https://doi.org/10.31925/farmacia.2021.2.7 **REVIEW**

HEALTH CARE DIGITALIZATION, THE STRAIGHTEST PATHWAY TO PERSONALIZATION

PASCALE GAUTHIER *, JEAN-MICHEL CARDOT

Faculty of Pharmacy, Auvergne University, Clermont-Ferrand, France

**corresponding author: pascale.gauthier@uca.fr*

Manuscript received: January 2021

Abstract

Digitalization appears as a full mutation in the entire world, including health care. From applications (apps) to sensors, the digital is now fully integrated in daily life for patients. Monitoring treatments more easily and improving the design for drug packaging remain the most challenging points for medicines and the digitalization appears as a useful alternative. An overview of some relevant proposals that integrates personalization to users and drug forms is proposed with a specific focus on cardiology treatments and COVID-19 innovations.

Rezumat

Digitalizarea apare ca o schimbare complexă în întreaga lume, inclusiv în sistemul sanitar. De la aplicații la senzori, digitalizarea este acum complet integrată în activitățile zilnice ale pacienților. Monitorizarea mai ușoară a tratamentelor și optimizarea designului ambalajelor pentru medicamente rămân cele mai importante provocări, iar digitalizarea este o alternativă utilă. Articolul propune o prezentare generală a unor alternative relevante care vizează personalizarea abordării terapeutice și a tipurilor de medicamente, cu accent pe tratamentele cardiologice și inovațiile apărute în contextul pandemiei COVID-19.

Keywords: digital, Apps, packaging, observance

Introduction

More than a passing fad, the digital is nowadays, fully integrated in our daily life. Communicate world-wide across borders seems definitely possible thanks to a large number of systems, accessible to all people, without age or price discrimination. Simplifying treatments, monitoring or offering easy reminders are definitely the main purposes of these digital healthcare proposals [25, 29]. This paper will present the digital healthcare innovations considering an extensive search on internet and journal publications. This approach will give a panoramic view of the paramount importance of digital healthcare nowadays.

Current situation and definitions

Drug dosage forms, packaging and design

A drug dosage form or medicinal product is defined as a product prepared and used to treat a disease (following the Public Health Code definition). It is highly regulated for its dispensing and delivery, depending on whether it is a prescribed drug or an over-the-counter (OTC) product. Medicines are available with a large diversity in delivery route (oral, injectable, pulmonary, ophthalmic), in type of release (immediate, prolonged) or in dosage forms (tablets, capsules, infusions, pressurized forms, powder inhalers). For all these specific drug forms, the packaging represents definitely much more than a simple container or a protection [27]. As for being efficient any product should be correctly used and taken, the packaging can help the monitoring, the distribution control and the usage. It is more and more an integrated part of the medication and it is seen by the patient as a true partner in dispensing and a compliance support. The secondary packaging that contains the product in primary pack has shown added value on the information and the protection. Indeed, safety and tamper evident systems are correlated with new rules for preventing counterfeiting, that represents a worldwide issue with more than 15% (as described by World Health Organization WHO [55]) and is now one of the main purposes of the secondary packaging (Guideline 2011/62/EU, serialization Feb 2019) [14, 15]. All those needs and trends imposed a global design approach that should be integrated in early stages of development. The design encompasses the ease of use and helps the medicine to be rightly and easily used by the patient, which is fundamental for the compliance which is a major issue, considering that more than 50% of patients with a chronic disease do not comply (as described by WHO statistics) [26, 29].

Users' definition

There is a large diversity of users, from the early age to the elderly, all of them are showing specificities that should be correctly understood and studied. The challenge of elderly people (over 80 years) represents a major issue; both, drug forms and packaging, have

to be specifically adapted or specially designed for them [52]. The youngest people, from children to teens, were previously described [28, 30] but now, the large target of "Z generation" is arriving. They are the first generation born with the internet and they know how to use it and represents for them a vector of knowledge. They are often hyper-connected (5 simultaneous screens compared to 2 for their elders) and – for example – "you-tube" and chats are the new sources of information for 13 - 17 years. This "Z generation" is diverse, but more mature than their elders, who were more dreamers. They invent their own codes and all the brands should consider them, because the "Z" likes to exchange and give their opinion [4]. This new generation has changed the rules, as example the Digital Native Vertical Brand (DNVB) are now free from regular distribution systems as they are directly connected with consumers with internet and mobile phones. The healthcare sector and drug forms remain specific products but should be associated with this society evolution; in any case, young people will be the main future users of medicines. They could be seen as born and linked with mobile applications and for them a fixed PC is hardly understandable, definitely, for them, mobility and instantaneity are the key words.

Aiming to have a current perspective on this topic, a search was performed though Google, Scholar Google, PubMed, but also search engines using keywords alone or in combination such as digital, medicine, personalized medicine, health apps, connected-devices, e-health, m-health, connected things, AI (artificial intelligence). In addition, guidelines, concept papers and approvals from health institutions or legal sites such as WHO, EMA, FDA, EudraLex were used.

On a larger extent similar queries were performed on newspaper sites and free magazines.

The survey was performed limiting the dates from 2015 to 2020, with exception of basic definitions and guidelines, to follow the fast evolution of this field.

Using the following keywords (digital medicine) OR (health apps) OR (e-health) OR (m-health) OR (connected things) OR (connected-devices), the results indicated a great interest of the digital world on health. Based on Pubmed, 46869 results returned from 2000 to 2020, on the period 2015 - 2020, 31083 results were displayed, with 9264 publications only for the year 2020, indicating the strong development of this field confirmed by the 1042 publications recorded for the sole January 2021. For the year 2020, Google scholar recorded 26600 entries. The same request in Google returns around 622 million of web pages.

On the same time period, 2015 - 2020, for news-papers such as the NY times site, the sole keyword Health Apps returns 3277 results and for connected things 4899. For economical journals like Forbes 484 and 243 results respectively. For medical journals, a reference such as the Lancet, with similar keywords, returned 32 articles or 10 for Health apps and connected devices, respectively.

In order to give an approach of the impact of digitalization in health, the main topics were assessed and summarized below using mainly common free access sources.

Digital world definitions

The digital world encompasses various elements of the healthcare system. Electronic health or e-health is defined by WHO as the use of electronic resources to provide healthcare information, to improve the public healthcare service (professional education) or to enable data transfer. M-health refers to e-health rendered accessible *via* mobile devices such as tablets or smartphones, intended for professionals or patients. The whole digital market appears huge and tripled between 2015 and 2020, representing nearly 400 billion dollars saved from the global bill in developed countries in 2017. Apps (mobile applications) represent applications tailored to a mobile platform and executed either locally or on a remote server. TeleHealth and eTeleHealth involve the consistent and accurate remote monitoring and management of health conditions, and vital signs monitoring. Digital also depicts bio-sensing wearables, (the analytical devices that convert a biological response into an electrical signal providing a continuous monitoring of all the changes in physiology). Finally, artificial intelligence (AI) corresponds to the creation of intelligent machines that work and react like humans (as example recognition, learning, problem solving), but need upfront to be programmed and trained by humans [25, 29, 53, 56].

Digital world main guidance

Regarding digital and healthcare, the Food and Drug Administration (FDA) recognizes that the progression to digital health offers the potential for more efficient patient care and all the guidance have been adapted to facilitate innovations. Medical Device Data System (MDDS) issued a classification from Class III (high risk) to Class I (low risk), without any specific pre-market review requirements. Distributors (that do not manufacture mobile medical apps) are not responsible and not subject to regulation [17, 20, 21]. The European General Data Protection Regulation (GDPR) has been implemented for the protection of all personal data [16].

Thanks to digital, there is a better management of treatments and pathologies. By 2030, an autonomous patient will emerge whose place is being reconsidered in a digitalized and modernized healthcare universe that provides to de-compartmentalized practices (Figure 1). It should not be forgotten that all these systems have been created by humans and all AI products have been taught with examples selected by humans [41].

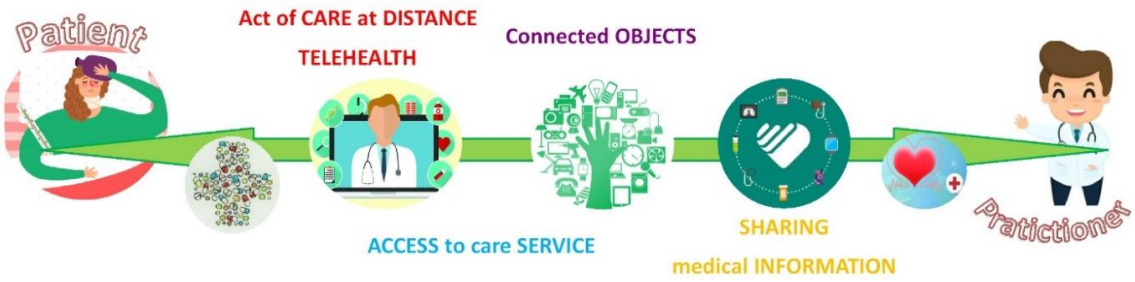

Figure 1.
Digital healthcare from patient to doctor [25, 41]

The Covid 19 pandemic crisis has moved one step further with digital assistance of Apps to track disease, cluster identification, contaminated and contact people; numerous new systems were developed and some of them pushed by authorities to monitor the pandemic situation [23]. As an example, in March 2020, the Loop system was launched, a new clinician-led monitoring service utilizing the company's proprietary FDA-cleared (Class II) solution, for reducing hospital visits and improving home monitoring for patients confirmed, suspected, or at risk for COVID-19 [45]. Numerous similar systems have been developed all over the world and it seems that the Covid pandemic situation multiplied the innovative digital systems.

World of health Apps

The world of Health Apps has shown a huge increase (threefold between 2015 and 2020) to reach more than 325,000 publications and more than 3.7 billion downloadings in 2017. This health market appears really fragmented (55% of Apps downloaded less than 5000 times) and it targets all diseases with a main focus on chronic diseases (31% of Apps market). Heart, circulation and blood (24% average activity level) have been noticed as the third healthcare sector, ranking just after Apps helping connect with MD (30%) and Apps dedicated to diabetes (27%). Diabetes remains the first leading therapy field for M-heath solutions, followed by obesity and depression. Looking on the greatest potential size market, hypertension (1.1 billion) and cardiovascular diseases (1 billion) are the two first, followed by obesity (600 million), diabetes (422 million) or depression (300 million) [46]. A better understanding, a real therapeutic education on diseases and drug forms, can be easily implemented and integrated into everyday life. This whole sector of chronic disease that needs to be correctly understood and managed represents a main issue. After cardiac diseases or diabetes, oncology is largely targeted by editors; an evolution emphasized in the *Lancet* [8]. Definitely, smartphones are useful tools for providing so easily information on health; people just have to check the topic they want, wherever they are.

As all these new systems are required elements of the digital native, they should be correctly conceived and integrated on the whole healthcare system. Various papers have emphasized how smartphone Apps can present a positive impact on medication adherence [43, 59]. As an example, they offered useful systems that help children to play an active role in their health treatment and they provide a helpful assistance with the knowledge of all diseases. In any of the cases, smartphone Apps should be tailored to age group children and should take into account professional experiences (from pharmacists to practitioners) for being simply used, as personalized tools. Definitely, compliance Apps will allow children to take responsibility for their health, to be full actors in their treatment and can help them during their transition to adulthood.

The Covid crisis has unfortunately represented a worldwide example of the challenge where digitalization can be helpful. Korean people have been tracked with specific Covid Apps, useful tools to follow people that have been infected by Covid virus and many other countries have proposed similar Apps very helpful during these hard-epidemic moments. As an example, an UK university has developed an innovative device to detect Covid 19 in 30 minutes, using an intelligent smartphone App, that incorporates AI, image processing and molecular virology [40]. Another research program is running to develop a standardized UK-wide system for detecting coronavirus in wastewater, in order to provide an early warning of future outbreaks and reduce reliance on costly testing of large populations. At any time, it should not be forgotten to use them correctly, with the sole aim of preventing the Covid dissemination and not aiming the personal tracking. Overall, those systems which could be seen as a restriction of freedom, are well accepted by the population in the crisis period we are facing. However, the border is minuscule and should be carefully observed, the digitalization should represent a progress and not a dangerous system.

World of Internet of Things (IoT)

The Internet of things (IoT), established as a mainstream technology in consumer markets (more than 25 billion in 2025) has shown a large development for the cardiology sector [31, 32]. At the beginning, products could follow easily the heartbeat during sport practice or in the case of different cardiac diseases. Going

one step ahead, in 2012 the first Lifewatch® V was proposed, and appeared as a classical mobile phone that integrates various sensors for measuring ECG and detecting abnormal heart rate in 30 seconds [6]. This helpful "all-in-one health" measurement can indicate the level of oxygen and glucose in the blood, and also inform people on their state of stress and their body fat. Various connected tools propose a large diversity of systems, going from a simple measure of blood pressure monitoring to a more complex IoT that can integrate a digital stethoscope and allows following more easily the main cardiac functions [58]. Patients have also the possibility to track their weight with connected scales or to analyse their sleep cycles during the night (tracking of heart rate and snoring detecting) [57]. All these connected tools easily integrated into everyday life are providing an easiness of monitoring the cardiac function, even by patients themselves. In 2015, the Apple watch® was used as a part of a hypertension program pilot to track several hundred patients who were struggling to control their blood pressure [44]. Typically, this system has been found as impactful for changing behavior and promoting lifestyle modification; definitely these watches can be seen as a game changer for patients (Figure 2). EMA will issue in September 2021 a new guideline on combined MD and drug taking into account the possible presence of software [11].

Figure 2.
IoT and healthcare [6, 44, 49, 57, 58]

World of smart wearable

Smart wearables are described in a reflection paper proposed by the European Commission and seen as providing unprecedented opportunities of solutions in healthy ageing and patient monitoring. They are defined as body-borne computational and sensory devices which can sense the person who wears them and/or their environment [18]. Wearables can communicate either directly through embedded wire-less connectivity or through another device and they have shown a continuous evolution (market forecast to grow into a multi-billion-euro business in the next 5 - 10 years from now). They are largely used for cardiac diseases and integrated as Blood Pressure Monitors, Defibrillators ECG Monitors. Watches can be used for monitoring cardiac functions and Bristol-Myers Squibb (BMS) - Pfizer Alliance and Fitbit are working together to help drive timely diagnosis of atrial fibrillation for improving earlier detection in individuals at increased risk of stroke [3]. There is a large development of textiles that integrate sensors [18], Servier and Bioserenity have launched in January 2019, Cardioskin™, a smart T-shirt which functions as a portable and wearable electrocardiogram that can monitor the heart for unlimited duration. The patient can input symptoms through a connected mobile App and that step further helps the cardiologist to correlate analysis of the data collected by the T-shirt and any related symptoms (Figure 2) [49]. Around 1.2 billion people suffer from hypertension (the main risk of heart disease and stroke) but only half diagnosed; all the system involved in detection (including digital offers) can be seen as really helpful. The first randomized controlled trial has emphasized on the efficacy as a social media-based home cardiac rehabilitation and secondary prevention program delivered *via* the platform *We chat* (Smart-CR/SP). Significant improvements have been shown in functional capacity, control of systemic blood pressure, awareness of coronary disease; users have reported the huge usability and acceptability of this system [7].

World of smart packaging for drug forms

After the idea of packaging as a partner, it is the era of smart packaging in relation with this full digital world which is now an ever-changing reality of our daily life. Datamatrix or NFC tag are easily integrated on secondary packaging for protecting drugs against counterfeiting [37], or for providing an assistance for monitoring regimen (Figure 3). They have been noticed

on EMA new information on electronic product information [19, 25, 29].

Numerous primary packs, directly in contact with medicines, integrate the digital (whatever the route of administration); all these proposals can be helpful for monitoring treatment or for a better use of devices: smart blisters for oral drug forms, smart bottles for liquid or numerous connected devices for injectable drug forms (from auto injectors to connectable pen in relation to Apps) [24, 26, 29]. Screen and digital counters can also be added in devices for ophthalmic or respiratory administration; they help the treatment monitoring, avoid overdosing, and explain the correct use of the devices (figure 3). Digital can also be directly integrated into the drug forms with sensors embedded in pills [5] (first drug form accepted by the FDA in the psychiatric disease); definitely all these systems are especially helpful for chronic diseases that request a perfect compliance of the treatment.

Figure 3.
Digital and drug packaging [2, 13, 42, 47, 48, 51]

World of 3D printing

There is a good condition for the global medical 3D printing with an average annual growth of 17.7% that should reach 3.51 Bn in 2025 [1]; a large development of 3D printing focusing on biomedical and prosthesis, mainly cardiac elements [34]. The 3D printing represents also a new tool for building biomaterials or manufacturing objects as human organ. As an example, a doctoral student from Zürich University has developed a method comprising magnets using 3D printing and used an artificial heart pump to demonstrate the operating principle [10]. Other research laboratories have teamed up to create a polymeric heart valve using a digital modelling prototype [54]; definitively the digitalization represents an essential tool, of which we are far from having exhaustively explored. Researchers from the UK and US have developed a 3D printed device with a controllable system for on-demand drug delivery *via* an integrated magnetic field. A system seen as a reusable method for localized disease treatment (oncology) where the 3D technology can achieve detailed and flexible spatial composition and provide easily available, starting materials (like colloidal inks, bio-inks) [50]. At last, 3D printing represents also a way to manufacture drug pills, in 2015 FDA has approved an antiepileptic drug pill that presents a quicker dissolution than regular manufactured tablets [38, 60].

Artificial intelligence (AI) and healthcare

The AI is arriving in health care with positive results to understand the computer science informatics of large datasets, but it should require a systematic evaluation prior to integration in clinical care. In the healthcare system, two definitions are put forward: the possibility of automating certain processes and the notion of machine learning where algorithms and programs sometimes perceive signals inaccessible to human understanding. Since 2017, there is a large development of AI in health care that presents a great potential with the need for systematic evaluation prior to integration in routine clinical care that should not be under-estimated [9]. In 2018, going one step further, the first AI system that detects diabetic retinopathy without oversight from a specialist received the FDA approval and now the AI is fully implemented as a useful tool in the medical diagnostic sector specially to detect and classify diseases [22, 33, 35]. One more example was given during the pandemic crisis by researchers from UK universities that have developed an innovative device to detect COVID-19 in 30 minutes using an

intelligent smartphone application. A current system is capable to perform diagnostic at any location with minimal training. With the AI, the App will automatically update the database and will track down all individuals in close contact with the newly identified patient [36].
There is a large development of intelligent medical diagnosis objects that can help practitioners and are recognized by FDA [9]. EMA issues also series of recommendations such as electronic product information for human medicines in the EU: key principles and strategic consideration (EMA Regulatory Science to 2025 strategic reflection [12]. In any case, AI represents a tool that has been imagined and created by humans, the digital system corresponds to unlimited memory and statistic process definitely helpful, but it remains (only) one more tool in the larger development of science machine.

Conclusions

In conclusion, the healthcare digitalization is no longer a dream and appears definitely fully established as a reality. After an exponential progression health apps seem better controlled, more focused, and have additional functions such as advisory utilities such as therapeutic education for example on severe diseases. The COVID-19 pandemic also accelerated the development of new systems. Looking on IoT, their full inclusion on daily life seems helpful for the healthcare management, as well as the large development of easy-to-use wearable systems. Smart packagings that enclose digitals are also increasing, and the next challenge is a better integration of all these tools. Now, the next challenge will be to integrate all these systems in the whole healthcare system and to choose their best use, without slaving ourselves to machine or enabling too many commercial offers, to create the best future integration for all new scientific developments. Digitalization is moving so fast that the next 5 years will comprehend a total revolution in the conservative world of pharmacy.

Conflict of interest

The authors declare no conflict of interest.

References

1. Allied Market Research, 3D Printing Healthcare Market Outlook, 2026, www.alliedmarketresearch.com/3d-printing-healthcare-market, 2019.
2. Biocorp Connected Devices, https://biocorpsys.com/en/our-products/connected-devices.
3. BMS, The Bristol-Myers Squibb-Pfizer Alliance and Fitbit Collaborate to Address Gaps in Atrial Fibrillation Detection with the Aim of Accelerating Diagnosis. https://news.bms.com/press-release/partnering-news/bristol-myers-squibb-pfizer-alliance-and-fitbit-collaborate-address-g, 2019.
4. Bonnafous P, La génération Z multiple et habile. *Addiactive*, 2017; 105 (oct-nov-déc): 6-7; https://fr.calameo.com/read/0061022600622eb0cfe0a?authid=XYIjDAIzzmHh
5. Cision PR, Newswire Otsuka and Proteus® announce the first US FDA approval of a digital Medicine system: Abilify My Cite® (aripiprazole tablets with sensor), www.prnewswire.com/news-releases/otsuka-and-proteus-announce-the-first-us-fda-approval-of-a-digital-medicine-system-abilify-mycite-aripiprazole-tablets-with-sensor-300555280.html, 2017.
6. Comstock J, LifeWatch gets FDA clearance to run cardiac monitoring software on Android phones. www.mobihealthnews.com/46767/lifewatch-gets-fda-clearance-to-run-cardiac-monitoring-software-on-android-phones, 2015.
7. Dorje T, Zhao G, Tso K, Wang J, Chen Y, Tsokey L, Tan BK, Scheer A, Jacques A, Li Z, Wang R, Chow CK, Ge J, Maiorana A, Smartphone and social media-based cardiac rehabilitation and secondary prevention in China (SMART-CR/SP): a parallel-group, single-blind, randomised controlled trial. *Lancet Digit Health.*, 2019; 1(7): e363-e374. *Erratum* in: *Lancet Digit Health.*, 2020; 2(1): e15.
8. Editorial, The Lancet. Artificial intelligence in health care: within touching distance. *Lancet*, 2017; 390 (10114): 2739.
9. Eidgenössische Technische Hochschule Zürich Heart pump from a 3D printer https://ethz.ch/en/news-and-events/eth-news/news/2018/10/heart-pump-from-a-3d-printer.html, 2018.
10. EMA, Guideline on the quality requirements for drug-device combinations, EMA/CHMP/QWP/BWP/259165/2019 Draft May 29, 2019, www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-requirements-drug-device-combinations_en.pdf.
11. EMA, EMA Regulatory Science to 2025 EMA/110706/2020. www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf.
12. Ethimedix solo smart bottle. www.ethimedix.com/wp-content/uploads/2016/02/SOLO-Flyer_EN-3.pdf.
13. Eudralex Directive 2011/62/EU on falsified medicines L174/74-87 of June 8, 2011, https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf.
14. Eudralex regulation on safety of medicinal packaging L32/1-27 October 2nd, 2015, https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2016_161/reg_2016_161_en.pdf.
15. European Commission What does the general Data protection regulation (GDPR) govern? https://ec.europa.eu/info/law/law-topic/data-protection/reform/what-does-general-data-protection-regulation-gdpr-govern; Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) L119/1-88 dated May 4th, 2016 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679&from=fr.
16. European Commission Medical devices sector overview https://ec.europa.eu/growth/sectors/medical-devices_en; and Council Directive 93/42/EEC concerning medical devices L169/1-43 dated June 14, 1993.

17. European commission Smart Wearables Reflection and Orientation Paper Including Feedback from Stakeholders December 2017, https://ec.europa.eu/newsroom/dae/document.cfm?doc_id=50020.
18. European Medicines Agency HMA–EC collaboration, Electronic product information for human medicine in the UK: key principles. EMA/503860/2019, www.ema.europa.eu/en/documents/regulatory-procedural-guideline/electronic-product-information-human-medicines-european-union-key-principles_en.pdf.
19. FDA, Guidance for Industry a Policy for Device Software Functions and Mobile Medical Applications, www.fda.gov/media/80958/download, 2019.
20. FDA Guidance for Industry Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices September 2019, www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-device-data-systems-medical-image-storage-devices-and-medical-image-communications-devices.
21. FDA News release FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems April 11, 2018, www.fda.gov/news-events/press-announcements/fda-permits-marketing-artificial-intelligence-based-device-detect-certain-diabetes-related-eye last access.
22. Fievet C, Santé 3.0: le Covid-19 a provoqué une épidémie d'innovations www.wedemain.fr/Sante-3-0-le-Covid-19-a-provoque-une-epidemie-d-innovations_a4728.html, 2020.
23. Gauthier P, A complete world of design adaptation and product specificities for injectable drug Delivery. *Therapeutic Deliv.*, 2017; 8 (11): 933-937.
24. Gauthier P, Electronic health and the role of software in drug dispensing and administration. *Therapeutic Deliv.*, 2016; 7 (10): 659-664.
25. Gauthier P, Packaging as a partner for patient compliance. *Aerosol Europe*, 2016; 2 (7): 17-21.
26. Gauthier P, Le design, atout indispensable d'un packaging innovant, 14th Perfume Cosmetic and Design, Paris, 1/02/18, Paris - 'Is design a weapon to make packaging more innovative?' *Aerosol Europe*, 2018; 26(6): 15-17.
27. Gauthier P, Cardot JM, Developing Drugs for Children and the Adjustment of Medication - Is It a New Challenge or an Adaptation of Past Ideas? *Journ of Pers Med.*, 2011; 1(1): 5-16.
28. 29 - Gauthier P, Cardot JM, 'How digital and healthcare can benefit to users.' *Packaging Digest*, 2019, www.packagingdigest.com/medical-packaging/how-digital-healthcare-and-packaging-benefit-users.
29. Gauthier P, Cardot JM, Teenagers as a Moving Target: How Can Teenagers Be Encouraged to Accept Treatment?. *J Personaliz Med.*, 2012; 2(4): 277-286.
30. GSMA Intelligence, Internet of Things. www.gsma.com/iot/resources/the-gsma-guide-to-the-internet-of-things-2, 2019.
31. GSMA Intelligence Global mobile trends, What's driving mobile industry? www.gsmaintelligence.com/research/?file=8535289e1005eb248a54069d82ceb824&download, 2016.
32. Hand S, IDx-DR Becomes First FDA-Approved AI-Based Diagnostic for Diabetic Retinopathy. https://xtalks.com/idx-dr-becomes-first-fda-approved-ai-based-diagnostic-for-diabetic-retinopathy-1274, 2018.
33. Hatton GB, Madla CM, Gaisford S, Basit AW, Medical Applications of 3D Printing, Medical Applications of 3D Printing. In: Basit AW, Gaisford S, 3D Printing of Pharmaceuticals, *AAPS Adv Pharmaceut Sci Series*, 2018: 163-182.
34. Hillman L, Artificial Intelligence How AI applies to cornea. www.eyeworld.org/how-ai-applies-cornea, 220.
35. www.lancaster.ac.uk/news/uk-scientists-develop-new-rapid-smart-testing-device-for-coronavirus.
36. International Chamber of Commerce Global impacts of counterfeiting and piracy to reach US$4.2 trillion by 2022, https://iccwbo.org/media-wall/news-speeches/global-impacts-counterfeiting-piracy-reach-us4-2-trillion-2022, 2017.
37. Kite Powell J, FDA approves 3D printed drugs available in the US, 2016; www.forbes.com/sites/jenniferhicks/2016/03/22/fda-approved-3d-printed-drug-available-in-the-us.
38. Lancaster University, Lancaster involved in UK system for estimating COVID-19 cases from wastewater. www.lancaster.ac.uk/news/lancaster-involved-in-uk-system-for-estimating-covid-19-cases-from-wastewater.
39. Lancaster University, UK scientists develop new rapid smart testing device for coronavirus. www.lancaster.ac.uk/news/uk-scientists-develop-new-rapid-smart-testing-device-for-coronavirus.
40. Les Entreprises du Médicament Santé 2030, www.leem.org/sites/default/files/2019-04/LEEM_Plateforme_Sante2030_BDSOMMAIRE.pdf.
41. Numera e-Novelia, www.nemera.net/smart-ophthalmic-add-on-e-novelia.
42. Olufunmilola A, Wytiaz R, Feathers A, Paediatric use of medications and adherence apps: a qualitative analysis of the perspectives of children and parents. *Journ Pract Res.*, 2019; 49(2): 123-129.
43. Pennic F, Oschner Health Pilots Apple Watch to Manage Chronic Diseases. https://hitconsultant.net/2015/04/27/oscher-health-pilots-apple-watch-to-manage-chronic-diseases/#.Xd_CLJNKjIU, 2015
44. Psry Health communication 'Spry Health Launches New Service, Loop Signal, to Assist in Surge of COVID-19 Cases by Reducing Avoidable Hospital Visits and Improving Patient Monitoring at Home', 2020; www.businesswire.com/news/home/20200320005135/en/Spry-Health-Launches-New-Service-Loop-Signal.
45. Research2 Guidance mHealth developers economics 2017-2018 How mHealth app publishers are monetizing their apps, 2018; https://research2guidance.com/wp-content/uploads/2018/03/R2G-mHealth-Developer-Economics-2017-How-To-Monetize-Mobile-Health-Apps.pdf.
46. Rondo Smart Packaging: Solutions for Manufacturers and Patients. www.rondo-packaging.com/fr/pharma-40.
47. Schreiner, Schreiner MediPharm Develops Smart Blister Pack for Clinical Trial www.schreiner-group.com/en/press/detail/schreiner-medipharm-develops-smart-blister-pack-for-clinical-trial.html, 2018.
48. Servier laboratories, Our Digital Therapeutic Solutions section Cardioskin™ in the cardiovascular field.

https://servier.com/en/products/digital-therapeutic-solutions.
49. Shi K, Aviles-Espinosa R, Rendon-Morales E, Woodbine L, Maniruzzaman M, Nokhodchi A, Novel 3D printed device with integrated macroscale magnetic field triggerable anti-cancer drug delivery system. *Coll Surf B: Biointerfaces*, 2020; 192, doi.org/10.1016/j.colsurfb.2020.111068.
50. Speech code Pharmaceuticals Accessible Package Insert 4.0 – Text AND Speech. https://speechcode.de/pharmaceuticals-accessible-package-insert-audio-label.
51. Stegemann S, Ecker F, Maio M, Kraahs P, Wohlfart R, Breitkreutz J, Zimmer A, Bar-Shalom D, Hettrich P, Broegmann B, Geriatric drug therapy: neglecting the inevitable majority. *Ageing Res Rev.*, 2010; 9(4): 384-398.
52. Technopedia Artificial intelligence AI definition. www.techopedia.com/definition/190/artificial-intelligence-ai.
53. Tillier Y, Modéliser des tissus biologiques pour concevoir des implants biomimétiques. *Device Med.*, 2019; 3: 26-27.
54. WHO, Bulletin of the World Health Organization Growing threat from counterfeit medicines. www.who.int/bulletin/volumes/88/4/10-020410/en.
55. WHO, Bulletin of the World Health Organization m-health New horizons for health through mobile technologies. www.who.int/goe/publications/goe_mhealth_web.pdf.
56. Withings page sleep analyzer. www.withings.com/fr/fr/sleep-analyzer.
57. Withings blood pressure page. www.withings.com/fr/fr/blood-pressure-monitors.
58. Wytiaz RM, Lee HM, Olufunmilola KO, 'Smart phone Apps: an innovative approach to improving medication adherence. *Innov Pharm.*, 2015; 6(4): 222: 1-4.
59. Zidan A, FDA CDER Researchers Explore the Promise and Potential of 3D Printed Pharmaceuticals. www.fda.gov/drugs/news-events-human-drugs/cder-researchers-explore-promise-and-potential-3d-printed-pharmaceuticals.