power of an integrated partnership with a company like Thermo Fisher Scientific brings focus to a pharmaceutical manufacturer's most pressing goals—improving processes, limiting interruptions, balancing quality and operational costs, meeting business needs, and maintaining a reputation for quality and dependability.

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