Fourth generation technologies in pharmaceuticals-Revolutionizing healthcare.

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Abstract

The pharmaceutical industry, being a highly regulated industry, has been slow to adopt innovation. However, as a result of spiralling costs and an increasing mandate to control the same, as well as an increasing cognizance of the need to drive patient centricity, pharma has opened the doors to innovation. Fourth generation technologies, ranging from 'earables' to 'digital pills', 'genomic-based AI augmented trials' and 'AI- driven drug disovery', 'virtual reality and virtual clinical trials', pharma has come a long way. Yet challenges related to interoperability, data security, data privacy, data ownership and data sharing pose hurdles to this path. This paper explores how fourth generation technologies are disrupting pharma and healthcare and empowering the patient.

A slow adopter, pharma has gradually begun opening its doors to technology and evaluating new operating models to drive a paradigm shift from 'an internal focus' to an externalized 'healthcare for you' approach, prioritizing the needs of the patient. The very fact that the FDA approved 51 connected health products in 2017, demonstrates clearly that while science is the backbone, the Internet of Things (IoT) is the game-changer. It is no longer just about one device or one tool, but about systems 'speaking to each other' and data flowing real-time and seamlessly between systems, and about analytics being leveraged to obtain meaningful, holistic, point of care insights. Digital transformation is now an integral part of corporate strategy and it has been estimated that within five years, 80% of companies would have digitized at last some part of their value chain. Indeed, with the current $55 billion global digital health market expected to grow at 21.4% per year, it has been rightly said that the patient journey is ripe for digital disruption.

Keywords: Artificial Intelligence, Fourth Industrial Revolution, Digital transformation, healthcare industry, fourth-generation DNA

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Introduction

The industry has come a far way, from mechanized production (first generation), to mass production, to automated production, and now to the Internet of Things (IoT) and Artificial Intelligence (AI), constituting the fourth generation [1-3]. Klaus Schwab, the founder of the World Economic Forum, has described it as a system revolution, in his position paper "Fourth Industrial Revolution: What It Means, How to Respond" [4]. Interconnected technology, artificial intelligence, advanced robotics, wearables and earables, blockchain, Ingestible Event Markers (IEMS) and a 'chip in a pill', 3D printed pills, continuous manufacturing, integrated platforms, virtual clinical trials (VCTs), nanopore-based fourth-generation DNA sequencing, 3D printed circuits, companion diagnostics / theranostics to name a few are innovations that are disrupting the pharma and healthcare industry. This paper will analyse how these technologies have been changing the way drugs are being manufactured, clinical trials are being conducted and healthcare is being implemented.

Digital transformation is now an integral part of corporate strategy and it has been estimated that within five years, 80% of companies would have digitized at last some part of their value chain [2]. Indeed, with the current $55 billion global digital health market expected to grow at 21.4% per year, it has been rightly said that the patient journey is ripe for digital disruption [3].

Wearable technology, with revenues of $20 billion in 2015, is expected to grow 3-fold to $75 billion within a decade (IDTechEx) (54). The FDA approved 51 connected health products in 2017 [5].

The 'Cardio Insight Noninvasive 3D Mapping System', a sensor-enabled single-use vest developed by Medtronic was approved by the FDA in 2017. It has 252 electrode sensors and provides a range of electro anatomic 3D maps of the heart, pairs body surface electrocardiogram (ECG) signals from the chest, then combining them with data from a computed tomography (CT) scan of the heart and connecting to the Cardio Insight Workstation, true example of interconnected technology [1].

While wearable's have been playing a key role in transforming healthcare, most of them have been in the form of a patch, wristband, or headband. Today is the generation of 'earables' - wearable electronics designed to be worn around the ear which can be worn like headphones and contain a thermopile infrared (IR) sensor, microphone, bone conducting actuator, integrated circuits (IC) for processing the incoming signals, and a wireless transmission system based on a Bluetooth module. The thermophile sensor is placed within the ear and this can monitor core body temperature far more accurately than skin temperature, which is significantly impacted by environmental conditions. As one needs to have a flexible earable system, the smart device containing ICs is 3D printed, using liquid metal

microchannel interconnects using Galinstan metal, rather than traditional metal wiring [6].

'A chip in a pill', which seemed like a fantasy not long ago, is now a reality thanks to the IEM technology developed by Proteus. The IEM, the size of a grain of sand, contains an IC on which an anode and a cathode are placed. Once the tablet (containing the sensor) reaches the stomach, it is activated by gastric juices. The electric signal generated creates unique signatures which are detected by a wearable patch applied to the skin of the patient. The data generated is confined to the body of the user, since a conductive method of communication is used, thus ensuring data privacy. The ingestible sensors communicate information for about seven minutes after which they become inactive and are eliminated in the faeces or are absorbed in the body [7].

This technology was approved by the FDA in 2012. In 2017, a 'chip in a pill', namely 'Abilify', became the first digital medicine to be approved by the FDA for the treatment of schizophrenia and bipolar disorder. A combination of ABILIFY MYCITE (the digital pill), the MYCITE® Patch (a wearable sensor, developed by Proteus) and the MYCITE®APP, a smartphone application (app), work together to increase patient adherence by tracking drug-ingestion real time. This technology can also significantly connect patients with healthcare providers (HCPs) [8].

Healthcare continuously struggles to deal with challenges of interoperability, and works towards building cloud-based integrated platforms, connecting multiple data sources – 'omics', clinical, Real World Evidence (RWE), etc (inevitably with varying data standards!) to develop a holistic view of the patient. It leverages healthcare integration standards, coding systems, blockchain, a rules-based clinical decision support systems, predictive analytics, customized visualizations and AI to drive real-time data driven decisions. Risk based monitoring (RBM), a methodology which is transforming the way clinical trials are conducted is based on data from diverse sources in a clinical trial being integrated in a centralized data repository and site monitoring visits being largely limited to those driven by Key Risk Indicators (KRIs) being fired when Quality Tolerance Limit (QTLs) or thresholds are being crossed. It is based on data integration tools, predictive analytics, AI to drive real time data driven decisions [9]. Along with clinical and RBM domain expertise, technology plays a key role in RBM and choosing the right partner is crucial [10].

The biggest challenge with electronic health records (EHRs) is the diversity of systems that exist today. For example, Boston alone has 26 different electronic medical records (EMRs). With a pointer tagging patient data to a blockchain, critical medical information could be captured in a cryptographic database and this could be accessible to anyone running the software. MIT Media Lab has developed a prototype system called MedRec (pdf), using a private blockchain based on Ethereum. Not only does it track who has permission to view and change medication records, it also incentivizes miners (such as medical researchers and HCPs) to verify data on the blockchain and rewards them by providing access to aggregated, anonymized data from patients' records that can be used for epidemiological studies. Patient consent is of course mandatory. Since this is computationally intensive, this feature may be removed and resources within the hospital may be leveraged [11].

Dictum Health's, FDA approved end-to-end telehealth platform has a "virtual exam room," which can assess SpO_2, blood pressure, height, weight, temperature, and ECG. This tablet that can connect to various device peripherals, enabling patients and doctors to conduct a secure, HIPAA-compliant video visit, while sharing patient's vitals data directly with HCPs, an example of 'patient-centric' healthcare [5].

Pfizer is leveraging Pega Systems to build a platform with 42 integrated processes towards automating clinical trials [12]. Apple, Johnson & Johnson and Medtronic partnered with IBM to develop the Watson Health Cloud in 2015, and provide analytics services to HCPs [13]. With an exploding world of information, the power, speed and accuracy that a Watson, the self-learning IBM AI tool, that can "read" 100,000s of academic papers in seconds, can bring to the hands of the highly information-swamped HCP is incredible [3]. Genomic-based AI augmented trials may help support a precision based medicine approach [14].

It is important to note that nearly 90 percent of the projects in the AstraZeneca oncology pipeline have a personalized healthcare strategy, and many will be launched with a companion diagnostic. AstraZeneca is also using an integrated genomics approach, where they intend to leverage information from up to 2 million genome sequences, including over 500,000 from AstraZeneca clinical trials [15]. Accenture Labs and 1QBit are using quantum computing to help Biogen accelerate drug discovery [16]. Similarly, Exscientia is partnering with GSK, Sanofi and Evotec respectively to accelerate their drug discovery programs leveraging AI [17] and IBM is partnering with Pfizer to drive drug discovery in its "immuno-oncology" pipeline [18].

Pfizer's is also leveraging virtual reality (VR), using a 3-D cube to explore the human body and it has created a Virtual Reality (VR) Medical Library for HCPs and patients, providing access to the VR 360 degree library [19]. Social media has also been changing the levels of awareness, and decision making authority that patients have been demanding in their own therapy. To quote Dr. Eric Topol, Director, Scripp's Translational Research Institute, 'The patient will see you now', is rapidly becoming a reality [20]. In 2017, the FDA allowed 23andMe (a patient community with over two million genotyped customers) to sell its direct-to-consumer, $199 genetic test kits that provide information about an individual's susceptibility to certain diseases such as Alzheimer's or Parkinson's [21]. 23andMe has already been selling the ancestry tests based on genomic data since 2007.

Since 37% of sites are failing to meet recruitment criteria and up to 10% not recruiting a single patient during a trial [22], 11% of clinical trials are currently leveraging social media for patient recruitment [23]. Social Media has also been effectively used to support virtual clinical trials (VCTs). "VERKKO", Sanofi's successful remote online Phase IV clinical trial to evaluate a wireless blood glucose meter to treat diabetes remotely, recruited 60 patients purely through Facebook. The average

patient age was 56, with some patients being older than 70 and patient satisfaction scores were 4.52 out of 5, demonstrating that social media is also used successfully by old people [24]. Pfizer paved the way for VCTs through its Research on Electronic Monitoring of Overactive Bladder (OAB) Treatment Experience (REMOTE) trial, a US based Participatory Patient-Centered (PPC) clinical trial designed to assess the safety and efficacy of Detrol LA, a treatment for overactive bladder (OAB). The goal was to recruit 600 patients, screened through the Internet, with patients actively managing their own trial activity and reporting results directly to the investigator. The trial used econsenting and recruited patient's online, but did not succeed [25].

While pharma has been very wary of applying digital technology to improve its manufacturing and supply chain operations as this is a highly regulated industry, it is rapidly acknowledging the fact that digitization holds tremendous potential in addressing growing challenges related to globalization, increasing supply chain complexity, escalating costs and price control, a lack of integrated planning tools, complex product portfolios, heightened customer segmentation as the world starts slowly moving towards a personalized medicine approach, the growing risk of counterfeit drugs and rising regulatory scrutiny [2]. The development of a block chain-based system to ensure a chain-of-custody log could save approximately $200 billion of losses due to counterfeit drugs annually [26].

Pharma is working towards implementing a digital supply chain ecosystem, including virtual supply chain control tools, cloud-based information architecture, and a digitally enabled physical supply chain, supporting real-time visibility and faster decision making [27]. Inventory could be monitored through RFID-tagged pillboxes and storage cabinets, enabling the automated replenishment of drug stocks, or smart pill bottles could be used in clinical trials tp monitor drug usage [28].

The use of sensors throughout the supply value chain can enable dynamic decision making by sales and operations. This can shorten lead times, drive efficiencies and reduce stockouts. Digitization and analytics can reduce downtime by 30 – 40 percent, improving overall equipment effectiveness downtime (OEE). Machine-to-machine communication and machine-learning algorithms can drive seamless processes, predictive maintenance, and automatic corrective actions and deliver major manufacturing efficiencies. It may help to look beyond pharma, at Siemens' Digital Factory offering, and GE's Brilliant Manufacturing suite, which optimize manufacturing through real-time analytics, process monitoring and sensor enabled automation [2].

Notably, GE launched its Brilliant Manufacturing suite in 2015 and planned to increase the connectivity of its machines and materials by 400% within one year [29]. Continuous Manufacturing (CM) technologies, supported by Process Analytical Technology (PAT) monitoring, is disrupting the batch processing mode of the pharma industry, driving efficiencies and shorter production times. It is critical to ingrain quality by design (QbD) in the product lifecycle. Orkambi, Vertex Pharmaceuticals' cystic fibrosis drug was approved by the FDA in 2015 and Janssen has worked with FDA's Emerging Technology Team (ETT) to leverage CM for Prezista, for HIV treatment. Continuus Pharmaceuticals, Novartis' commercial spin-off of the Novartis-MIT Center for Continuous Manufacturing, was awarded a $4.4 million contract for establishing a scientific and risk-based approach to monitoring drug quality in an integrated continuous manufacturing (ICM) model [30].

3D printing of drugs can not only decentralize production, but drive huge cost-efficiencies, even at low volumes. Aprecia's 3D printed drug, Spritam for the treatment of seizures, became the first 3D printed drug to be approved by the FDA in 2015 [31]. This may also help the precision medicine approach, where customized drugs could be printed out at a low cost. Advanced robotics, augmented reality (AR), a live, direct or indirect view of a physical, real-world environment whose elements are augmented (or supplemented) by computer-generated sensory input such as sound, video, graphics or GPS data and mixed reality (MR) - where physical and digital objects co-exist and interact in real time, will further transform human–machine interaction and automation. One area where this has been effectively leveraged is robot-assisted surgery (RAS), assisting surgeons to manipulate robotic instruments [32].

The objective of Novartis' 'Trials of the Future' initiative is to digitally connect and aggregate medical device data during clinical trials. It is partnering with Qualcomm, leveraging its 2net Platform, 2net Hub and 2net Mobile technologies and automating the collection of patient data from patient's homes during clinical trials [33].

Novartis' two pronged digital strategy includes "around the pill" and "beyond the pill" applications. The 'around the pill' approach leverages technologies that include adherence tools and applications, intelligent drug delivery systems, monitoring tools, precision diagnostic tools, and behavior change applications. The 'beyond the pill' approach includes things such as digital therapeutics. Vasant Narasimhan, CEO, Novartis, believes that digital technology could save up to 25% on the cost of clinical trials. He believes that Novartis' future as a medicines and a data science company is centred on innovation and access [34].

Another interesting development is the handheld digital scanner developed by Smith & Nephew which enables clinicians to make an on-the-spot diagnosis as to whether a wound is infected with harmful bacteria. The diagnosis is over 50% more accurate than the current methods and 90% faster [35].

Fourth-generation DNA sequencing technology, using nanopore-based sequencers, enables the rapid sequencing of the entire human genome for less than $1000, and the single-molecule techniques enable the study of the interaction between DNA and protein, and protein and protein [36]. Further, AI can be applied to drive a systems biology approach, using high throughput biology data sets, including genomic, metabolomic, and proteomic data [37] to define multi-omics molecular "portraits" and assess relative health risk against the population baseline, to discover disease fingerprint markers and provided diagnosis/prognosis risk stratifications, especially in the field of oncology [38]. Dr. Daniel Kraft's vision of patient-centred,

tech-led healthcare is undoubtedly the future. His perspective, that while companion diagnostics are often being prescribed along with drugs, there may well be a time where apps will be prescribed along with drugs instead and doctors may be held medically negligent for not using AI to diagnose cancer, indeed is indicative of where healthcare is heading [3]. AI systems are expected to generate $6.7 billion in global revenue from health care by 2021, as compared with $633.8 million in 2014, as per Frost and Sullivan [39].

The $ 1.45 billion funded, Precision Medicine Initiative (PMI) / 'All of Us', which is currently in the beta phase, plans on sequencing the genomes of over a million participants over five years. Notably, the sequencing of a million people for rare, genetically dominant conditions is expected to yield 49,500 false positive results, as against only 8,000 true positive results [40]. The only way that one could practically derive meaningful insights from such a large volume and variety of data sets is by leveraging AI. In 2016, China launched a PM initiative, where it is investing no less than $9 billion towards the sequencing, sharing and analysis of more than one million human genomes. Statistics are telling - for every $1 the US will spend on the PM Initiative, China will spend $43. iCarbonX from Shenzhen plans to collect sequencing data for more than a million people, along with other biological data using tools, ranging from biosensors to 'smart toilets'. It will leverage AI to develop a "digital form of you" Wuxi Nextcode (an early investor in 23&Me) has one of the largest cloud computing based genomic data platforms using Machine Learning (ML) for the storage and computing of the huge amount of data that results through PM for the diagnosis of rare diseases and cancer, and for the development of new therapies [41].

Deep Genomics's AI software uses predictive algorithms for identifying mutations in DNA and correlates these to genetic disorders and also predicts the effect of the mutation on the overall genome as well. It already has a pre-existing library of over 300 million genetic variations, which has provided significant insights for the treatment of autism, cancer, and spinal muscular atrophy; genetic tests complemented by AI will significantly facilitate point of care decisions [42].

Liquid biopsies or the liquid gold rush of healthcare, (a non-invasive procedure for analyzing the DNA in blood samples for diagnosing cancer) are expected to be worth $40 billion in 2017. Frost & Sullivan have predicted that by 2025, between 100 million and 2 billion human genomes could be sequenced. Speed, scalability and accuracy required to achieve these goals will be enabled only by AI [41].

The future goal of healthcare is to minimize patient burden and to optimize passive data capture, enabling clinical decision support based on algorithms running on real-time dynamic data. Yet only 6% of healthcare and pharma have described themselves as digital-first as compared to 11% in other sectors, probably owing to the stringent regulations impacting healthcare and the nature of this industry which has always been slow to accept change [43].

In a world where cyber-physical systems are inter-connecting humans, machines, and resources, one needs to prioritize data security, privacy, ownership and transparency [44]. In 2016, the data of 34,000 patients of Quest Diagnostics, which employs IBM Watson's Genomics platform, was hacked. The consequences of cyberespionage could result in insurance fraud, identity theft, and the intrusion of patient privacy, employment hurdles and the payment of ransomware. While Health Insurance Portability and Accountability Act (HIPAA) and the Genetic Information Non-Discrimination Act (GINA) have been implemented to cover some of these challenges, an intellectual pool of interdisciplinary experts across areas such as genomics, AI, healthcare, clinical research, data-sciences, intellectual property, ethics, sociology and governance should be created to help define the right approach towards ensuring data security and protecting the rights of people, while driving scientific progress. At the end of the day, one cannot forget the basic principle: 'beneficence first, access to all [44].

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