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Rapid Adoption of Medication Adherence and Smart Packages – Key factors driving interest and consideration

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Premise

Smart packs to support medication adherence in clinical trials have been around for more than 20 years, but have rarely been used, let alone adopted. A conducive ecosystem, however, has been observed in the recent past where there has been a noticeable change in the drivers of adoption. Regulatory compliance and societal openness to adopt the technology, as well as the industry's desire to digitize and deliver inclusivity and diversity by becoming more decentralized, mean that the benefits of adopting pack-level technology for medication adherence may be realized now more than ever before.

We see a lot of movement with trial sponsors and drug developers shifting their focus to digital trials, and subsequently making its way into the trial medication supply chain solution. To realize this, sponsors need digital solutions that deliver into their data lake, driving the need for interoperability across platforms including out-of-the-box interfaces to reduce custom integrations. This would speed up the setup time and accelerate the adoption of digital solutions by eliminating cost and complexity of establishing sponsor specific integrations. Decentralized trials has evolved to support direct-to-patient supply chains and medication adherence as a larger concern if patients receive Investigational Medicinal Product (IMP) directly at home.

Since DCT provides limited capabilities for site staff to provide instructional advice for patients to take the medication, it puts an emphasis on technology solutions to support medication adherence insights during the treatment period. Medication adherence via technology adoption is now seen as an essential parameter to monitor if IMP is being taken correctly or not. Digitalization serves as a better option than manual counting of the returned pills.

Digital innovations and its adoption

The system innovators' strategic priority when introducing new technologies and innovations is to ensure that technology fits seamlessly with existing infrastructure in existing production environments. They need to ensure that clinical platforms and other services can use embedded technologies such as smart packages in the various supply chains and digital eco-systems. This is achieved using software libraries, that help with seamless integration into existing systems, apps and web portals. These libraries are devised taking into consideration the painstaking tasks across clinical trials that require maneuvering across different digital solutions and platforms.

Our society too has pivoted towards digitalization and digital adoption, that is exemplified by the increased adoption of "bring your own device" (BYOD) apps and other smart devices. Apple opened its operating system, iOS, for Near-Field Communication, NFC, to app developers in 2018 [1], sometime after the Android Operating System. This led to a wave of applications using smartphones and apps for aspects such as making payments, accessing hotel doors, starting cars, controlling heating, lighting and other security-related things. People cutting across age groups are using smartphones to scan and record their health,

including their COVID vaccination status and other healthcare-related matters, including telemedicine and scanning QR codes for track-and-trace using apps on BYOD devices. Suffice to say, this trend will carry over into everyday life for trial participants.

Smart devices and its usability ecosystem

Previously, you had to be a large pharma organization to process smart packages in your own GMP facility. However now, ready-to-use software programs enable the possibility to manufacture smart packages at outsourcing contract packaging partner/CDMOs in both (1) manual low-volume process for use in early-phase clinical trials and (2) fully automated large scale smart package production process, making it much more accessible for all.

The regulatory climate is also promoting digital solutions to support trial outcomes. Smart adherence packages enable precise compliance with the requirements and dosage regimens for drug development, according to the proposed clinical trial protocols of the FDA and EMA. The FDA Guidance on Digital Health Technologies (DHT) [2] gives everyone confidence on how best to adopt and use DHT in trials. EMA Clinical Trials Regulation Annex VI [3] has caused challenges in expiry date management which digital labels may be able to support. Also, the UK Medicines and Healthcare Product Act (MHRA) [4] is looking for opportunities to use digital solutions to take a leading role in clinical trials and innovation.
On the technology level, in recent years, multiple digital technologies have been launched for detecting and continuously recording events in or on clinical trial medication packs. In addition to temperature logging, security features, and track and trace functions, digital measurements of medication intake and adherence has also become established.

Options for radio communication technologies that may be used for smart packages to transfer their data include NFC/RFID, Bluetooth, Zigbee, and Wi-Fi. However, most smart packages will use NFC technology for the simple reason that it is the only technology that doesn't need power and is relatively cheap. The need to develop special Bluetooth Low Energy interfaces for smart packages for use in these circumstances arise because clinical studies have special requirements, for instance, where one needs immediate or real-time response, or passive data transfers running via an app on the participant's phone in the background.
The digitization trend is also driving application of these technologies within clinical trials. In a controlled and regulated environment, increasing number of use cases are being established, and the benefits are also more obvious and better understood. The valuable support for analysis of the targeted clinical endpoints will be more visible. Indeed, non-adherence in clinical trials leads to enrolling more patients to reach endpoints, increasing the study timeline, and thus enhancing operational costs. Non-adherence can increase variance, lower study power, and reduce the magnitude of treatment effects. Medication adherence in traditional trials is already worse that one would expect, as can be currently underestimated by traditional methods like pill counts or self-report. Finally, the trend toward less site visitation and more diversity may well amplify the problem of adherence.

Many know that poor adherence is prevalent in practice but believe that the statistic is good in trials, which is untrue. Adherence is poor across the board compared to the 80% compliance that is considered acceptable for medication adherence [5]. What's more, some sponsors may not even realize that they have a non-adherence issue in their trials, and this is simply because of the concept of 'what isn't measured can't be managed'. The hidden consequences are underestimations of drug efficacy, safety concerns, and

draining study power to the point of study failure. It's a fact that approximately 50% of the patients do not take the medication as prescribed [6][7]. This subsequently has a negative impact on the analysis and interpretation of the clinical endpoints.

Robust and reliable adherence monitoring can be addressed quite easily with digital adherence measurement via smart packages. This approach to manage adherence is evidence-backed. Finally, more sponsors are openly advocating the need for better adherence in clinical trials, and time has shown that hurdles to using new digital tools is decreasing with each passing day. Typically, e-diaries are deemed as a source of medication adherence record. However, they are often seen as a burden for patients, and therefore the data quality and reliability of e-diaries is questioned. e-diaries eliminate the need for pill counting or drug accountability because they are completely disconnected from the pill intakes.

Advanced digital technologies based on smart packages enable more objective and precise adherence monitoring. It is a frictionless approach with the option for real-time tracking and insights if required.

Embedded technologies for adherence monitoring

One of the most relevant criteria and differentiators for the use of smart adherence packages is its high usability for patients combined with seamless integration into existing packaging designs. These factors increase the acceptance of the technology, as no intervention from patient is required. Adherence data is automatically generated when the patient takes the medication, post which the e-diary gets updated automatically. It's a highly appreciated tool where automated data entry drives accuracy and adoption of e-diary completion by the patient.

Other measurement methods, such as camera- or video-assisted tools, always require an additional step. Studies have already shown that patients rarely use such tools or apps, resulting in missing adherence data and negative consequences. Solutions that avoid adding another app or proprietary device, such as a diary or sensing device and can work with or on the patient's own devices with minimal intervention, are desirable. Continued ease of use is also key, since digitalizing a manual process should not lead to more work to complete the task. As an example, smart blister wallet packaging can be used to visually differentiate between a morning and evening intake requirements using printed prompts, and in addition, the embedded chip records a time, number, and exact cavity (cavities), i.e., the dose(s) from the pack. This can help to understand and share clear and precise adherence insights, as well as automate significant amounts of the drug reconciliation and accountability process.

The biggest flaw in the traditional approach of pill counting in site monitoring, whenever a patient arrives for a visit and demonstrates the used medication pack is that patients sometimes take their entire medication late in the treatment period and dump their pills in one go. Thus, we do not obtain any certainty about the real intakes with pill counting.

We know that drug accountability is one of the most important aspects in clinical research since it can greatly influence the quality and integrity of study data and results. Inadequate accountability is the third most common reason why sites fail FDA inspections [8][9]. As a sponsor, it can also lead to major complications when performing reconciliation at the end of the study. Making site drug accountability an automated digital process via smart blister wallet use has an attractive upside to also opening the

opportunity for more real-time medication adherence and less operational efforts with time-consuming site monitoring. It is also a safety factor where patients not taking drugs, taking more than prescribed, or taking the wrong drug can be identified a lot closer to when it happens, than during manual or traditional approaches when packs are returned "used" and "empty" or "part empty".

Summary

In summary, the case for adopting digital solutions in trials to provide real-time insights on medication adherence has grown stronger. The fundamental drivers of change include societal norms, legal requirements, and sponsors' desire to digitalize and adopt decentralized trial procedures. CDMO service partners are now supplying sponsors with GMP-compliant medication kits in smart packaging that provides data interoperability into GCP-facing platforms via mobile apps and web portal access to patients and site staff. It is a case of where and what solutions are adopted sooner than when or if it is going to happen at all.

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About the Author

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During Dr. Ingram's 25-year career, his work has focused on pharmaceutical research and development and medical devices. He has over 15 years of experience in clinical supplies, working in both Phase 1 unit manufacturing suites and trial supplies service companies, including Quintiles (later Aptuit), Fisher Clinical and Catalent. Dr. Ingram obtained his doctorate in pharmaceutical development from Strathclyde University in Glasgow, U.K. Most recently his focus has been on defining and then establishing innovative and strategic solutions within the clinical trial supply chain to leverage agility while supporting digitalization in decentralized and patient centric trials.