Chapter 2
Health 4.0: Application of Industry 4.0 Design Principles in Future Asthma Management

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2.1 Industry 4.0

Industry 4.0 is a well-known industrial concept leveraging individualization and virtualization across different industrial domains. At its core Industry 4.0 strategies empower industries to evolve from manufacturers to service providers, allowing growing amounts of individualization and personalization as a service to client, customers and most likely to patients and formal and informal carers. Recently Hermann, Pentek and Otto proposed an Industry 4.0 definition and suggested Industry 4.0 core components and design principles for Industry 4.0 scenarios on the basis of a comprehensive and systematic literature review [1]. The aim of this chapter is to investigate the applicability of the authors' findings on to the health domain and in particular investigate the scalability of Industry 4.0 design principles into relevant sub-domains such as the pharmaceutical industry.

2.2 Industry 4.0 Components

Hermann et al. started their investigation by suggesting Industry 4.0 components based on their literature analysis. The proposed core components are:

- Cyber-Physical Systems
- Internet of Things (IoT)

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- Internet of Services
- Smart Factories

2.2.1 Cyber-Physical Systems (CPS)

According to Lee, Cyber-Physical Systems (CPS) refer to "integrations of computation and physical processes. Embedded computers and networks monitor and control the physical processes, usually with feedback loops where physical processes affect computations and vice versa" [2]. More recent work on CPS includes socio-economic factors into the definition stating, that "Through cyber-physical systems, the physical world is linked with the virtual world to form an Internet of Things, Data and Services" [3]. For the health domain concrete applications might be the connection of Body Area Networks and sensors in Smart Pharmaceuticals to disease management platforms with either autoregulatory feedback loops or feedback via accessories such as smart phones.

2.2.2 Internet of Things (IoT) and Internet of Services (IoS)

There can be no doubt that things as well as an Internet of Things (IoT) are playing an increasing role in the health care industry and in ambient assisted living, (AAL). The Hyper-connected Society is a vision where the Internet of Everything [IoT, Internet of Services (IoS), Internet of People(IoP)] will create added value and generate growth and prosperity by unleashing digital technological progress [4]. It is arguable if the IoS and the IoT can really be distinguished under an Industry 4.0 approach as the very objective of Industry 4.0 approach seems to be the virtualization of physical processes and its translation into services. However, for the health domain it is clear that things such as smart devices, biosensors, artificial organs, and smart pharmaceuticals are a reality, and one of the key targets of the European digital agenda is clearly to group services around these objects to virtualize the provision of care. The European eHealth Action Plan 2012–2020 is described by the European Commission as "The European Commission's eHealth Action Plan 2012–2020 provides a roadmap to empower patients and health care workers, to link up devices and technologies, and to invest in research towards the personalised medicine of the future" [5]. This clearly constitutes a justification for research on the medical Internet of Things and its enabling technologies such as the 5th generation network (5G).

2.2.3 Smart Factory

Smart factories are considered a key feature of Industry 4.0 and are defined as: "a factory that context-aware assists people and machines in execution of their tasks. This is achieved by systems working in the background, so-called calm-systems and context aware means that the system can take into consideration context information like the position and status of an object. These systems accomplish their tasks based on information coming from the physical and the virtual world. Information from and about the physical world is e.g. position or condition of a tool, in contrast to information from and about the virtual world like electronic documents, drawings and simulation models" [1, 6]. Hospitals and distributed health care providing structures such as GP networks, community nurses, pharmacies, etc. can be without doubt considered "factories" which "context-aware assists people and machines in execution of their tasks." This happens for example through hospital information systems (HIS) or practise IT systems. Current flaws in health care environments are clearly that real time information is only available in a limited manner, so that work-flows cannot be depicted accurately. Sometimes it is not possible to establish beyond doubt where the patient or professional is located or what their current status is. The typical fall-out are disruption to operating schedules when the team is ready in the operating theatre but the patient has not arrived or if patients experience extended waiting times in A&E and outpatient departments. The smartness of "medical factories" might be lagging behind the "smartness" used in other industrial domains. However, this is likely to change in the near future as socio-economic requirements will force health care providers and national economies to find ways to enhance efficiency and effectiveness of health care systems.

2.3 Definition of Industry 4.0 and Its Scalability into the Health Context

Based on the findings of their comprehensive literature analysis Hermann et al. define Industry 4.0 as follows: "Industry 4.0 is a collective term for technologies and concepts of value chain organization. Within the modular structured Smart Factories of Industry 4.0, CPS monitor physical processes, create a virtual copy of the physical world and make decentralized decisions. Over the IoT, CPS communicate and cooperate with each other and humans in real time. Via the IoS, both internal and cross-organizational services are offered and utilized by participants of the value chain [1]."

Value chain organization is paramount to health care industries in order to enhance their effectiveness and efficiency in the face of growing budget pressure. Good examples for shortcomings are counterfeiting issues and unnoted expiry of drugs and medical consumables. Counterfeiting or selling of faked drugs can have a devastating impact onto the quality of care. "Counterfeiters have claimed around a third of the entire market—worth some $200 billion—and are implicated in the deaths of up to one million people each year due to toxic or ineffective drugs" [7]. The uncontrolled expiry of drugs and medical consumables is a substantive challenge to health care organizations in Europe and elsewhere worth billions of Euros each year. Patient flow and patient pathways are the classical models of value chains within the health care industry and thus the health care industry is not any different from any other industry with regard to value chains. It is likely to benefit highly from the implementation of Industry 4.0 technologies and concepts. Future health care will definitely be structured in a modular manner as specialization grows and the global health care model is progressively shifting from a hospital-based professional oriented to a distributed, patient centred care model [8]. One of the core features of distributed patient centred care is that care elements and services are grouped around the patient. Cyber-physical systems (CPS) are not yet introduced to the medical domain but the process has begun. Pharmaceutical companies are working on smart pharmaceuticals, which are fitted with biosensors in order to enable and support the link between the physical and virtual world. Big Data strategies are being tested to cater for individualization and personalized care. New strategies such as Precision Medicine will be based on real time connectivity between patients (physical world) and cloud based algorithms and autonomous systems (virtual world). This will lead to individual combination of cross-organizational services which will be heavilly depending on real time information. This development is coming at a time where new care models call for individual patient budgets offering patients and informal carers more influence and control in managing their health and putting the relevant resources at their disposal [9]. This will have to be supported by new features and functionalities of 5G such as multi-domain orchestration and multi-tenancy.

2.4 Industry 4.0 Design Principles

Industry 4.0 design principles have recently been investigated through a comprehensive literature review by Hermann et al. [1]. The authors analyzed 51 publications related to predefined search terms and identified a set of recurring design principles closely linked semantically to Industry 4.0 and the predefined search terms. The following design principles have been proposed by Hermann et al.:

- Interoperability
- Virtualization
- Decentralization
- Real-time capability
- Service orientation
- Modularity.

2.4.1 Interoperability

The importance of interoperability has been highlighted frequently in the IOT discussion and has recently been pinpointed again in the context of health in the

EU-China white paper on the IoT [10]. In “smart factories” and “factories of the future” interoperability is crucial to enable the seamless flow of contextual information on all levels. Looking at biosensors as part of cyber-physical systems and their back-ends in the virtual domain seamless interoperability is important to enable the entire system loop to perform and continuously exchange information. In cyber-physical systems, it is also important that different services can be aggregated and integrated in order to establish the quantum leap from data readings towards the generation of meaningful information. In a report published by the European Commission on the public consultation on eHealth Action Plan 2012–2020 lack of interoperability has been identified as one of the main barriers preventing the large-scale deployment of eHealth in Europe [11]. In this context, there can be no doubt that interoperability is an important design principle of Health 4.0 solutions.

2.4.2 Virtualization

Hermann et al. highlight that “CPS are able to monitor physical processes” and that “a virtual copy of the physical world is created.” According to Hermann et al. in Smart Factory plants “the virtual model includes the condition of all CPS.” Doubtless these trends are valid for the health domain in many ways. The monitoring of physical processes is the very essence of what is happening in health related processes every day. Patients are being monitored by cyber-physical systems during surgical procedures involving anesthesia every day in a widely standardized process everywhere in the world. However, the sensors placed onto or into a patient by a medical practitioner during syrgery are island solutions. One key challenge is that in most cases these islands are closed loop systems and cannot be connected with other systems, for example the hospital information system (HIS). Also, due to the complexity of the system “human being,” it is so far not possible to create a copy of the entire “physical world” at any time. However, in the health context a valid question is certainly in how far this is reasonable and necessary. The monitoring and virtualization of defined sections of the system might be sufficient until future technologies will allow for more extensive and easier virtualization. The challenge in the health domain is currently the seamless and autonomous virtualization anywhere, anyhow and at any time. This is of particular interest to new strategies, which are aiming to allow for individualization of therapies especially in order to treat chronic, non-communicable diseases [12]. Interesting enough the use of sensors to create CPS in order to enhance the value chain is a concept which is currently boosted by all major pharmaceutical companies for certain chronic, non-communicable conditions, including asthma. Details shall be discussed in the use case section on asthma later on in the paper. Summarizing the analysis, it is fair to assume that the design principles of virtualization seems to be valid for the health domain.

2.4.3 Decentralization

Decentralization in health care has been ongoing since the late twentieth century. Hospital bed numbers have been in decline almost all across Europe and OECD countries for years [13]. This trend is generally perceived as challenging as it does not seem to give sufficient credit to the demographic developments in most countries. On the other hand, more and more patients are being treated in GP surgeries, day clinics, their homes, and over the Internet. Market analysis by the European Commission suggests that mHealth market value will increase to almost 18 billion Euro worldwide by 2017 [14]. Also more and more devices are sold in a bit to measure fitness and wellbeing, such as fit-bits, smart watches, and others. However, there are concerns regarding the accuracy and suitability of these devices. Governance and liability issues are still pending and are so far not solved. The estimated amount of health and wellness related applications on the market is well beyond 100,000. In fact, Forbes predicts that "in 2016, users will trust health apps more than their doctors" [15]. Again only very few apps have been undergoing rigorous testing and even fewer offer guarantees with regard to accuracy.

While there can be no doubt that health care is moving toward a distributed patient centred model with patients, professionals and formal and informal carers increasingly using sensors, smart devices, smart phones, applications and cyber-physical systems, ever more sophisticated requirements are building up with regard to network and telecom providers. Distributed patient centred care requires a seamless and reliable flow of information across different networks and domains. The sophisticated requirements of various industrial domains including health care have led to a variety of white papers by the telecommunication industry [16, 17]. A recent document from the National Health Service (NHS) in England lays out strategy plans to utilize information communication technology to enable patients and their carers to shift more treatment from hospital to home without necessarily increasing the pressure on their outpatient services [18]. Herman et al. explicitly referred in their paper to the use of license plate technology such as barcode and radio-frequency identification (RFID) in Smart Factories in order to enable autonomous decision making. This practice has been used widely in the NHS in England and other national health services [19, 20]. Another important aspect is the consideration of the deployment of intelligence and processing powers into networks. Mobile Edge Cloud (MEC) computing has become more than a buzz-word. It is an attempt to support decentralized decision making at the edge of the network in order to reduce latency and enhance security. MEC is now a popular topic for major network technology providers.

Overall there can be no doubt that decentralization is an ongoing trend in the health domain causing a strong technology pull in order to realize Industry 4.0 design principles. This development is crucial in order to release efficiency reserves in health care and meet the socio-economic requirements of the next decade.

2.4.4 Real-Time Capability

Real-time capability is of general importance for any factory style operation regardless of which domain to ensure proper orchestration of processes. Part of the concept of Individualized Medicine or in the US Precision Medicine is clearly the real-time recognition of individualized requirements in a distributed manner. Patients should wherever possible be treated outside hospitals with exactly the amount of medication required to maximize therapeutic effect and minimize side effects. Disgnostic and therapeutic processes should confluctuate and form a spatio-temporal entitiy. This is related to the concept of "theragnostics" where therapy and diagnostics amalgamate and move closer to real time [21]. Real-time capability as a crucial requirement in the health domain in order to move closer to the implementation of personalised medicine, smart pharmaceuticals and supply chain management.

2.4.5 Service Orientation

Herman et al. give a high level overview of "customer centred" service aggregation where the IoT, the IoS and IoP may add to a set of individualized aggregated services in their Smart Factories vision. This vision is in principle also valid for the health domain and service orientation can therefore be acknowledged as a design principle of Health 4.0. Moreover there is a clear trend by pharmaceutical Industrys towards a shift from being a manufacturer of drugs to becoming a service provider in the health industry. The general underlying idea is to harvest "Big Data" from a huge variety of sensors in smart pharmaceuticals such as smart inhalers and Insulin pens in order to prevent exacerbation and serious episodes, reduce sick days and hospital admission and increase the quality of life, thereby cutting costs and dependencies. From a business model perspective this might mean that a pharmaceutical company not only will sell a drug but will sell disease management as a service. On the other hand procurers for health care providers might soon only accept products, which go beyond the bare delivery of drugs and the ability to deliver patient health data via a defined interface might be an entrance requirement to enter a tender. Patients might be able to authorize the use of their data as a service and sell the data to pharmaceutical companies to speed up trials. All of these scenarios are currently under discussion and the upcoming 5G networks will act as an enabler to boost the service orientation in the health domain. Eventually network slice technology and edge cloud technology will leverage service aggregation across different domains and networks.

2.4.6 Modularity

Herman et al. state that "Modular systems are able to flexibly adapt to changing requirements by replacing or expanding individual modules. Therefore, modular systems can be easily adjusted in case of seasonal fluctuations or changed product characteristics." The advantages of modular systems have been already proven for the health domain as part of a recent large-scale research project funded by the European Commission [22]. Under the FI-STAR project modular software components (Generic Enablers and Specific Enablers) were utilised to create new functionality by simply recombining the different active groups. The application of rules reflecting norms and standards together with software modules has proven to be an effective way of building code faster and establishing new functionalities from predefined building blocks [23]. In the future software modules and algorithms will be offered by vendors such as Google and IBM Watson and will be readily deployed as Software to Data in hospital or health care facility edge clouds. FIWARE, a pan-European initiative has already published a catalogue where the features and interface specifications of modular software elements are highlighted. User may assess and evaluate the catalogue in order to choose from a variety of products to suit their needs [24].

2.5 Safety, Security, and Resilience

Hermann et al. do not touch in their article onto the security dimension. However, from the point of view of the health domain this is an aspect, which cannot be left uncommented. Health care is considered a "critical infrastructure" vital for the day-to-day running of any state. The protection of the functionality of health care infrastructure and the privacy of the personal data is paramount. This might be different from a Smart Factory where security breaches might cause economic losses or structural damage but does not trigger massive liability for personal "secrets" or loss of lives. From a Health 4.0 perspective safety, security and resilience need to be considered hard design principles to protect confidentiality and prevent all stakeholders from incalculable and unpredictable risk. Trust is one of the fundamental principles of health care and is a legal requirement anchored in national legislation and European directives. While there might not be an immediate need to prioritize safety, security, and resilience as a general Industry 4.0 requirement these topics are basic requirements in the Health 4.0 domain. As such, we are suggesting to extend the design criteria established by Hermann et al. for the health domain.

2.6 Health 4.0

Health 4.0 is a strategic concept for the health domain derived from the Industry 4.0 concept. The aim of Health 4.0 is to allow for progressive virtualization in order to enable the personalization of health and care next to real time for patients, professionals and formal and informal carers. The personalization of healthcare will be achieved through the massive use of CPS, (Edge) Cloud computing, the Internet of Everything including things, services and people and evolving mobile communication networks (5G). With the help of cyber-physical systems, software building blocks and Big Data tools (algorithms) "objects" will be virtualized involving a spatial temporal matrix. The virtualization will enable the analysis of snapshots of the physical world in next to real time and allow for theragnostics. This again will allow for Prsonalized/Precision Medicine.

2.7 Health 4.0 Use Case: Narrow Band–Internet of Things (NB–IOT) Hyper-Connected Asthma Inhalers

Asthma is a chronic respiratory disease with symptoms such as wheezing, shortness of breath, chest tightness, cough, and reversible airflow limitation. Symptoms and airflow limitation both change over time. The prevalence of asthma ranges from 1 to 18 % in different countries. Currently, there are about 350 million patients with asthma worldwide, and about 30 million in China [25]. In Scotland the prevalence of Asthma is 18 %. The large-scale epidemiological survey of asthma among children in China in 1990 and 2000 indicated that the prevalence of asthma in children increased by 64.84 % in 10 years. Each year approximately 25 million people worldwide die from asthma. The societal burden of asthma is significant. It is in the interest of all stakeholders, including patients, doctors, carers, and pharmaceutical companies to reduce the societal burden while at the same time to increase effectiveness and efficiency of asthma therapy as well as the perceived quality of service.

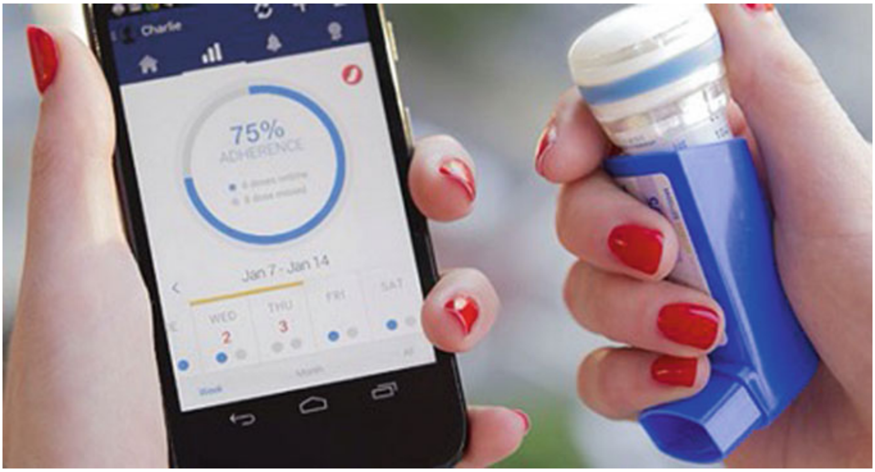

Fig. 2.1 Teva smart inhaler development 2016

New technologies including the IoT, industrial internet, network slice technology (such as the Chinese mIoT), next generation network technologies such as 5G, Narrow Band IoT (NB-IOT), LoRa, Big Data, CPS, edge cloud computing, and new strategies for the safe and secure aggregation of services hold the key for new and massively improved treatment strategies for asthma, allowing for progressive individualization of asthma treatment anywhere, anyhow and at any time and the integration of pharmaceutical and non-pharmaceutical therapy. First conceptual strategies in the asthma domain have been developed by the pharmaceutical industry. Smart asthma inhaler concept studies are available from Teva (Fig. 2.1), Boehringer, GSK, Astrazenica and others [26–30].

In 2004, a global survey involving 29 countries showed that only 5 % of asthma patients could achieve complete control of standardized treatment. Recent studies demonstrate that about 45 % of patients fail to achieve good asthma control in Europe [31]. The reason is mainly because of poor adherence to the treatment of asthma [32].

2.8 Improving Asthma Control Through Cyber-Physical Adherence Management

The improvement of asthma requires adherence and long-term behavioral changes. In order to achieve these objectives latest technologies from the areas of 5G, IoT, Big Data, cloud computing and security have to be orchestrated in order to generate interactive, cyber-physical systems, which can operate in real time. First technology proposals are available based on micro sensors embedded in asthma inhalers. Initially smart phones have been suggested as back-end device to store data and provide processing intelligence by establishing connections to the pharmaceuticals via Bluetooth. Smart phones can serve as gateways to share data with remote servers thus enabling amalgamation of data and big data analysis. Although the use of smart phones as processors and potential gateways is possible in principle some questions have been raised with regards to its reliability, suitability and practicality. Typically asthma patients use not only one single inhaler but two or more different types of aerosols or powder based medications. Many patients store several units of each kind in different places to ensure that it is readily available if needed. All in all this means that several inhalers would have to be connected to the phone via Bluetooth at any time, which is a challenge to battery life and also to the phone's blue tooth router. Another challenge is a conflict with regard to reliability between mobile phones and medical devices in general. While mobile phones generally operate on a "best effort" basis some medical devices are considered "mission critical." "Best effort" and "mission critical" refer to the quality of service (QoS) and can mean very different things. While "best effort" means that data may or may not be sent, "mission critical" offers guarantees with regards to the reliability of a device or process. Clearly, in the interest of the quality of care and quality of experience medical devices to manage asthma cannot operate on a best effort basis as this would jeopardize the very key objectives of asthma therapy, namely maximizing adherence and minimizing the occurrence of severe asthma attacks, hospitalization, and death. Other important aspects include energy efficinency and data protection. Using smartphones as gateways might seem more energy efficinet on the first glance. However, using Bluetooth to connect to the phone and then using the phone to access the radio network is everything but energy efficient. Given the fact that asthma inhalers could account for more than 1 billion connections in 2025 this should be investigated more closely. With regards to security Bluetooth and phone signals cannot be assumed to be safe to the standards legally required in the health domain.

Alternative technologies are at hand to significantly improve the current Bluetooth-based smart pharmaceutical strategy for the treatment of asthma. Narrow Band—Internet of Things (NB–IOT) technology is a low power wide area radio access technology (LPWA RAT) which seems promising. It has recently been standardized and accepted by 3GPP, the global relevant standards organization and is ready to use (technology Readiness Level (TRL) 7–8). Similar technologies have been successfully implemented into smart electric meters and lately into water meters to establish water consumptions of households more accurately. However, this does not mean that smart phones and tablets will not play a role in individualized asthma therapy in the future. Patients will use their smart devices to manage their personal data and obtain therapy recommendations as video downloads. They will also be able to authorize and follow up on the use of their data by medical professionals and researchers.

NB–IOT modules offer an interesting and viable solution in order to allow for enhanced connectivity by utilizing different segments of the spectrum in comparison to smart phones. Typically NB–IOT utilizes significantly lower frequencies (around 800 MHz) than mobile phones (typically around 2 GHz). Due to its physical properties lower frequency waves show better penetration and reach. However, data amount and bandwidth is limited due to requirements for energy efficiency of the devices. The question will be can a cost increase of 3–10 % for the medication be justified through the value added by providing Industry 4.0 features, such as cyber-physical capability, modularity (several drugs and sensors to be connected at the same time), service orientation and interoperability (several services and cyber-physical systems may be aggregated to achieve better asthma control).

In general crucial requirements for Health 4.0 based smart pharmaceutical asthma therapy are:

- QoS needs to be predictable
- Safety and security. Privacy is paramount
- The technology needs to be network agnostic and interoperable
- The technology needs to be safe, secure and resilient
- Connectivity anywhere, anyhow, at any time
- Global product and service interoperability and network capability for global service orchestration

Currently shared demonstrators in Europe and China are under preparation. Standards and interoperability have been discussed during the EU-China dialog on the IoT and have been included in a recent EU-China white paper on the Internet of Things (IoT, mIoT) [10].

2.9 Medical Internet of Things (mIoT) in China

Lack of knowledge about asthma and lack of proper management are important causes of asthma aggravation and high mortality. With the successful application of mIoT in the management of heart disease and diabetes, mIoT is now applied in the management of asthma. Asthma education is an important part of asthma management. With mIoT and 5G, all kinds of video and audio material related to asthma education can be delivered to the mobile terminals of asthma patients, enhancing patients knowledge about asthma and integrating pharmaceutical and non-pharmaceutical therapy. In addition, mIoT makes the assessment and monitoring of asthma easier. For example, asthma patients could complete their asthma control tests and asthma control questionnaires on their cell phones routinely, so that physicians could monitor the condition of their patients regularly. On the other hand health authorities and service providers could utilise the mIoT to assess the dynamics of the condition and the interaction with environmental or behavioural factors.

2.9.1 5G Driven Personalized Asthma Care

The treatment of asthma is frequently based on the use of different types of inhalers to apply pharmaceuticals. However, so far commercially available inhalers do not include CPS to inter-connect the physical with the virtual world and support personalized medicine strategies. This is about to change. While latest generation of sensor technologies now enable the capture of important therapy key performance indicators (KPIs) at the point of care such as adherence, physiological parameters and timing 5G will provide multi-frequency connectivity and multi-modal capability including NB–IoT and mobile telephony to enable the information exchange between the physical and the virtual world. This will in particular enable the use of theragnostic algorithms and also offers the possibility of easy and seamless integration of pharmaceutical and non-pharmaceutical therapy.

The use of smart inhalers will:

- Reduce the number of serious incidents
- Enhances the efficiency of pharmaceutical therapy
- Improve the quality of experience of patients and professionals
- Reduce the number of hospital admissions, sick days and outpatient visits
- Improve documentation and individual risk analysis.

2.10 Conclusions

There is plenty of evidence suggesting that Health 4.0 should be considered a subset of Industry 4.0. Due to the definition of health infrastructures as a critical infrastructures safety (safety, security and resilience) has to be accepted as a mandatory additional design principle in Health 4.0. Mobile phones are unlikely future gateways for smart pharmaceuticals as their current limited Bluetooth routing capability, limited battery life and their "best effort" paradigm make them incompatible with the requirements of smart asthma therapy and general personalized medicine approaches ("mission critical" QoS, multi-tenancy). However, smart phones and tablets will play a role for the reception of video files and reports. Smart pharmaceuticals enabled through 5G technologies including NB–IoT are close to market and will be available within the next years. This will trigger new business models. The pharmaceutical industry might shift from a manufacturing industry to a service industry by taking on new responsibilities beyond the mere manufacturing of pharmaceutical products.

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