Parenteral Manufacturing and Industry 4.0

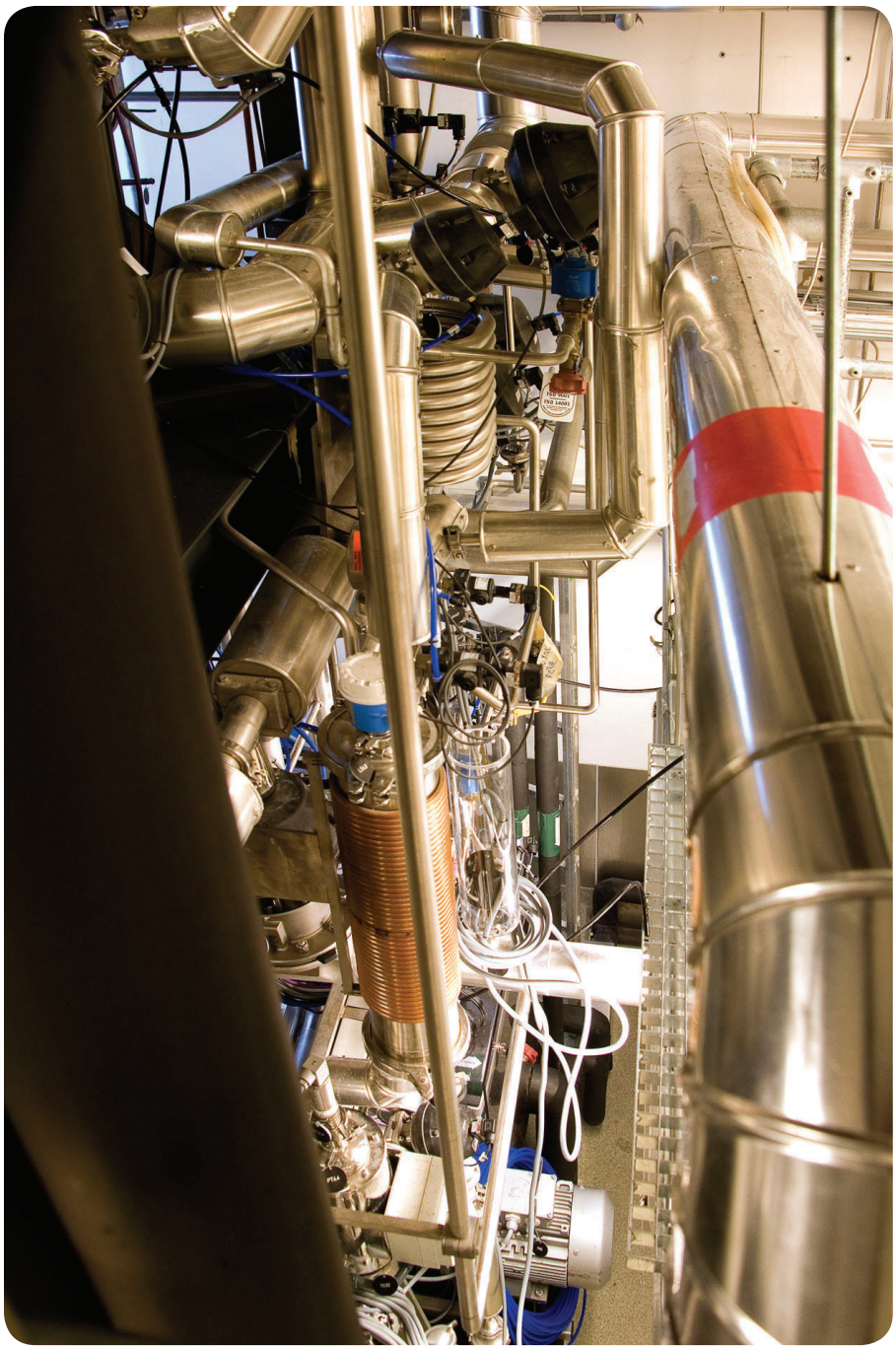
Please don't be surprised that Industry 4.0 has anything to do with parenteral manufacturing. You may also have heard about it as Internet of Things (or IoT) or the next manufacturing paradigm. Actually it has to do with "everything" - and therefore also with parenteral manufacturing.

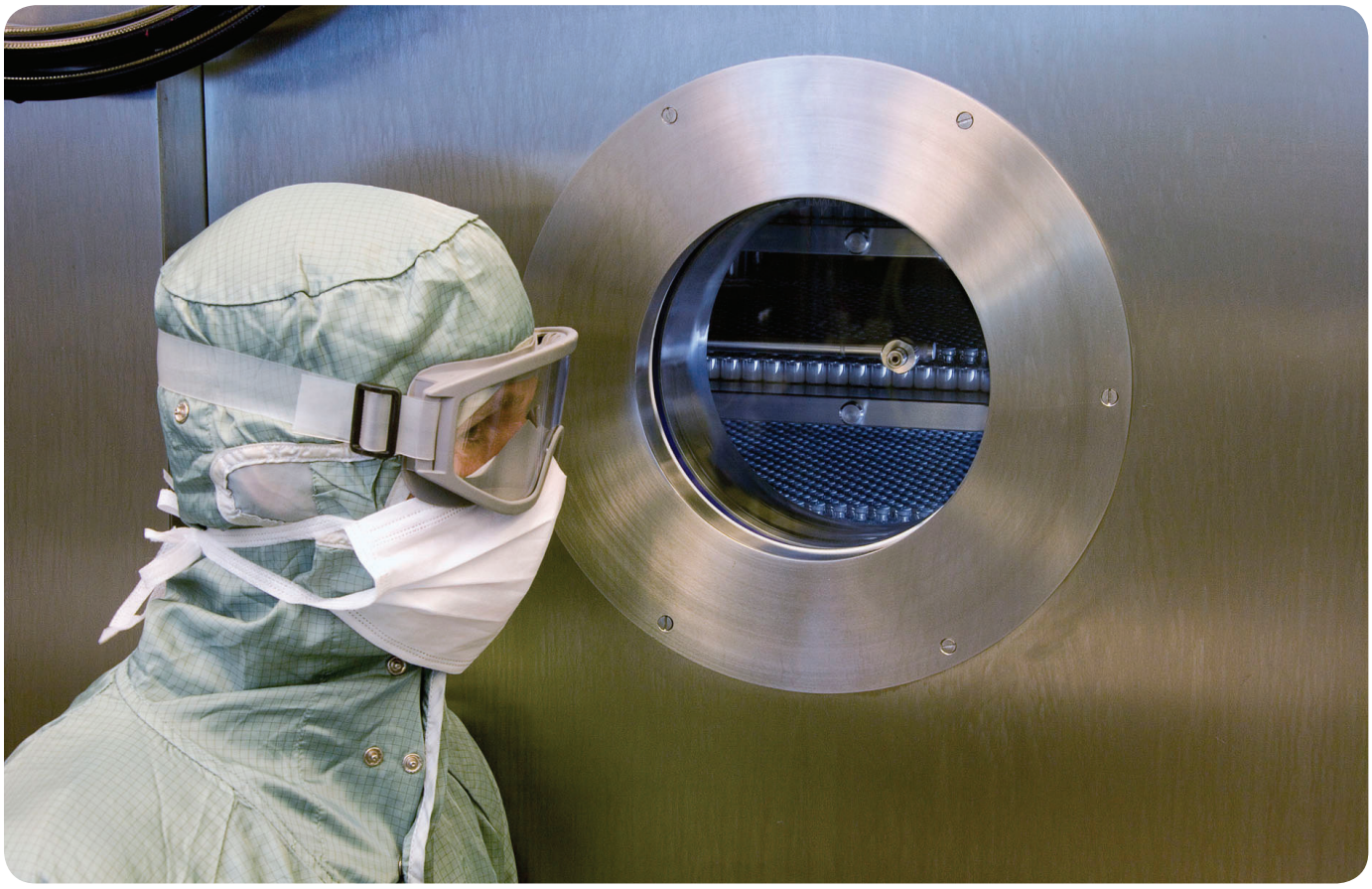
Industry 4.0 will be a game-changer in how the end-user (the patient) will interact with all the partners who are involved in all aspects of the wellbeing of the end-user. Real-time data on the status of the health situation of the individual will have the possibility to flow seamlessly to an array of partners. You might already now have an Apple Watch on your wrist, which has the possibility to submit data on your health situation to relevant partners if you should want to do so. However, this is only the first step in a new area of exchange of information, which can be used to make healthcare decisions not only around you, but also for a larger population.

Industry 4.0 will also affect the manufacturing of sterile products, being one of the most challenging areas of pharmaceutical manufacturing. Not only is it complicated and difficult, but it is one of the most vulnerable areas from a patient and regulatory perspective. Patients and regulators expect high-quality products but still there have been many manufacturing issues, even in recent years. These include finding particles, including human hair and other impurities found in parenteral products. It has caused severe inspections, which in some situations have resulted in warning letters, consent decrees and drug shortage situations. Part of the problem is due to several existing facilities becoming aging facilities that do not live up to current expectations.

Many of the new technologies that are part of Industry 4.0 will enable better control of the manufacturing processes. A rapid development within sensors, cameras and advanced controls are benefiting many industries but are struggling to be utilised in pharmaceutical manufacturing equipment. Some of the leading areas of sterile manufacturing are within semiconductors, cell phones and automotive parts; not in pharmaceuticals yet. This is partly because the technology for pharmaceutical manufacturing is not available yet, but probably also because the industry does not have the innovation skills and the culture to adapt those new technologies.

Some of the more advanced sensors have found their way into closure integrity through headspace laser monitoring and rapid microbiology measurements. Machines are starting to include integrated checkweigher equipment after filling, as well as integrated camera inspections and environmental monitoring. However, only a few lines can run with high efficiency without operator intervention, and the best current protection of isolator filling lines are still





complex and time-consuming. Besides, it is still inflexible and time-consuming in regard to changes in products, format parts and supply of materials.

The ultimate goal could well be to have the operators totally out of the cleanrooms. There is considerable inspiration to be found in the semiconductor industry, where this has been the norm for many years, simply in order to ensure the high yield of silicon wafer processing so that microchips are ensured a high build-in quality. Manufacturing equipment for semiconductors has been highly automated through robots and highly efficient systems that ensures the high effectiveness that is necessary with the low margins earned in this business.

In pharmaceuticals, aseptic processing robots are still only used rarely. The main focus has been on the overall equipment efficiency and almost no companies have had the courage and focus in innovation to go to the next level. It has been pointed out in recent reports from McKinsey and other consulting companies that the opportunity is there for pharmaceutical manufacturing – but with limited impact so far.

With Industry 4.0, new types of sensors and interconnectivity in the near future must be expected; bioreactors with build-in cell-level measurements of activity and build-in wireless communication. The first tablet products with build-in monitoring have been FDA-approved and advanced sensors for process analytical technology (PAT) have been state-of-the-art in tablet manufacturing for some years now. In fact, some OSD facilities have implemented continuous manufacturing and have in this way avoided the inflexibility and risk of traditional batch manufacturing. Still, the examples from parenteral manufacturing are few and there have only been a few successful case studies so far.

However, the opportunities are available. Bio manufacturing would benefit tremendously from adopting the principles of continuous manufacturing, although there is a gap on the sensor side. Instrumentation is more complex because connectors add a risk to the integrity of closed systems. Wireless data transfer is an integral part of the Industry 4.0 paradigm. The sensors are starting to arrive. Battery life is improving and the necessary energy for measurements and data communication is decreasing. It is becoming possible and it is very much needed.

The new paradigm of single-use biopharmaceutical manufacturing opens a new opportunity to rethink the way we measure, monitor and control the bioprocessing. More and more process steps have become available with single-use technology and the new solutions are still so new that you may not have heard of them yet. Some will be shown at this years' Interphex exhibition in New York, following the new product introductions shown at the 2015 Achema exhibition in Frankfurt, but still the technology is evolving so fast that the new solutions becomes available nearly on a daily basis. So one has to stay tuned.

Every single-use technology has some challenges around instrumentation, as it is important to try to avoid ports for instruments. In general, ports should be avoided as they add significant risk to the manufacturing process through, e.g., infections or other sources that threaten the well-controlled environment. However, there are benefits in operating within a closed system in modern single-use manufacturing, as well as improved technologies which are constantly developed to solve those challenges. These include the benefit of taking advantage of Industry 4.0, which should be able to

add significant benefits compared to the traditional instrumentation solutions.

Industry 4.0 is all about connectivity. It does not have to be wireless connectivity, but part of the Industry 4.0 solutions are actually based on wireless technology, mainly WiFi or other wireless communications. There are wireless industry communication standards, while the wireless instruments for biopharmaceuticals are still a mix of many solutions, with no clear winner on the communications approach, unfortunately.

One of the key areas is standardization, and for single-use bioprocessing it should preferably be based on sensors that require little or no power supply. Sensors that run on batteries or which can be charged wirelessly would be preferred, as solutions that communicate directly from the process liquid hold the highest potential. Everybody wants to avoid connectivity problems, and the risk of having wireless communications hacked within a closed facility are possible to handle. Thus, there is a need for a new generation of single-use sensors for single-use bioprocessing solutions that can be used in closed systems such as bioreactors, with no need to add or charge batteries.

Industry 4.0 is not only connectivity and networked communication between devices, be they processing equipment or pharmaceutical products. The next-generation pharmaceutical products can well be imagined to include further integration between processing equipment and pharmaceutical products. One example could be an "artificial pancreas" insulin pump with associated blood sugar measurement. Another interesting example is the product that FDA approved in 2015 which communicates to ensure the patients' compliance with the prescribed treatment that may last several weeks.

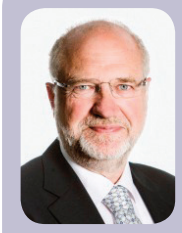
In these examples and others, innovation has been around for some years and the future requires better and more efficient communication. But what about in the manufacturing of pharmaceutical products? Here the picture is very different. There is a strong belief in many pharma companies that new technologies should be, if not directly avoided, then considered very carefully. Or in other words, someone else should do it first. This is despite the fact that the FDA is actively promoting pharma companies to think differently in terms of "emerging technologies" and their public support for some of the new technologies such as continuous manufacturing.

Despite the new FDA effort on various initiatives to stimulate "an agile and flexible pharmaceutical manufacturing sector", the willingness to try new technologies is still low. Hopefully times are changing when the FDA actively promotes new technology and solutions such as continuous manufacturing, stronger supplier engagement, process analytical technology (PAT) and other forward-looking initiatives.

The pharmaceutical industry has a great opportunity to accept the invitation from the FDA's Emerging Technology Team and seriously work with the regulators in the FDA and the suppliers to the industry, who want to provide innovative solutions. This could form a triangle where the next generation pharma needs to start. Serious pharma companies now realise that they need to change and also that the FDA is changing attitude to new technologies, as long as new technologies are evaluated based on science and a risk-based approach, with a focus on quality, safety and efficacy of the pharmaceutical product.

The industry is missing some of the good, thought-stimulating examples that lead the development towards the next generation of parenteral manufacturing. Industry, suppliers and regulators need to work closely together, similar to 20 years ago when the first solutions for barrier technology and isolators were developed. These solutions are now state-of-the-art in parenteral facilities, although many aging facilities still have a long way to go. However, with a strong and trust-based cooperation between visionary pharmaceutical companies, innovative equipment manufacturers and regulators looking for emerging technologies, it will be possible.

The real question is not whether Industry 4.0 is applicable to be part of the solution for the parenteral manufacturing of the future, but when the breakthrough will come.



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Morten Munk joined NNE Pharmaplan in 2015 as Senior Technology Partner, supporting all aspects around biopharmaceutical development and manufacturing. In 2001 Morten co-founded CMC Biologics A/S, where he held a position as Vice President for Business Development. Prior to founding CMC Biologics, Morten held a position as principal scientist at Novo Nordisk A/S in which he was responsible for the CMC part of several projects, which have bene commercialized successfully.

During his career, Morten has completed work assignments in both the US and EU.
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