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Raijada, Dhara; Wac, Katarzyna; Greisen, Emanuel; Rantanen, Jukka; Genina, Natalja

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Integration of personalized drug delivery systems into digital health

Dhara Raijada, Katarzyna Wac, Emanuel Greisen, Jukka Rantanen, Natalja Genina

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A B S T R A C T
Personalized drug delivery systems (PDDS), implying the patient-tailored dose, dosage form, frequency of administration and drug release kinetics, and digital health platforms for diagnosis and treatment monitoring, patient adherence, and traceability of drug products, are emerging scientific areas. Both fields are advancing at a fast pace. However, despite the strong complementary nature of these disciplines, there are only a few successful examples of merging these areas. Therefore, it is important and timely to combine PDDS with an increasing number of high-end digital health solutions to create an interactive feedback loop between the actual needs of each patient and the drug products. This review provides an overview of advanced design solutions for new products such as interactive personalized treatment that would interconnect the pharmaceutical and digital worlds. Furthermore, we discuss the recent advancements in the pharmaceutical supply chain (PSC) management and related limitations of the current mass production model. We summarize the current state of the art and envision future directions and potential development areas.

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A B B R E V I A T I O N S:
AI, Artificial intelligence; AM, Additive manufacturing; ANDA, Abbreviated new drug application; API, Active pharmaceutical ingredient; CAD, Computer-aided design; CBT, Cognitive behavioural therapy; CPSC, Circular pharmaceutical supply chain; DEEP, Data-enriched edible pharmaceuticals; DSCSA, Drug supply chain security act; EMA, European medicines agency; FDA, Food and drug administration; FMD, Falsified medicines directive; GMP, Good manufacturing practice; IoT, Internet of Things; NDA, New drug application; PCID, Physical-chemical identifiers; PDDS, Personalized drug delivery systems; PSC, Pharmaceutical supply chain; RFID, Radio-frequency identification; TNO, the Netherlands organisation for applied scientific research; TnT, Track and Trace; QR, Quick response.

* Corresponding author.
E-mail address: natalja.genina@sund.ku.dk (N. Genina).

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1. Introduction

More than 100 years ago, a renowned Canadian physician, William Osler, quoted that, “if it were not for the great variability among individuals, medicine might as well be a science, not an art.” Over the past century, most therapeutic strategies were developed based on randomized clinical trials and applied for a “statistically average patient.” Although medicine may continue to remain an art, the 21st century brings new hope with success of, for example, the “human genome” project to take consideration of genetic variability and deliver personalized therapy solutions [1]. Recent advancements in the field of pharmacogenomics have made it possible to start implementing tailor-made and increasingly personalized therapies. One such example is the marketed anticancer drug product Herceptin®, which has been successfully used as targeted monoclonal antibody therapy for 25–30% of breast cancer patients, where HER-2 protein is over-expressed [2]. One aspect of personalized medicine is designing molecules based on pharmacogenomics and targeting specific patient sub-group, as mentioned above. The other aspect of personalized medicine is tailoring the dose, the dosage form and drug release kinetics to fit the needs of the individual person, as well as severity and stage of the disease [3]. In this review article, we are mainly focusing on this latter aspect of personalized medicine, which is hereafter phrased as “Personalized Drug Delivery Systems” – PDDS.

Another revolution we have witnessed in the early 21st century is an advent of digitalization. The modern society is becoming increasingly digitized and dependent on the virtual world and enormous amount of data. This is changing how we design products and deliver them to customers – an example of this is the recent revolution in value creation and customer demand due to the COVID-19 pandemic that has spiked the whole e-business industry. This development is partially dependent on the efficient use of online services and traceability of products. Recently, distribution of pharmaceutical products has been one of the key challenges and, among others, the established “Pharmaceutical strategy for Europe” from 2020 is aiming to “make sure that patients across Europe have new medicines and therapies in their countries quickly and under all circumstances and that there are fewer shortages of medicines” [4]. This should be ensured while at the same time (1) delivering solutions allowing for personalized medicine, (2) combating falsified and counterfeit products, and (3) reducing the environmental footprint of related manufacturing. One solution for this challenge is integration of data elements into drug products. This would allow for simultaneously (a) secured distribution, (b) more precise and timely dosing of an active compound, and (c) tracking of each consumed dose by involved actors (i.e., healthcare professionals, patients, caregivers) and in this way, transforming the regular drug products into digitized drug products. Similar approach has revolutionized the monetary transactions with the introduction of digital currencies. In the healthcare sector, this would provide healthcare professionals with better treatment overview by keeping the digitally retrievable records of medicine intake by patients with simultaneous monitoring of their surrogate markers [5], such as heart rate, blood pressure and oxygen saturation. In turn, this can help healthcare professionals making the informed decision for subsequent treatment options, ultimately resulting in better therapeutic outcome. In addition, traceability aspect of digitalized medicines will aid towards more efficient pharmaceutical supply chain (PSC), facilitating new strategies for reducing the medicinal waste, designing more sustainable products, and finally, achieving the PSC with elements of circular economy (cf. Section 4.3) [6]. Furthermore, these digitalized drug products should be designed to be functional, and at the same time accessible and affordable to be also used in low and middle-income countries.

Digitalization of the healthcare sector is proceeding fast by a gradual integration of diagnostic point-of-care sensors and connected computation platforms into patients’ everyday routine [7]. Nowadays personal mobile and wearable sensors, so called Internet of Things (IoT), can measure, amongst others, functioning, respiration, biomarkers from sweat and even assess the emotional state of the individual [8,9]. The transmitted signals from IoT can be received, quantified and visualized with a help of, for example, a standard smartphone. These digital possibilities enable a completely new type of a human–machine interface in the healthcare sector [10]. There is already an increasing number of digital solutions providing virtual visits with medical doctors based on an app-based communication between the patient and the medical doctor [11–13]. Even the clinical trials are becoming more and more virtual [14,15]. In this digital revolution, the weakest link in a chain is the drug product. This is because the options for its traceability, on-dose verification and its integration into the existing digital health platforms are limited. To be able to deliver a truly personalized care, a holistic change in the healthcare sector is needed – and a key element in this change will be the way we design and manufacture PDDS. The current mass production model of drug products does not allow personalization [16], while modification of the product based on the individual patient’s genomic, metabolic and activity level needs implementation of mass customization principles [17–21]. In this review, we report the rationale for PDDS in the current pharmaceutical sector. Furthermore, we provide an overview of advanced approaches for manufacturing personalized medicines and more specifically, how to bridge pharmaceutical and digital worlds with the appearance of new products such as digital drug products and digital therapeutics.

2. Patient need for personalized medicines

The current set-up of conventional pharmaceutical manufacturing is based on mass production of selected dosage strengths. This creates challenges especially for treatment of chronic diseases including cardiovascular diseases, type 2 diabetes as well as brain disorders. Many of the disease treatments require multiple doses to be delivered to the patient based on severity of the disease, lifestyle changes, co-administration of other medication, as well as going off medication [22,23]. Furthermore, different subgroups of
patients such as, paediatrics and geriatrics, would require age-appropriate doses (Fig. 1).

In this context, there are three major challenges with currently marketed oral drug delivery systems: (1) the absence of on-demand personalized and precision dosing (especially for paediatric population), (2) non-adherence and lack of treatment overview due to the use of multiple drugs, so called polypharmacy (especially for geriatric population), and, (3) the deficiency of easily reachable tailored information regarding the drug products.

2.1. Personalized & precision dosing – significance in paediatric delivery

Most of the paediatric medicines are liquid formulations provided with measurement cups or as measurement of tea-spoonful or table-spoonful. In case of solid dosage forms, available doses are divided by e.g. crushing or splitting into halves or smaller, and then consumed as such or by dispersing in oral liquids [25]. These are not very accurate measurement systems and are quite susceptible to human errors [26]. Furthermore, the age, weight and metabolic capacity of children can be crucial factors in determining the correct dose [27–29]. The significance of the right dose for paediatric use has quite often reflected in market recalls related to dosing precision needs [30,31]. Such recalls are cumbersome and costly, and could cause the loss of the trust in the recalling company.

Recently, the dosage forms that have captured attention for paediatric medicines are minitablets and granules [32]. Minitablets are miniaturized tablets, which could be counted to get the required dose. They are suitable even for new-born infants [32,33]. However, there is a need to use a separate device that would allow the precise counting of minitablets, such as a specially designed pen. This adds to the cost of the drug product. Furthermore, although production of minitablets is well-established, the same involves various technical challenges including content uni-

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Fig. 1. (Top) Patient need for personalized medicines; (Bottom) Paradigm change for increased variety of drug products and decreased production volumes. Modified from [24].
formity as well as maintenance and mechanical stability of multi-
tip punches. Also, due to their small sizes, minitablets are not
easier to handle independently, which may impart additional chal-
lenges for patients with impairment of motor functions and geri-
atriac patients [34]. The granules in hard capsules or sachets for
paediatric use have also been designed to improve administration
of the required dose. The desired amount of granules is supposed
to be dispersed by parents or caregivers in semi-solid food, like
apple pudding, yogurt or fruit juice, to make children eat the med-
icine unnoticed and by that minimize spillage, spitting out and
refusal to take the medicine [35,36]. However, such an approach
might incur additional challenges with insufficient drug intake
due to e.g. child’s unwillingness to intake the entire food portion
as well as additional stability requirements of active pharmaceuti-
cal ingredients (APIs) and other ingredients in the presence of food.
The other innovative way for overcoming administration chal-
lenges with granules have been inserting granules in a straw
[37]. To add, even though minitablets and granules are currently
mass produced; on-demand manufacturing of the same does not
exist yet.

2.2. Significance in value-added geriatric medicines

Polypharmacy, patient morbidity and poor adherence are the
major factors contributing to sub-optimal outcome of drug deliv-
ery systems in the elderly. Poor adherence to medicine is caused,
among the others, by patients’ inability to recognize their medicine
due to similar appearance, oblivion or misunderstanding of the
administration regimen, unwillingness to follow the complex dos-
ing regime and/or swallowing difficulties [38]. A key challenge in
developing appropriate geriatric drug delivery systems is to pro-
vide the innovation that best meets the specific physiological, psy-
chological and multiple drug requirements of individual elderly
patients [39]. Although digital literacy might be a challenge for
elderly patients, care-takers at nursing homes may be well-
trained to use the digital media. Additionally, the population,
who is in their 50 s and 60 s and advancing in their age, is already
well-versed with the digital world.

2.3. Accessible information

Due to the digital revolution, patients are more informed than
previously. According to a 2019 report, there are over 1-billion
health related searches on google everyday [40]. Various studies
have shown specifically that more and more people search for their
medications and related information online [41–43]. Furthermore,
people find it useful to check the origin of raw materials and their
logistics, especially if patients have allergies or trust concerns. This
aspect would be increasingly important when pharmaceutical
products and PSC are being modified towards more sustainable
solutions with circular economy elements. For example, by changing the physical dimensions of the dosage
form, print density (resolution), internal geometry and the amount
of printed layers, the dose and the release profile can be cus-
tomized [48] (Fig. 2). Interestingly, the use of AM offers the possi-
bility for producing a ‘polypill’, where multiple APIs with a desired
dose and pre-programmed release profiles for each API can be
incorporated into a single dosage unit [23,49]. Reduction in the
number of dosage forms to be consumed per day could signifi-
cantly improve patients’ adherence to medicine and provide cost-
savings to the healthcare sector [50,51].

The first and so far the only 3D printed drug product developed
by Aprica - Spritam® (generic drug product of Keppra®), contain-
ing anti-epilepsy drug levetiracetam, has been approved by the US
Food and Drug Administration (FDA) in 2015 and is available on
the market [52]. It has an advantage of orodispersible formulation
in terms of easy swallowing, combined with the potential for dig-
ital dose adjustments on-demand. In February 2021, FDA gave the
Investigational New Drug (IND) approval for 3D printed drug pro-
duct T19 by Triastek [53]. The company expects to file a New Drug
Application (NDA) for T19 in 2023. Recently, 3D printed chewable
PDDS have been tested in paediatric population with a rare meta-
bolic disease in a hospital setting [54]. The physical appearance in
terms of size (different doses) and colour together with the taste of
the dosage form were manipulated as an attempt to improve the
treatment outcome. The implementation of additive manufactur-
ing as a better alternative to the compounding practice with
regards to cost and safety and overall benefits to the patients,
has been demonstrated in clinical settings [55]. In another study,
comparison of the dosage forms prepared by 2D printing, 3D print-
ing and conventional compounding in the hospital setting has been
reported [56]. The production of PDDS by printing appeared to be
more precise, though the overall production speed by printing
(preparation of feedstock, printing, cleaning) could be slower than
the conventional compounding by mechanically altering the dose
of already marketed drug products (e.g. grinding, mixing, weigh-
ing, cleaning) [56]. Merck Group has invested into 3D printing pro-
cess with the “OneZeroMed” business concept to allow cheaper
drug development by cost savings during clinical studies, where
small batches with escalating doses are needed. In turn, this will
potentially allow bringing urgently needed medicine, such as
orphan and oncology medicine, faster to the patients [57]. In line,
the Netherlands Organisation for Applied Scientific Research
(TNO) has recently started 3D printing of paediatric dosage forms
for treatment of heart diseases in the hospital settings [58]. Overall,
2D and 3D printing techniques were positioned as an automated
approach with a high digital flexibility and precision dosing that
have a small footprint with a possibility of the remote control, con-
sumption of less materials and possibility of mass customization of
PDDS.

With a current demand of the society for PDDS to offer a better
treatment for patients [45], these recent advancement in manufac-
turing could allow the production of the medicine upon patient
request at industry setting, pharmacy setting, both compounding
and community, and even at patient’s home [48]. These possibili-
ties would challenge the conventional pharmaceutical supply
chain (PSC) and rearrangement of the same with new solutions would be needed.

4. **Pharmaceutical supply chain (PSC)**

4.1. **Conventional supply chain model**

The Pharmaceutical Supply Chain (PSC) is quite complex and with special characteristics, which are typically not seen in supply chains for other consumer goods. These special characteristics include the need for higher security, complete traceability and secured record keeping, especially if records contain sensitive information. A study by McKinsey & Company found that in the United States, supply chain accounts for nearly 25% ($230 billion) of pharmaceutical cost [59]. This fact alone is indicative of the complex nature of the conventional PSC model and engagement of multiple stakeholders (Fig. 3). It involves the flow of raw materials to pharmaceutical manufacturers, followed by a flow of finished pharmaceutical products through the chain of wholesalers and distributors, retailers, and, ultimately to end-users (patients and healthcare professionals).

There are various risks associated with the conventional model of the PSC [61], such as (1) drug shortage; (2) compromised sustainability of the PSC, (3) falsified medicines (fake medicines, designed to mimic real medicines) and counterfeit (medicines that do not comply with intellectual property rights or infringe trademark law) [62,63] and tainted products (resale of expired products) and (4) ambiguity (the absence of transparency for end-users).

The recent pandemic crisis of COVID-19 has revealed many loop-holes in the conventional PSC [64]. There are important lessons to be learned in such a crisis. Firstly, contingency plans need

![Fig. 2. The possibilities of additive manufacturing by both 2D and 3D printing in provision personalized drug delivery systems (PDDS).](image-url)
to be ready to avoid drug shortages. Furthermore, repurposing of the existing drug(s) for new therapeutic indications could reduce the gap, where no treatment is available [65]. Nowadays, the volume of drug production is calculated based on the expected drug consumption, and not on the actual patients’ demand. This is one of the reasons for the accumulation of the enormous pharmaceutical waste that needs extra resources for its utilization. This is because the conventional PSC is mainly linear chain, working on the concepts of take, make, use and dispose. The full digitalization of the PSC, when even a single dose is traced in the digital system, would provide a better overview of the produced, consumed and unused/expired drug products. This together with the actual needs of patients would create a basis for mass customization options. Furthermore, the Circular Pharmaceutical Supply Chain (CPSC) has been suggested as a future strategy to support sustainability in the pharmaceutical area to reduce among others drug shortages and stockpiling [6]. Already now, there are some innovative examples in the PSC, where basic 3R (Reduce, Reuse, Recycle) principle of circular economy is being implemented [66,67]. There have been major initiatives like pharmaceutical take-back programs to implement mainly the principles of “Reuse” and “Recycle” in the PSC [68]. The CPSC is further extension of 3R principle to 9R model, which includes Refuse, Rethink, Reduce, Reuse, Repair, Refurbish, Remanufacture, Repurpose, Recycle, and Recover, to further optimize circular economy (Fig. 4) [6]. The 9Rs can significantly contribute towards United Nation’s sustainable development goals via three main strategies, (1) better use of products and manufacture by Refusing use of less environmentally friendly materials, by
Rethinking intensive use of certain products and by Reducing consumption of natural resources by increasing production efficiency; (2) expanding the lifecycle of product by Reusing the discarded product, which is still in good condition or by Repairing, Refurbishing or Remanufacturing the old product; (3) finding useful application of product by Repurposing the product for another function, or by Recycling to achieve better quality, or, by Recovering energy from incineration of used material. The 9R model is yet to be implemented fully to achieve more sustainable pharmaceutical and healthcare sector.

Secondly, distribution of fraud medicines, both falsified and counterfeit, should be circumvented as it has become a serious threat worldwide, especially in the developing countries such as Africa, Asia and Latin America, where the presence of counterfeit medicine is higher and even cases of death due to substandard drug products have been reported [69]. It has turned out to be also a huge problem for the developed countries, especially in a pandemic situation such as COVID-19 [70]. To minimize the risk of fraud, the pharmaceutical companies design a unique shape, colour, size, debossing, imprinting, etc. of both dosage form and the package to assist in identification and genuineness check of a drug product outside the manufacturing unit [71]. However, these measures could not be sufficient to guarantee the protection against counterfeiting [72]. The recent opioid crisis in the USA, in the context of which, among other things, a very potent opioid fentanyl was manufactured illicitly and consumed by patients, underlines the vital need for in situ control of drug genuineness [73]. Therefore, increased transparency for the end-users would be essential, especially if the drugs are directly distributed to the patients through local delivery, bypassing the involvement of the pharmacy as the safeguard in quality control and as the consultation provider. The increased public use of online pharmacies with e-prescription make the PSC even more vulnerable for introduction of suboptimal medicines for both lifestyle and lifesaving drugs [63,74]. Although, European Medicines Agency (EMA) has introduced safety measures for buying medicines online [75,76], and have also suggested purchasing medicines from only registered online pharmacies, it cannot be excluded the distribution of fake medicines [77,78], because the falsifiers become more sophisticated [69,77].

Drug shortage, circulation of substandard medicines, impossibility of instant genuineness check and lack of the drug product traceability throughout the PSC, together with the social desire for more easily reachable information and sustainable solutions, push the regulatory bodies and researchers to advance the field.

4.2. Regulatory efforts & technological advancements in supply chain management

Various laws and regulations have been enforced by regulators to secure the PSC. In 2011, US FDA published a guideline to incorporate physical–chemical identifiers (PCIDs) into solid oral dosage forms for anti-counterfeiting, wherein a PCID is a substance or combination of substances possessing a unique physical or chemical property that unequivocally identifies and authenticates a drug product or dosage form [79]. Incorporation of PCIDs to a non-functional tablet film coating is covered by this guidance, however, incorporation of PCIDs into packaging or labelling is not covered by this guidance. One of the latest advancements for incorporation of PCID has been TruTag Technologies, Inc. that combines secure edible barcodes with mobile apps to tag, track and trace drugs [80]. More detailed discussion on latest advancements is compiled in section 5. Subsequently, as a more visual and robust initiative, the US government passed a law in 2013 called the Drug Supply Chain Security Act (DSCSA) to codify the requirements related to the PSC [81] (Fig. 5). Since 2018, FDA has enforced the requirement in the DSCSA to include a product identifier on the prescription drug packaging. The ultimate goal of the series of regulations enforced in the PSC is to achieve a unit-level traceability by 2023, where unit is defined as a single sealable entity [82]. A sealable unit can be the primary package with multiple dosage units, e.g., a blister package with
tablets or capsules, or a primary package with a single dosage unit, e.g., an oral film.

A similar regulation, called Falsified Medicines Directive (FMD), has been implemented in the European Union (EU) (Fig. 5) [85]. Its aim was to prevent introduction of falsified and counterfeit drug products by requiring serialization of all medicines traded in the EU region on a sale package level.

There is an on-going paradigm shift towards inclusion of Internet of Things (IoT) in each involved part of the PSC, including manufacturing plants, analytical equipment, tracking the transport of drug products and monitoring the crucial conditions (e.g., temperature) during transport etc. to enable digital interconnection and by that, advance the entire PSC. In this context, for example devices like movement sensors, digital thermometers, relative humidity meters, with the short-range connectivity (e.g. Bluetooth and Wi-Fi) option are considered as IoT that transmit detectable signals to the digital platforms, allowing continuous and real-time signal monitoring and automatic adjustment of essential parameters during storage and transport of drug products.

### 4.2.1. Unique Identifiers

To enable traceability of the drug products at a sale package level, 2D barcodes have been introduced by GS1 standards [86]. The data density and small layout of 2D barcodes in comparison to 1D barcode (Fig. 6) make them suitable for printing the high amount of data needed (approximately 48 characters), despite the physical constraints of the small packaging used for medicine. There are numerous types of 2D barcodes, but the most known are data matrix and quick response (QR) codes. However, the most

<table>
<thead>
<tr>
<th>Criteria</th>
<th>1D Linear</th>
<th>2D Data Matrix</th>
<th>2D Quick Response (QR)</th>
<th>Universal Product Code</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual Appearance</strong></td>
<td>![1D Barcode]</td>
<td>![2D Data Matrix]</td>
<td>![QR Code]</td>
<td>![Universal Code]</td>
</tr>
<tr>
<td><strong>Primary Purpose</strong></td>
<td>Reduce medication error</td>
<td>Identify and trace prescription drugs</td>
<td>Provide information (website) about the product to which it is affixed</td>
<td>Keep track of sales and inventory products</td>
</tr>
<tr>
<td><strong>Contains</strong> (Minimum Requirement)</td>
<td>National Drug Code (NDC)</td>
<td>NDC, serial number, lot number, expiration date</td>
<td>Not applicable</td>
<td>12 digit number that identifies the specific product</td>
</tr>
<tr>
<td><strong>Requirement</strong></td>
<td>Required on nearly all drug products</td>
<td>Required on the smallest saleable package</td>
<td>Not required by FDA on product labels and labeling</td>
<td>Required for OTC items</td>
</tr>
</tbody>
</table>

![Fig. 6. (Top) Types of barcodes, modified from [87,88]; (Bottom) Example of GS1 data matrix barcode, encoding product code, expiry date, lot number and serial number, modified from [86].](image-url)
used within the pharmaceutical industry is the data matrix code, especially for track and trace purposes. The industry adoption of data matrix code is most likely attributed to the fact that it can be printed with different high-speed printing technologies. The primary benefit of using QR codes is being the adoption of built-in reading capabilities in consumer smartphone camera apps, their data storage capacity and interactive nature. However, printing of readable QR codes at a high throughput is difficult, making them less ideal for high-speed production lines. Furthermore, QR barcode in contrast to data matrix is not used for the purposes of automated product identification (autocoding) [87].

According to the FMD, each unit of sale package should be imprinted with a 2D barcode that encodes product code, randomized serial number, expiration date, batch or lot number, and if required, national health reimbursement number (Fig. 6). Decommission of the barcode should take place after scanning and dispensing the medicine to prevent its reuse on a fake medicine. In this context, decommission would mean marking of the scanned 2D barcode as used in the central database in Europe.

Besides 2D barcodes, the use of radio frequency identification (RFID) tags is the common strategy to provide instantaneous recognition and primary level protection against counterfeiting [74,89]. The RFID tags have high data storage capacity and enable tracking of the product and contactless recognition. However, they are expensive and their reuse can threaten the safety of the stored data [89].

4.2.2. Track and trace possibilities

Track and trace (TnT) technologies have emerged to enable following the current and past locations of pharmaceutical drug products throughout the entire PSC. Mackey and Nayyar (2017) [63] identified five categories of either established or under development digital solutions for detection of among others fake medicines (Fig. 7). Mobile solutions, RFID together with other digital tools and web-based platforms were grouped as the most mature technologies, whereas machine-learning, advanced text processing and blockchain technologies [90] are still emerging, and their developers are looking for their real life applications. In addition to detection of fake medicines, these technologies would strongly support implementation of mass customization model. Encouragingly, the recent real life example is the use of blockchain in tracking the storage and logistics of COVID-19 vaccines [91].

5. Latest advancements in “on-dose” identification in context of PDDS

Despite all safety and traceability features on packages, it is difficult with the conventional solid dosage forms to reveal the suboptimal drug product [92] and trace it, especially if the secondary and/or primary package is lost, not available or fake [69]. To promote traceability even at a single dosage unit level independently of the existing packaging, inclusion of new entities, so called smart tracers, onto the dose itself is needed. In this context, smart tracers are defined as unique identifiers that enable identification, verification and traceability of a drug product at a unit-level (dose) throughout the entire PSC. They can consist of either digital or physical identification features, or combination of them. The smartphone-readable 2D barcodes, especially QR codes, as smart tracers have gained significant interest (Table 1). The use of them has been suggested for improving drug identification, for instance, by applying fluorescent inks in the pattern of a QR code on the finished dosage units [89,93] or manufacturing biodegradable labels in the shape of QR codes attached onto the capsule/tablet itself [94]. An edible QR code-containing microtaggant (traceable micro-tag) with fluorescence elements was proposed to be included inside the capsule for drug identification purposes [95]. The digital pioneer for using “on-dose” QR codes in the pharmaceutical industry was Freund-Vector with its TABREX Rev. – a brand...
new concept machine for printing QR code on tablets (2017) [96]. The drug-free QR code is printed on each tablet to be digitally scanned and verified during manufacturing and dispensing. However, it is important to point out that the dimension of the tablet, the resolution of the print and the speed of production has to be taken into account when using this technology. It requires a relatively large size of the dosage form, smooth surface and high resolution of the print to make QR code readable, at least with a standard smartphone without a microscope. Our research group has recently introduced an approach for fabrication of dosage forms, data-enriched edible pharmaceuticals (DEEP), in the pattern of a QR code on the edible orodispersible “paper” by 2D printing (Fig. 8) [97,98]. The novelty of this approach is that besides the encapsulated information, QR code pattern contains the personalized and precise dose of the API(s), paving the way towards precision treatment. The German company DiHeSys has invested into advancing similar technologies [99,100], wherein the drug is printed onto the edible carrier in the form of QR code. Though, the current DEEP technology by 2D printing is limited to highly potent low-dose APIs [97]. Recently, it has been shown that DEEP containing an API can be produced in a single step process using a 3D printer with a directly printing nozzle [101]. Pre-fabrication of drug-free edible ‘paper’ and inclusion of colorants in an ink were not required in this process in contrast to 2D printing. Though, the physical dimensions of 3D printed DEEP and the amount of encoded information could be outside the desired range.

One of the first companies involved in the inclusion of unique physical identifiers (targants) into a single dosage unit is Colorcon®. It introduced smart tracers into its Opadry® film coating technology for tablets and capsules to be the first to follow the PCD guideline. In 2019, together with Applied DNA Sciences Inc. (APDN) [104], Colorcon® incorporated DNA targants into the coating formulation that enabled identification of a single dosage unit by using e.g., a portable DNA reader. Furthermore, Colorcon® has teamed with TruTag Technologies, Inc. to reveal a coated dosage form, where the coat contains edible silica microtags with unique optical signature, identifiable by a smartphone-based app and thus providing mass digitization solution [105,106]. To circumvent the need for very special taggants, InfraTrac® offered the “formulation-as” tag approach, based on the idea that each drug product composition has a unique spectral fingerprint [107]. It is very challenging to formulate the fraud drug product that would match e.g., NIR spectra of the authentic formulation. With the current availability of affordable hand-held spectrometers, this approach is becoming realistic for non-destructive on-dose/in-dose identification of medicines in the point-of-care [58]. Furthermore, digestion of the special taggants such (metal) nanoparticles or allergens with the potential safety issues is avoided in this approach [107]. However, the need for an internal instrument-specific spectral library of the authentic dosage forms limits its widespread use [108]. To further in, Zhang et al. (2020) have given a thorough overview of mostly the physical possibilities of ‘in-drug labelling’ of oral capsules.
and tablets in order to minimize the circulation of counterfeit medicine [69].

"On-dose" identification by the DEEP technology has many benefits (Fig. 8). Firstly, the presence of the 2D barcode on a single dosage unit makes it possible to instantaneously verify the authenticity of each dose freely from the package [69]. Secondly, a serialized 2D barcode allows track-and-trace the supply chain of each dose. The concept of cryptopharmaceuticals, based on blockchain technology, together with a proof-of-concept smartphone app was introduced to showcase the feasibility of tracking each DEEP along the distribution chain: from the manufacturing unit to the end-user (e.g., a patient) [106,109]. This allows not only an instant verification of a drug product by end-users, but also an automatic report to the responsible service provider in case of identification of forged and tainted drug products. Moreover, DEEP allows tracking back the origin of all ingredients to ensure that a high-quality product with minimum variation reaches the end-user. As an example, the pharmacological effect of cannabinoids differ between the strains, therefore, it is essential to supply a drug product with the particular strain [98]. Furthermore, a dose-level traceability can help in early detection of the drug misuse, and potentially avoid economical burden by timely stopping it [110]. Regulatory authorities (e.g., EMA) encourage and support the use of 2D barcodes and mobile technologies to provide additional information to patients [75,111]. Scanning of QR codes could help in getting the customized information of the medicine instantaneously on the display of a smartphone in a desired language and font, avoiding reading enormous often irrelevant information presented in the data sheet supplied with the medicine. In addition, scanning of the 2D barcode can generate digital reminders in the form of, e.g., an alarm or an SMS to ensure that patients/care-providers administer/give the right medicine at the right time without forgetting it or mistakenly consuming a double dose [56,97]. To add, “on-dose” labelling would help in waste management when the secondary and primary packages are not available.

Despite the evident advantages of DEEP, ease of duplication of visible QR code patterns limits its popularity for drug anticomterfeiting [89,112]. To overcome this challenge, invisible three-dimensional (3D) QR codes with multiple printed layers were developed [89]. The QR code became visible only after excitation with Near-Infrared (NIR) light in the dark room. In addition, a specialized smartphone app was developed that could decode the printed 3D QR code and display the encapsulated information [89]. Cloning of QR codes could be further minimized by anticounterfeiting watermarking technology [112]. It is done by embedding digital watermarks into the spatial positions of QR codes, by using various algorithms. After that the digital watermarks can be extracted and the genuineness of the QR code can be verified. In this case, the visibility of QR codes is not a limiting factor as the present digital watermarks protect and secure QR codes from duplication. Besides the 2D barcodes, digital “on-dose” physical uncloneable functions (PUFs) based on various admixtures of edible and digestible silk and fluorescent proteins were proposed to maximize protection against duplication and forging [74]. This asymmetric technology allows generation of cryptographic keys (response) that is extremely challenging to clone. "On-dose" identification would add extra costs to the production and consequently to the drug product itself. Price is one of the key criteria for patients’ acceptance of a new dosage form or a new functionality [48]. Too expensive solutions would not overbalance even a useful feature if it were not of critical importance. The expensive treatment could also cause the segregation of the society in who can afford and who cannot. Furthermore, scanning of each dose may be unnecessary for patients with chronic illness, whose drug administration regimen is a routine. Though, patients with a short-term treatment and altering drug administration

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**Fig. 8.** (Top) Examples of data-enriched edible pharmaceuticals (DEEP). (A) orodispersible dosage form, where QR code contains the drug [98], (B) 3D printed tablets with drug-free data matrix and QR codes [102], (C) 3D printed orodispersible films, where QR code contains the drug [101], (D) biodegradable label, containing QR code, attached to the capsule shell [94]; (Bottom) Benefits and pitfalls of DEEP.
schemes, e.g., cancer or transplant patients, would benefit from in-time updates. To add, not everyone is able and willing to do continuous monitoring and be under surveillance\[113\]. Therefore, these new functionalities should be optional, and the overall treatment should not be worse if, e.g., the scanning of QR codes was not performed. “On-dose” labelling would presume an availability of at least a smartphone by end-users. Any challenges associated with malfunctioning of a smart device and/or accessibility of the network (Internet) all the time should be foreseen\[97\]. Furthermore, sensitive information encoded in QR codes should be protected by all possible means to ensure patients’ privacy and security even in case of cyberattacks\[98,114\]. Furthermore, dyes and pigments in the inks should be edible and non-toxic in the concentrations presented in the 2D barcode pattern\[115,116\]. Last but not least, any physical damage of 2D barcodes such as dye migration due to for example high humidity, discoloration due to e.g. UV light and mechanical distortion due to transport, can lead to readability problems. To increase reliability of the printed 2D barcodes, it is suggested to use barcode patterns with higher level of error correction\[98,117\]. Nevertheless, these and many other human factors may limit the acceptance of such new technologies and solutions (cf. Section 7.4).

DEEP is a novel technology for next generation pharmaceuticals and, therefore, has its own benefits and challenges. However, it definitely offers unique opportunities such as digital flexibility and encapsulated data that the conventional manufacturing solutions lack. Inclusion of such digital features on pharmaceutical drug products can well be integrated in the modern era of digital health, which is further discussed in section below.

6. Digital health

PDDS and digital health are at the moment developing rapidly at parallel tracks, however, they could strongly complement each other. As an example, the same QR code can be used for track and trace purposes as well as this code can contain useful and unique information for both patients and healthcare professionals. Thus, integration of these areas could bring advancement in healthcare systems, provide cost-efficient treatment solutions and improve the overall healthcare outcome.

6.1. Internet of Things (IoT) & continuous monitoring

To get an overall picture of persons’ health status at the best possible accuracy, technologies for an automatic, minimally intrusive monitoring, tracking and continuous assessment of human behaviours and context are emerging. This is enabled by the widespread availability of personal computing and communication devices and services – including personal wearable devices and mobile applications and services. These devices and services collect multiple types of high-resolution data (e.g., location, physical activity) longitudinally and unobtrusively. They also provide some type of data visualization to the user. The 2018 literature review revealed 438 wearable devices\[118\] positioned differently at/
around the body, from feet to top of the head, and related to different behavioural patterns (Fig. 9). A network of the devices and services that assess given behaviours constitutes the Internet of Things (IoT). Simultaneous collection and analysis of multiple responses can give, e.g., a better picture of the severity of the disease and help in choosing the right treatment.

Additionally, IoT could be leveraged in non-adherence to medication due to, for e.g., elderly people’s forgetfulness to take medicine. Overall, non-adherence is a huge health economic burden for the society [119]. To improve adherence, smart containers for medicines have been developed to detect the can/pill box opening and bottle pick up. They may be considered as IoT, especially if they are connected to the Internet, and collect data about medication adherence in longitudinal, real world environments and contexts [120]. There exist mostly lab-based prototyped wearables that detect motions related to cap twisting [121,122], hand-to-mouth [123], pouring pill into the hand and hand motion related to pill swallowing [122,124] or swallowing itself [125].

The potential of technologies using IoT is broader and can include technologies tracking behaviours and individual states related to medication adherence, or related to the therapeutic outcome (e.g., release of pain) due to medication [118]. When considering specifically the IoT technologies encapsulated within wearables, i.e., on the individual body, they can track behaviours or phenomena including sleep, physical activity, eating, foot pressure, urinary infections or dreaming [126]. None of the wearables identified within 2018 literature review [118] has been explicitly for it (via buttons, touches for self-reported medication adherence), or for tracking symptoms (e.g., sleep), longitudinally, in the individual’s daily life environment (Fig. 9). Many of these IoT technologies may be highly personalized; specifically, wearables that assume a specific individual owner. The personalization may imply features spanning from the simple fixed, time-based reminders, via a management of the complex medication schedule (including rescheduling in case of missed doses), to just in time, context-aware systems that, for example, recognize that the individual has just woken up, or is currently eating, remind to take the specific type of medication [118,127]. The designers and providers of the devices and services put growing efforts in their availability, usability and usefulness, also for persons with lower digital literacy [128].

6.2. Standard smartphone

The use of the personal and mobile devices, e.g., smartphones, has shown to possess a huge potential to advance healthcare, including disease prevention and treatment [129–131]. Over the past decade, 85% of the European and US mobile phone users had a smartphone. A smartphone, its sensors and associated mobile applications can be used as a tool for gathering quality data for medical research, or regular healthcare practice, as data can be gathered from the subjects obtrusively for long periods of time, in a laboratory, as well as in a subject’s natural environments. The smartphone can also become a “sensor for medication adherence” – either by acting as a reminder or engagement service to take the medicine or avoid double dosing, or relying on smartphone sensors – quantifying human states and behaviours related to adherence or tracking symptoms (or lack of those) in the individual’s daily life environment. It is also used as processing and displaying tool with a sharing possibility to track the drug intake [132], decide on the treatment plan [133–136], potentially adjust the administration of a medicine(s) and/or personalize dose for ingestible electronics sensors (IESs), also called ‘smart pills’. IESs, such as Abilify MyCite® and Atmo Gas® capsule, have been developed to facilitate monitoring and improve medication adherence, as the non-ingestible sensors do not guarantee the intake of the medicine. Additionally, a smartphone can track the medication adherence by “proximity” sensing with the pill bottle/device – near-field-communication (NFC) or radio-frequency identification (RFID) for bottle pick up [137] and dosage form removal [138,139] (Fig. 10). Furthermore, the smartphone can be used as an analytical tool to identify and verify the drug product and/or dosage form [140] by detecting the incorporated smart tracers, including 2D barcodes (Table 1).

6.3. Digital therapeutics

FDA has defined Mobile Medical Applications (MMA) [141], and digital therapeutics is a subgroup of MMA. Digital Therapeutics are evidence-based software products for prevention and/or treatment of diseases, which have emerged at high density in the last decade, especially at the start-up level [142]. They rely on some existing hardware (wearable and/or smartphone) and, are providing, among others, game-based and questionnaire-based diagnostic tools and suggestions for treatment and, potentially, feedback loop-driven alteration in the treatment regime. In the long term, digital therapeutics aim to have the potential to make patient’s life drug-free for certain conditions [143] or at least reduce the consumption level of pharmaceuticals. They are implementing the algorithms that are ranging from simple rule-based ones to the artificial intelligence (AI) and machine learning ones [144,145]. They come into play and gain user acceptance as “the illusion that all therapy must be delivered in-person is now fading” [146]. In October 2020, the Digital Healthcare Act (DVG) officially granted doctors in Germany permission to prescribe insured health apps to their patients for the first time. Currently, ten apps have been approved, amongst which there are for example are (1) Kalmveda®, an app, which aims to help with tinnitus [147], and (2) Velibra®, a therapy program for anxiety disorders [148]. Both apps are non-
pharmacological; they operationalize the evidence-based cognitive behavioral therapy (CBT) programs along their code service. The other prominent examples of digital therapeutics are listed in Table 2.

Digital therapeutics offer non-pharmacological treatment of the specific conditions and diseases as a sole therapy, or as a complimentary approach to other types of therapies (Fig. 11). That could be especially beneficial in the context of elderly care, as many elderly people are polypharmacy patients. They could use digital therapeutics, yet, likely have also other diseases that would still need pharmacological approach to control and/or treat the conditions. This would mean that patients would continue to receive multiple medicines, however, the number of the medicines and their doses could be significantly reduced with the complimentary use of digital therapeutics. In this situation, PDDS would be of significant importance to provide patient-tailored precise doses with desired release profiles.

Additional technologies could be incorporated for better patient’s outcomes. For example, incorporation of smart tracers, i.e., 2D barcode into the PDDS at a dosage unit level could help the individuals (patients, caregivers and healthcare professionals) to identify and track the medication adherence in the same app. The scanned data from the dosage forms can be integrated with the outcomes of digital therapeutics in the same platform, and potentially provide the guidance for the next dose(s). To add, digital therapeutics have the potential to be used as the indicators for effectiveness of the drug treatment, especially when the change in the consumed drug is required [142]. They could also be used to evaluate the response of the patients to the investigational drug products during clinical studies [142,157]. There is a huge potential for integration of PDDS into digital health for the benefits of the society.

7. Challenges for implementation of PDDS

PDDS is a new way of manufacturing and distributing medicines. There are multiple challenges to be solved before PDDS can be implemented in the real life treatment scenarios.

7.1. Technological and economical challenges

PDDS such as DEEP entails the personalized dose and data in the same dosage unit. Regular dose adjustment would require robust, reproducible and safe manufacturing equipment (including e.g., printers) operated under good manufacturing practice (GMP) environment, and reliable software that could be compliant with regu-
latory requirements equivalent to FDA’s 21CFR Part 11 [158]. Currently, there are only a few customized printers available on the market that would fulfil the pharmaceutical GMP standards. Similarly, exploring potential applications of existing excipients and development of new materials for manufacturing of innovative PDDS remain one of the key challenges. There is a specific need for development of more sustainable solutions, such as biodegradable and biosourced polymers for AM applications [159].

Both printers and software need to be designed in a way to provide integration to the overall IoT within a personalized use case. Collecting and processing of accumulated health data for a given individual would require advanced, minimally-biased, maximally personalized mathematical algorithms [160,161], some of which would need to adapt, for example – N-of-1 approach to establish the most effective treatment regimen for a given individual (N = 1) in a given context [162]. Similarly, the misuse of the printers that would potentially be used to supply standard drug products should be prevented [114]. As each batch of PDDS would look different due to the patient-specific dose and design, “on-dose” verification would be of primary importance. Preferably non-destructive, but very sensitive analytical tools would be required to assure the quality of each PDDS, e.g., verifying that the correct drug in the correct dose, encapsulating the correct information is present in each dosage form [163]. Moreover, a proper packaging that enables traceability and data retrieving at a dosage unit, as well as protection against environment and mechanical damage, would be required. These all will add to the overall cost of PDDS.

In the PSC, the added challenge would be the different way of tracing the drug product. By using AM, the traceable element, for example, data matrix, would be on the intermediate feedstock materials, such as API ink cartridges for 2D printing or filament roll for 3D printing containing the API. In mass customization, each dose from the same intermediate feedstock material should get its own unique identifier that matches the patient and dose, which may be traced back to the “intermediate API cartridge”. However, the entire PSC would trace “intermediate” product only in this case, and the unique identifier connected with particular dose for particular patient will only be generated in the last phase of the current PSC, i.e., at hospital pharmacies or retail pharmacies.

7.2. Regulatory challenges

The regulation of pharmaceutical drugs and medical devices involves competing goals of assuring safety and efficacy through the investigative and regulatory processes as quickly as possible. Both US & EU approach these challenges in different ways. The US has always relied strictly on centralized processes through the FDA. On the other hand, the EU regulates through a network of centralized & decentralized agencies throughout its member states [164]. Details can be found in various scholarly articles [164–166]. The regulatory pathway that can be used for PDDS at mass customization level is still unclear at least to the best of our knowledge. The major regulatory challenge for introducing on-demand personalized doses is that the current regulatory pathways for new drug application (NDA) and abbreviated new drug application (ANDA) filings is dose-specific. For mass customization of PDDS, regulatory approval needs to be for the specific dosage range (e.g., 1–10 mg) instead of fixed doses (e.g. 1 mg, 2 mg, 5 mg, 10 mg). The potential solutions for adaptation of regulation could be e.g. “bracketing” and “matrixing” that allow testing only highest and lowest doses, implying on those in-between. Another potential way to implement PDDS is to use the regulatory framework that is applicable to magistral/compounding medicines to meet the needs of individual patients. Production of magistral drug products at the pharmacies or compounding facilities has less stringent quality criteria when compared to the current GMP guidelines for industrially produced medicines [167].

The challenge with regulation of digital therapeutics, unlike typical medicinal products, is that the former are not suitable to be a subject of randomized controlled trial executed (usually once) at the product launch. Specifically, the design of ‘placebo’ condition for digital therapeutics may be in many cases impossible, if not detrimental to the patients’ health. To overcome that, the regulatory framework enables the healthcare professionals to provide “real world data” as evidence. The FDA defines real world evidence data as “data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources” such as electronic health records, medical claims and billing data, data from product and disease registries, and patient-generated data [168]. The evidence for digital therapeutics is therefore an evidence regarding the usage and potential benefits or risks of digital therapeutics, i.e., “a drug product”. The use of real world evidence is a major difference with the current way of regulation of a typical drug product.

7.3. Ethical, privacy and security challenges

In the context of the medical adherence solutions, there are several aspects to be considered, because the data collected via a solution and interactivity features (e.g., digital reminders) may directly impact the behaviour and the state of the health of its user. First of all, the terms and conditions of the service must be clear and understandable for the user, who, can only use the service, if accepts them. The terms and conditions must respect all relevant international and national regulations [169].

Defining and prescribing the patient-tailored dose for PDDS with encapsulated information would require collection, management and storage of enormous amounts of personal health-related data. There have been evidence of data leakage and systematic misuse of personal data with social media such as Facebook and Cambridge Analytica [114]. This underlines the significance of a thorough design of big data platforms to avoid the misuse of sensitive information. Data cybersecurity with the use of the computer clusters and supercomputers would be a key factor for implementation of PDDS. So far, only authorized parties, e.g., patients, healthcare professionals (e.g., doctors, nurses, pharmacists) have access to the patients’ private data, whereas pharmaceutical industries do not. The question is who will define the personalized dose and how will it be defined and at the same time to comply with data privacy and security regulations such as European General Data Protection Regulation (GDPR).

7.4. Influence of human factors on the acceptance of PDDS

The PDDS have the potential to enable better (self-) management of treatment regimen and can lead to improved patients’ health outcome. However, PDDS must be further refined to address different human aspects of their use by the patients and their informal and formal caregivers. We discuss the human factors, in light of recent research results on technology (non)use by the chronically ill patients (N = 200) [128]. Namely, around 20% of the patient population will not be willing to use any personal technologies, including PDDS ones, despite their miniaturization or personalization or other advanced features. These patients are non-adopters and shall be accounted for. Additional 20% will be sceptic towards the use of technologies, and an educational program, or a peer support service may help to gain their acceptance. As for the patients, who may accept the use of PDDS, there are following human factors that will influence the system use and its collected data quality. First, the interface design and especially the system notifications, should be user-friendly and allow for person-
alization. Patients are unlikely to accept a solution that is designed poorly, and that make them feel that they do not have a control over it. It became clear that the patients would rather abandon the system use, than let it to rule and interrupt their daily activities. Further, the aspect of the battery efficiency of the system is crucial. If the battery lifetime of the system is too short and the system requires extended charging – for example every day, that is likely to interrupt the flow of daily activities of the patient, and the patient is likely to forget it. Not only such a situation risks data loss, but, if unattended, it may influence the patients’ medication adherence and hence his/her health outcomes. The overall psychological adherence is related to the fact that the patients are optimizing their daily life for improved quality of life, and their actions are driven by their perception of self-efficacy; and they do not want to be reminded by a PDDS or any other system that they are sick and incapable of taking care of themselves [113,128,170–172]. The second critical human factor, influencing the PDDS acceptance, relates to the system/service performance experienced by the patients. Namely, if the system is not accurate (e.g., launches wrong notifications) or is not timely enough (e.g., notifications are late, out of date), the users will lose trust in it and stop using it as well [128,173,174]. The third aspect relates to the potential costs of using the PDDS that may influence its usage and the collected data quality. The examples of cost influencing the medication intake include a potential patient’s belief that a given costly medical treatment can be taken more sparsely with the same therapeutic effect, while incurring less costs [128,175–177].

Overall, there are many human factors that relate to the design and use of the PDDS and that may influence the patients’ health outcomes. To maximize the patients’ acceptance, any PDDS design choices must be easy to personalize to match closely the existing patient’s routine and lifestyle choices. For example, for the medications taken upon waking up or at the meal times, the interactive design (i.e., number of interactive steps to activate the system or size of the system to be accommodated at the patients’ cabinet or breakfast table) of a PDDS must match the patient’s morning routine or around the meal routine. Overall, the previous research results show that the design elements and personalization choices of system like PDDS must be operationalized such that they make the users feel good about themselves; enable them to become empowered and motivated for self-care [128]. Any design elements that may feel for the patient too complex to understand, or perceived as stigmatizing, will lower the system acceptance, and may result in the failure of the medication adherence service provision, in turn, possibility having implications on the patients’ health outcomes. The overall recommendation would be a design of the PDDS solution that makes it easy and enjoyable for the patients to adhere to.

8. Conclusions

There is an increasing demand of the society for the patient-tailored therapy to improve the overall healthcare outcome with better overall cost-efficiency. Personalized drug delivery systems (PDDS) offer an innovative digitally designed solution that can overcome the challenges of the currently marketed drug products, especially, (1) provide personalized and precise on-demand dose, dosage form and release kinetics, (2) improve medication adherence and give a better overview of the treatment, (3) provide the possibility of track and trace and verification of the genuineness of the drug product by inclusion of unique identifiers, e.g., 2D barcodes, at the individual dosage unit, and (4) offer an easy access to tailored information regarding the drug product. Furthermore, PDDS can establish a bridge between pharmaceutical and digital world as the healthcare sector is becoming increasingly digitalized with an invention of a completely new type of therapies, such as digital therapeutics. However, to make the overall PDDS concept operational and sustainable, related technological, economical and data privacy and security challenges should be solved, and related human factors should be taken into consideration. Furthermore, the regulatory framework for the flexible on-demand dose also need to be well-defined.

References
