Industry 4.0 – A vision also for personalised medicine supply chains?

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Abstract
Industry 4.0 foresees a digital transformation of manufacturing resulting in smart factories and supply chains. At the heart of the concept lies the vision of interconnected materials, goods and machines, where goods find their way through the factory and the supply chain to the customer in a self-organised manner. Industry 4.0 is gaining traction in high value manufacturing sectors. This perspective paper explores what this technology-driven vision has to offer for the biopharmaceutical industry, and in particular cell and gene therapies.

Keywords: Industry 4.0, Cyber Physical Systems, Internet of Things

What is Industry 4.0?

Industry 4.0 envisages factories and supply chains where goods and machines are all connected to the internet, communicating with each other, exchanging, collecting and analysing data, and coordinating processes in a distributed fashion. This data-driven integrated system will enable improved responsiveness in manufacturing leading to more flexible factories of the future.

It is derived from several strong technological trends: First, computer chips, sensors and transmitters are increasingly miniaturized and become ever less expensive, which allows embedding them into more and more machines and also goods. Second, wireless communication becomes ubiquitous, which allows connecting almost everything to the internet, blurring the boundary between the digital and the physical world, allowing machines and products to communicate directly and autonomously. Together, these technologies allow for the creation of self-organising systems that collect and exchange data on an unprecedented scale, and make decisions autonomously, intelligently and in a decentralised fashion. Add to this mix other technological advances such as cloud computing which offers scalability even to small enterprises, big data analytics which enables the handling and interpretation of massive amounts of data in real time, and artificial intelligence which allows machines to learn and adjust, and you get a powerful mix that is able to transform industry processes and take them to a new level.

Industry 4.0 started as a German initiative [1], and its name was chosen because its promoters see it as the fourth industrial revolution, after the introduction of the steam engine, mass production, and electronics and IT (robots and

programmable logic controllers). But the topic is gaining momentum across the world, and similar concepts are known as “Smart Factory”, “Advanced Manufacturing”, or, not limited to industrial processes, “Cyber-Physical Systems” [2] and the “Internet of Things” [3].

What Industry 4.0 promises

The typical and most prominent scenario of Industry 4.0 is the self-organising factory, where half-finished goods find their way through the shop floor and negotiate their processing with machines autonomously. This scenario resonates very well with the manufacturing industry, because it promises *cheap and efficient mass customization*. Yet, the vision of Industry 4.0 goes far beyond this example, and hopes include:

- *Real-time control*. Aggregating all the collected information centrally, it will be possible to generate a digital real-time image of the entire physical production process in the control centre. Production becomes fully transparent and thus offers more opportunities for monitoring, supervison, control and optimisation, even across locations.
- *Integrated maintenance*. Smart production lines will constantly monitor themselves, and can alert the appropriate personnel quickly if any problems are detected or anticipated, or even resolve many problems themselves. Machines may be able to predict optimal service intervals and order spare parts autonomously. Technicians will be able to monitor and interact with the machines remotely. Together, this promises to reduce machine downtimes and the cost for maintenance.
- *Better adaptability*. A self-organizing production system that can make intelligent decisions in a decentralized manner is much more flexible and responsive than centrally controlled production systems. This promises much greater adaptability to changing demand or unforeseen events such as machine breakdowns or contamination.
- *Enhanced collaboration across the supply chain*. With goods carrying information across the supply chain, and a more integrated approach to communication and end-to-end information exchange, Industry 4.0 will allow a much better coordination of the entire supply chain.
- *Better track-and-trace capabilities*. Industry 4.0 means that individual goods will obtain a unique identifier, and be able to keep track of all the information related to their individual production process. This will allow for more efficient and more effective quality control, and help quickly identify problems in the production process. This is also an important prerequisite for Quality by Design (QbD) processes.
- *Smarter products and new business models*. Connecting goods to the internet will not only help in coordinating their production, but also allow for better customer services, new product features and new business models. This includes provision of “in-use” information on the product back to the manufacturer; this can be used to improve product and process design for future products.

Industry 4.0 in the Biopharmaceutical Industry

The predominant mode of operation for the manufacture of biopharmaceuticals, including cell and gene therapies, is batch rather than continuous processing [e.g. 4-7]. This makes the benefits of Industry 4.0 with its vision of a self-organising factory less obvious for the biopharmaceutical industry. However, the biopharmaceutical industry is currently undergoing a shift away from the one-drug-fits-all paradigm towards personalisation, with therapies targeted to particular groups of patients (stratified) or individuals (personalised) such as the case of patient-specific autologous cell and gene therapies. This will require a corresponding shift in manufacturing to agile small-scale individualised production that can make-to-order cost-effectively. The resulting challenges will be similar to the mass customisation challenges that made Industry 4.0 so popular in other manufacturing industries (e.g. automotive), heightened by the regulatory constraints paramount in the biopharmaceutical industry and the complex biological and living nature of the materials and products.

But when looking at all the associated benefits of Industry 4.0 mentioned in the previous section, it should become clear that this paradigm has a lot more to offer to the biopharmaceutical industry.

Quality trumps cost in the biopharmaceutical sector. Embracing Industry 4.0 will facilitate the biotech sector's move towards QbD, including a more flexible process based on having enhanced product and process understanding that can be used to adapt the process to manage critical sources of variability [8,9]. This is because Industry 4.0 will connect Process Analytical Technologies (PAT) comprised of sensors with multivariate data analytics and control algorithms as well as electronic data records and enterprise systems to enable efficient knowledge sharing across components in the supply chain.

Such a knowledge-driven Quality by Design approach will provide the ability to control variability in factors such as raw materials and donor source material, which are particular concerns for autologous cell therapies. As PAT and sensor technologies develop, it will be possible to develop feedforward control algorithms so as to adjust the process parameters throughout the manufacturing process to cope with feed variability. For example, for autologous cell therapies if the starting cell concentration is lower than expected in the donor source material. Industry 4.0 can potentially make an informed decision on the increase in culture time required (within validated limits) to produce the required final number of cells for treatment. Feedback control, for example, using cell characterisation assays and associated online analytics to control cell culture operation will also be desirable in future so as to consistently achieve desired product quality attributes. This will not only have benefits one might expect such as reduced wastage and improved yields, but more critically for patient-specific cell and gene therapies this could be the difference between treating a life-threatening disease and having a failed patient treatment; it may not be possible to repeat manufacturing in the event of a batch failure, especially if new patient source material is required, due to the already immune-compromised health of the patients.

Furthermore, the trend towards more patient-specific therapies will result in an explosion in quality data, batch manufacturing record reviews and release testing required. For example, QC/QA functions will need to be more automated with continuous real-time release methods to handle larger numbers of patients per year so as to avoid becoming a bottleneck. As can be seen, the quality infrastructure will lie at the heart of the digital transformation of cell and gene therapy manufacture.

Enhanced track-and-trace capabilities are critical for cell and gene therapies and in particular for patient-specific therapies so as to provide assurance that the patient's' treatment is from their own starting material. In such a setting, the supply chain changes from a linear to a circular one with the patient or donor at the centre.

Furthermore, autologous immunotherapies such as CAR T-cells require careful orchestration of three main manufacturing pathways (plasmid DNA, viral vectors, cells) with the additional challenge of different centralised versus local manufacturing setups. Whether cell therapies (allogeneic or autologous) are shipped fresh or cryopreserved, both require temperature-controlled conditions with real-time temperature reports. Blood banks already address some of these issues with barcoding of supplies and managing the logistics of handling blood products requiring controlled temperature storage and distribution. However, it is clear that innovative solutions from Industry 4.0 will provide real-time visibility and control across complex cell and gene therapy supply chains from material sourcing through to manufacturing and temperature-controlled transport to patients. This is particularly critical given that here an expensive asset ($50k+) needs to be tracked needle-to-needle so as to guarantee chain of custody and ensure timely delivery to the correct patients. This needs to be achieved whilst managing temperature and time risk, co-ordinating with manufacturing sites for capacity sourcing and planning, and clinical sites manufacturing , as well as factors such as customs challenges when shipping [10]. It is encouraging to note that there are already important developments in track-and-trace for cell therapies and these are more advanced than elsewhere in the biopharmaceutical sector.

The enhanced track-and-trace capabilities of Industry 4.0 will also make it easier to comply with different geographical regulatory jurisdictions that may have differences in formulation, packaging or quality control requirements. Further drivers for Industry 4.0 adoption are based on new EU regulation that is likely to require a unique serial number for most prescription drugs from 2018 [11], as well as WHO estimates that about 10% of drugs in Europe may be counterfeit drugs [12]. If every item has its own specific identification label, it is straightforward to envision a system where every patient could easily check the origin of the drug they have been given by simply holding its packaging in front of their computer's webcam.

Industry 4.0 will also help in the biopharmaceutical industry's transition towards increased industrialisation. In some cases this will include moving from batch to continuous manufacturing. Continuous biomanufacturing is actively

being investigated in the therapeutic protein manufacturing space with a potential end-to-end continuous manufacturing vision [e.g. 13-15]. For viral vector manufacture for cell and gene therapies, continuous biomanufacture is being explored on the upstream front, with perfusion culture in fixed bed bioreactors [16] or stirred tank bioreactors, as well as the downstream front with continuous chromatography [17]. For cell therapy manufacture one can also envisage the use of perfusion culture to enhance productivities within a smaller footprint linked to continuous volume reduction, washing [18] and purification, where appropriate. For continuous biomanufacture, the sophisticated monitoring and control capabilities expected from Industry 4.0 will be even more important for successful implementation and track-and-trace.

Industry 4.0 will support also the formation of company networks, or virtual organizations, by enabling more efficient communication across company walls. Given the general trends towards specialisation and outsourcing in the industry, this could become an effective coordination mechanism. Furthermore, current (bio)pharmaceutical supply chains are characterised by low velocities and large amounts of stocks present at all levels in the supply chain [19]; the adoption of Industry 4.0 should lead to more effective material management and improved responsiveness.

Last but not least, Industry 4.0 will enable both forward flow of information through the supply chain as well as backward flow of real-time patient data with direct communication between manufacturer, clinician, payer and patient, in various ways. Monitoring devices worn by the patient would allow automatically adjusting the treatment (such as time and dosage) to a patient's individual lifestyle, or notify a doctor if it detects that intervention would be beneficial. It would also allow a much better monitoring of efficacy and detecting side effects more quickly. A pharmaceutical pill box or biopharmaceutical self-administered injection (e.g. sub-cutaneous or intramuscular) linked to the internet could send the patient automatic reminders via email or call if they forget to take their medicine, leading to better patient compliance. It could also automatically re-order medicine as needed, which would be immediately known to the manufacturer. Such approaches not only promise improved delivery of the drug, but also lead to higher customer loyalty and retention. With many more possibilities enabled by a connected patient, and radically new business models, this clearly has the potential to change the healthcare industry substantially.

Challenges

As exciting as the vision of Industry 4.0 may be, there are still numerous challenges that need to be addressed. With the increased interoperability required by the internet of things, systems need to be able to communicate, not only on the technical level, but also on the application level. This means global standards and data sharing protocols are absolutely crucial for its success.

Obvious concerns when connecting everything to the internet are safety and data security. Related to data security is also the question of data ownership. Data security is important for example for protection of intellectual property and company data, but is of particular concern to the (bio)pharmaceutical industry

because health data is very sensitive. And an increased connectedness also comes with an increased risk of cyberattacks, which in the pharmaceutical industry could for example lead to tampering with the production process and result in ineffective or even harmful manipulated drugs delivered to the patient. Even without a maleficent attacker, one has to think about liability and accountability in a self-organized production network consisting of multiple parties if something goes wrong. And even for a single smart machine, one can ask the question whether it is the drug manufacturer's or the machine manufacturer's responsibility if the "intelligent" machine makes incorrect decisions.

Finally, self-organising systems require new tools and paradigms for effective control. Since these systems are very complex and rely on many decentralized decision making entities, the use of exact and provably optimal techniques will not be possible. Instead, those systems will be inherently of heuristic nature (e.g., [20]) and the regulatory framework which currently tightly controls every step in the biopharmaceutical industry would have to become much more open to allow for a new type of flexible and self-organized production processes.

Translational Insight

It may be too much to say that Industry 4.0 means another revolution also for the biopharmaceutical industry. But the technology certainly bears great potential, in particular in terms of fusion of automation and robotics systems, track-and-trace capabilities, real-time quality testing and control, greater collaboration between manufacturers and suppliers and end-to-end communication. This will enable the supply chain to be redesigned and customised around the patient and to bring manufacturing closer to patient when desired. Industry 4.0 will play a crucial role in the shift to personalised medicine and enable a higher level of mass customisation than is possible today.

Implementation will require disruptive approaches to transform the supply chain, vendor-manufacturer relationships and datasharing protocols to increase manufacturing flexibility whilst allowing for cost-effective production of small lot sizes. In order to take full advantage of Industry 4.0 the cell and gene therapy sector will need to move more strongly towards digitally integrated and automated or robotically-controlled equipment [e.g. 7, 21-22] rather than the manual, labour-intensive kit in use today. With the supply chain including healthcare providers and patient data, it will also need to consider challenges around data ownership and the implications from patient feedback data. The creation of automated manufacturing and testing solutions, standardisation of procedures across the supply chain as well as real-time traceability has the potential to be game-changing and a critical lever for survival and success for the cell and gene therapy industry. Industry 4.0 adoption will also be a key factor in ensuring increased patient access to these novel biological therapies in an affordable manner.

Acknowledgements

Funding from the UK Engineering & Physical Sciences Research Council (EPSRC) through the EPSRC Centre for Innovative Manufacturing in Emergent

Macromolecular Therapies (EP/I033270/1) and the EPSRC Frontier Engineering Programme (EP/K038648/1) is gratefully acknowledged.

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