Improving Patient Outcomes through Digital Combination Therapies

Driving improved patient outcomes through smart medicine.

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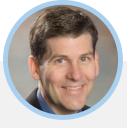

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During the drug development process, pharma companies invest a significant amount of time and resources into finding the proper dose level and schedule. Yet, patients do not always adhere to the guidelines for the medicines they have been prescribed. As a result, patients may not see the maximum benefit of therapies, or worse, may cause severe or irreparable harm to their health.

Smart medicines provide an innovative opportunity to improve patient adherence and outcomes. By digitizing medications and using digital interventions to encourage and capture their proper use, pharmaceutical companies can help patients to improve their health outcomes.

WHAT IS A SMART MEDICINE?

Smart medicines are traditional tablets or capsules that have been enhanced through digitization. Digitization adds a "digital identity" to the physical product. Digitized medicines are typically composed of three components:

- **Medicine:** The physical drug product being digitized.
- **Target (emits a signal):** Contains the information embedded in the digital identity.
- **Sensor (detects a signal):** The technology capable of reading the information in the digital identity.

Currently, most digitization practices center around adding targets like data matrices or RFID tags to the outer packaging. New technology, however, is revolutionizing this area by

providing the opportunity to apply a digital identifier directly to the drug product (e.g., tablets and capsules).

An example of this capability is the addition of spectrally-encoded microparticles of high-purity silica to a traditional tablet or capsule via pharmaceutical coatings or inks. Silica is an edible GRAS material that can be incorporated into the coating or ink on a dosage form and does not impact the product's aesthetics or clinical efficacy. A standard cell phone camera is capable of detecting the silica particles by scanning the tablet or capsule. The camera decodes the digital signal from the particles, and the signature is confirmed and logged in a database, creating a record of the event.

EXPLORING THE BENEFITS OF SMART MEDICINE

Smart medicines deliver benefits throughout a pharmaceutical company's range of operations, from clinical trials to commercialization, by improving data collection and facilitating patient engagement. Digitized medicines provide value in three broad categories.

Improved decision making. With smart medicines, each medicine dose represents a data point. As with any company, having accurate, actionable data improves the decision makers' ability to choose the option most likely to yield positive results. Increased insight into the most granular data point available—the individual dose—can facilitate decisions with previously unavailable data. Supply chain trends and market safety surveillance can be transformed from opaque events into actionable sets of data. Similarly, patient adherence to protocol dosing schedules can be tracked in real-time and linked to clinical outcomes and provide investigators information that can aid patient engagement.

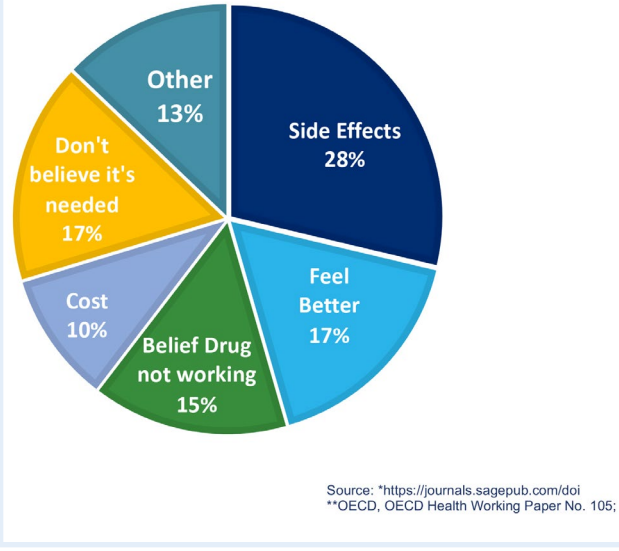
Reducing supply chain risk. Modern supply chains have grown increasingly complex. Unauthorized, illegitimate, and diverted medicines have created public health and safety risks for brands and patients alike. Whether it is licensed manufacturers producing too much product, expired medication being reintroduced to the market, or counterfeits being sold as authentic, pharmaceutical companies can struggle to track inventory throughout the supply chain.

Smart medicines offer a cost-effective, easy-to-implement solution to manage these risks in several ways:

- Worldwide, instant, and unequivocal identification of medicine at a granular level
- Root cause identification for adverse events to guide reactions to supply chain or adverse events
- Verification of correct product and dose levels during consumption by patients

Concerning the final point, medication errors cost an estimated $42 billion annually, according to the World Health Organization. In the United States, the FDA reports that medication errors cause at least one death each day and injure approximately 1.3 million people a year. Smart medicines can help mitigate these errors by linking the prescribed medications with those being ingested.

Figure 1: Reasons for medication non-adherence.



Improving patient outcomes. Smart medicines have been demonstrated to increase patient engagement and improve adherence. Patient non-adherence is a significant challenge for the healthcare industry. Healthcare providers prescribe medicines based on medical needs, so patients who fail to follow the appropriate dosing regimen may not experience the desired therapeutic effect. FIGURE 1 illustrates the reasons patients do not take medication as prescribed stem from various causes. By leveraging technology in an innovative and carefully-planned manner, smart medicines can help modify patient behavior and increase adherence to medical regimens.

EXPLORING PATIENT NON-ADHERENCE SOLUTIONS

Non-adherence takes many forms, many of which are rooted in fears of candidly discussing concerns with healthcare providers. Some patients may not believe the medication will provide a positive outcome and simply do not fill their prescription. Others may think the dosage prescribed is insufficient and take more than recommended. Affordability can be a barrier to adherence, and patients may cut pills in half to extend the prescription duration, substitute over-the-counter options, or fail to fill the prescription once the cost has been revealed.

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Perhaps the most understandable reason for non-adherence is the discomfort of side effects experienced. Although some side effects may only last for a short period, their impact may be exacerbated by interactions with other medications. Data suggests that roughly one-third of patients will stop taking a medication without ever notifying their physician.

Pharmaceutical companies have begun relying on increased education and support to change patient behavior, which has been shown to improve the tolerance of short-term side effects. These tools are frequently either wholly or partially digital and fall into two broad categories.

Therapy-agnostic digital interventions. A key advantage of a smart medicine solution is that you can track the physical act of taking the medication. This event can then be recorded and with a patient's consent, the information

can be shared with a health care professional or brand owner.

When the digital record of a patient taking their medicine is recorded or not recorded, brands have the potential to message patients in real time offering encouragement or reward. These messages serve to reinforce positive patient behaviors.

As a whole, these digital interventions can be used across therapies and have already proven an effective tool for changing patient behavior through increased engagement.

Therapy-specific digital interventions. While broad-based digital interventions are very effective, there is certainly an opportunity to do more by offering custom digital interventions for specific products or therapies.

Often, patient-support programs do not recognize that the underlying reasons for nonadherence may be complex and driven by individual perspectives.

The advent of novel digital tools based on behavioral science principles provides an added opportunity for improving patient outcomes including a combination of digital and live interactions with counselors and HCPs specifically trained in behavioral science.

Tying these behavior-based interventions into existing support programs offers an added catalyst for changing patient behavior and improving patient outcomes.

When combined with smart medicines, the digital intervention can be linked with ingestion's physical activity, strengthening the tool's benefit and adding key action-based

Figure 2: Digital interventions – custom messaging.

Source: Application of the COM-B model to barriers and facilitators to chlamydia testing in general practice for young people and primary care practitioners: a systematic review

information. FIGURE 2 illustrates the relationship between the behaviors and capabilities, opportunities, and motivation and the areas a digital companion may impact. Action-oriented alerts serve several purposes:

- **Remind:** Reminders that require medication to be in hand to dismiss the alert are more effective
- **Reassure:** Scanning the tablet or pill allows the app to confirm the correct medication and dosage are being taken
- **Reinforce:** Patients can opt to share their actions with a healthcare provider who can reinforce behavior and message the patient in real-time. The app can also provide information related to a side effect.

One case study showed the benefit of such a tool involves a cancer therapy with solid clinical evidence that the intervention reduced the reoccurrence of cancer. The treatment had been proven effective but required six months of taking a daily tablet that caused extreme diarrhea. For some patients, this side effect created concern over whether it was expected or an adverse event, and for others, it generated shame and embarrassment. As a result, more than half of patients failed to continue on the drug after four weeks.

An app was provided to patients to provide education and reassurance. Patients could directly message an oncology nurse and discuss whether side effects were temporary and likely to subside or if they were more serious. The program also provided guidance on how to offset side effects and shared clinical data about the events' typical duration. The result was patients remaining on treatment for longer periods (FIGURE 3).

Figure 3: Case study: Addressing MNA through digital interventions.

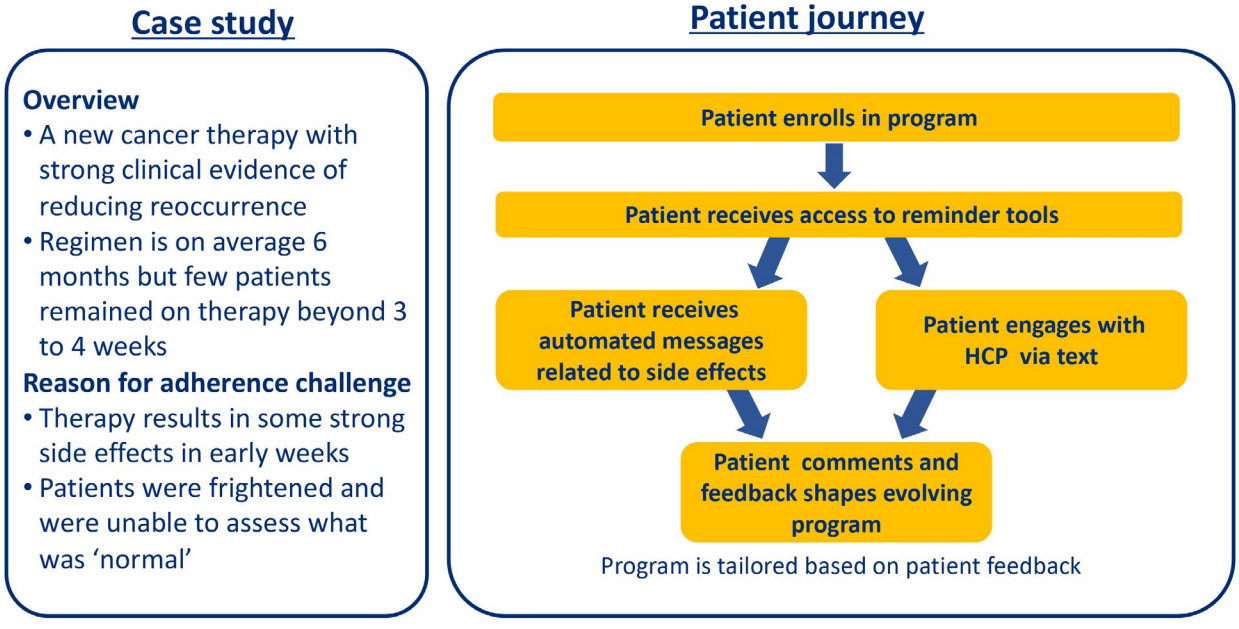
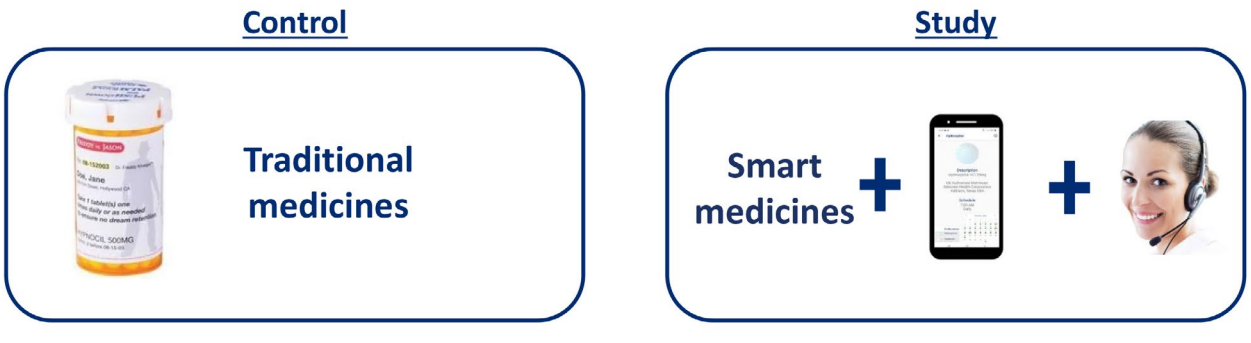


Figure 4: Digital combination therapy demonstrated marked improvement in patient adherence.



Interim Study Findings

	# Patients	Reported days	Medication missed	Level of adherence	Max adherence	Min adherence
Control	15	300	96	68.0%	100%	13%
Study Group	15	450	22	95.1%	100%	77%

PUTTING IT ALL TOGETHER: DIGITAL COMBINATION THERAPIES

The FDA defines combination therapies as those that combine two or more regulated components. A *digital* combination therapy adds a digital element to traditional medicine and pairs it with a digital companion to interact with the drug and positively influence patient behavior.

To demonstrate the efficacy of digital combination therapies, a trial simulation divided 30 participants into two equal groups: a study group and a control. The study group received silica taggant-coated tablets and a cell phone app as a digital companion. To dismiss alerts, patients scanned medication, which was reported to a simulated healthcare professional. The study group's adherence rose to 95% versus 69% in the control group, showing digital combination therapies' capability to influence patient behavior positively (FIGURE 4).

CONSIDERATIONS WHEN ADOPTING SMART MEDICINES

When combined with a digital companion to create a digital combination therapy, smart medicines have a wide range of demonstrated benefits. When adopting smart medicines into one or more traditional drugs, pharmaceutical companies should consider several aspects of the implementation.

Regulatory concerns. The FDA supports the use of smart medicines, which it calls physical chemical identifiers (PCIDs), and has published guidance on the application of markers directly onto drugs. When using a substance that is GRAS and applied to the immediate-release segment of the dose (i.e., the outer film coating), regulatory adoption is reasonably straightforward.

Leveraging a smart device, as opposed to developing a proprietary sensor, can ensure scalability and that the tool lowers the threshold of effort required by patients and caregivers.

PCIDs can be added to the approved drug product in the United States as a Level One Post-Approval Change included in the Annual Report. The approach is similar in other regulatory jurisdictions. In the European Union, the change can be reported as a Type One Minor Variation in the EMA Annual Renewal. For drugs in development, smart components can be added as an ingredient in a New Drug Application (NDA) filing.

If a brand wants to demonstrate improved patient outcomes due to the addition of PCIDs, pharmaceutical companies can submit a supplemental NDA to the FDA to obtain classification as a digital combination therapy. This route may be preferred to demonstrate improved adherence and outcomes, which may be a convincing argument when establishing the value of digital combination therapies to payers.

Manufacturing considerations. The validation of the manufacturing process can be costly and time-consuming, and changes to the validated process can be cost prohibitive and delay production. Fortunately, the incorporation of smart medicine into existing production lines is relatively seamless, and in many cases, does not require re-engineering or revalidation of the process. In cases where smart medicines can be applied to standard film coatings or inks, little to no capital expenditure may be required. The new application may only require ordering a different SKU from a current vendor that has already completed development and demonstrated its stability and effectiveness.

Cost implications. In addition to implementation costs, including hardware, software, material, and process re-engineering, brands should consider the variable unit cost required to add the target to medicine. Also, the cost of developing and maintaining digital and behavioral support materials and resources should be considered.

Ultimately, the cost of smart medicine solutions should be a fraction of a cent per dose concerning the total cost of ownership. Keeping costs at this level will make smart medicines a worthwhile investment by increasing market access and compliance.

Sensor ease of use. In several examples provided here, a smartphone was the digital companion delivery tool used as a sensor to read the information encoded on the target medicine. Leveraging a smart device, as opposed to developing a proprietary sensor, can ensure scalability and that the tool lowers the threshold of effort required by patients and caregivers. As a general rule, the easier the adoption and use, the more successful your rollout will be.

SUMMARY

The digitization of medicines provides pharmaceutical companies with discrete benefits across their value chain in terms of quality assurance, risk management, and decision-making. These smart medicine solutions can also offer significant benefits to patients through the creation of digital companions that can interact with smart medicines. These companion tools can drive digital interventions that seek to change patient behavior and improve adherence. Digital combination therapies can offer improved health outcomes over traditional medicine.

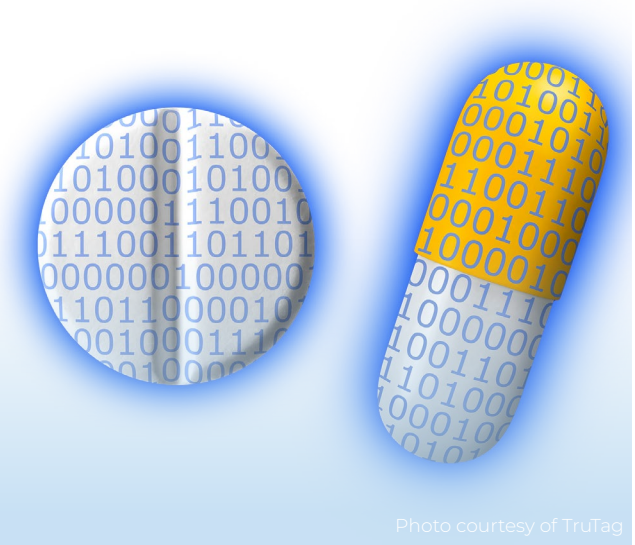


Photo courtesy of TruTag

TruTag Technologies is fueling new digital health solutions through the mass digitization and deliver of smart medicines.

Colorcon is a world leader in the development and supply of film coating systems and excipients and offers innovative digital on-dose technologies and detection services for the authentication of medications.

Diligent Health Solutions is a multifaceted healthcare contact center providing communication services to pharmaceutical, biotech, medical device, medical technology companies and healthcare organizations.