MEASURING AND MANAGING MEDICATION ADHERENCE FROM CLINICAL TRIALS TO ROUTINE CARE: THE INJAY MEMS AS® INITIATIVE

In this article, Arnaud Guillet, Business Development Director, Biocorp, and Bernard Vrijens, PhD, Scientific Lead, Aardex Group, discuss the issue of medication non-adherence in both clinical trials and commercialised drug products, and how Biocorp's Injay connected prefilled syringe solution combined with Aardex's MEMS Adherence Software provides a means to tackle this ongoing problem.

Low adherence to prescribed medication is a well-known issue to all healthcare stakeholders, its clinical and commercial impact having been quantified and heavily documented for many years now. The effects of this issue aren't limited to commercialised drugs and real-life conditions, they also massively affect clinical trials, which impacts the assessment of drug efficacy. When it comes to injectable molecules, and specifically to medication delivered by prefilled syringes (PFSs), patients face additional challenges compared with other types of drugs, such as difficulties with handling the device or needle phobia. These challenges exist right from the drug development stage and persist with increased intensity in routine care. This calls for a solution adapted to the specifics of the field.

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Based on this observation, Biocorp, a company that specialises in connected drug delivery devices, and Aardex, a leading player in the field of digital adherence management solutions for clinical trials, have decided to join forces and put together two of their key assets: Biocorp's Injay, a connected PFS solution, and Aardex's Medication Event Monitoring System Adherence Software (MEMS AS®). This combination offers a comprehensive solution to effectively measure and manage treatment adherence for PFS-based medication, both at clinical and commercial levels.

SOLVING THE PROBLEM OF NON-ADHERENCE DURING CLINIC TRIALS

The Consequences of Non-Adherence During Clinical Trials

Clinical trials are designed to evaluate the efficacy and safety of new medical treatments and are fundamental to the drug development process. However, when study participants do not take their medications as prescribed, it can result in underestimated drug efficacy and delay the approval of the investigational product. Strong evidence suggests that up to 50% of trial participants, including those in Phase II, III and IV studies, across most therapeutic areas, do not adhere to the protocol-specified dosing regimens.[1]

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This non-adherence affects medications across delivery routes and life-threatening diseases. The reasons for it are as numerous as they are complex. When it comes to injectables, patients face specific challenges, such as the aforementioned difficulty with handling the drug delivery device and needle phobia, but there can also be issues with complex treatment plans involving various injections spaced out over a period of time. This is particularly true with medication delivered via PFS, which is increasingly being used in clinical trials, especially those evaluating biologics.

While autoinjectors have been introduced to overcome many of the usability issues related to using PFS in routine care, this is not the case during clinical development. There is an urgent need, then, to help patients follow their self-injection regimens in future drug development programmes.

Measuring and Managing Adherence During Clinical Trials

Non-digital methods of monitoring medication adherence, such as pill counting or patient self-report diaries, can be biased, meaning they are not robust enough to be effective during clinical trials. More advanced digital monitoring methods provide a complete understanding of patient adherence behaviours and risk indicators that matter most for the success of a study.[2]

Electronic detection of treatment administration is a robust indicator of when a patient took a prescribed dose – in fact, it is 97% accurate when compared with blood concentrations. It is fair to say that this advanced method of digital monitoring provides the most accurate measure of medication adherence.[2]

Aardex's MEMS incorporates microcircuitry into pharmaceutical packages and devices of various designs. It detects when the medication is administered, then automatically timestamps and stores the dosing history data, before securely transmitting it to the cloud-based MEMS AS®, where it is appropriately analysed.

MEMS AS® is a secure, cloud-based platform that provides sophisticated analysis of medication-taking behaviours for powerful visualisation and focused feedback for the patient (Figure 1). This digital solution can be connected and integrated into third-party applications for risk stratification and patient empowerment. In recent years, MEMS AS® has grown its connected package device offering to a complete ecosystem of delivery systems covering all routes of drug administration, including injectables and inhalers.

Figure 1: MEMS AS® includes both a mobile app and a web portal.

Biocorp's connected PFS Injay (Figure 2) is now part of the MEMS AS® ecosystem and collects essential information such as injection completion, time and date, type of drug, batch number and expiration date. This data is transmitted wirelessly via near-field communication (NFC) through a simple tap of a button. This solution, when combined with MEM AS®, could be the most appropriate response to PFS-specific non-adherence issues during clinical trials.

MEMS AS® Mobile is an app dedicated to patients. It uses onboarding screens to ensure participants have the information they need about the clinical trial, such as dosing regimens, instructions and adherence information, as well as advice on developing strong adherence behaviours. Throughout a clinical trial, participants can access their scheduled appointments, reminders and medication history; can transfer their data to the central system; and can send additional adherence-related information by answering simple questions.

During clinical drug development, the MEMS AS® processes patient data from various compatible smart packages/devices. Using more than 70 proprietary and validated algorithms, it can present a comprehensive picture of patient adherence based on electronically compiled dosing history data. MEMS AS® facilitates connectivity with electronic data capture (EDC), interactive response technology (IRT) and third-party applications.

This advanced approach is a feasible, non-invasive, reliable and easily implemented method of quantifying medication adherence. Therefore, it is an effective way to monitor adherence, and mitigate the associated risks, during clinical trials.

Measuring and encouraging adherence is essential to the success of clinical trials and avoiding errors in the interpretation of patient risks and benefits. Every effort should, therefore, be made to incorporate digital monitoring measures into drug development.[3]

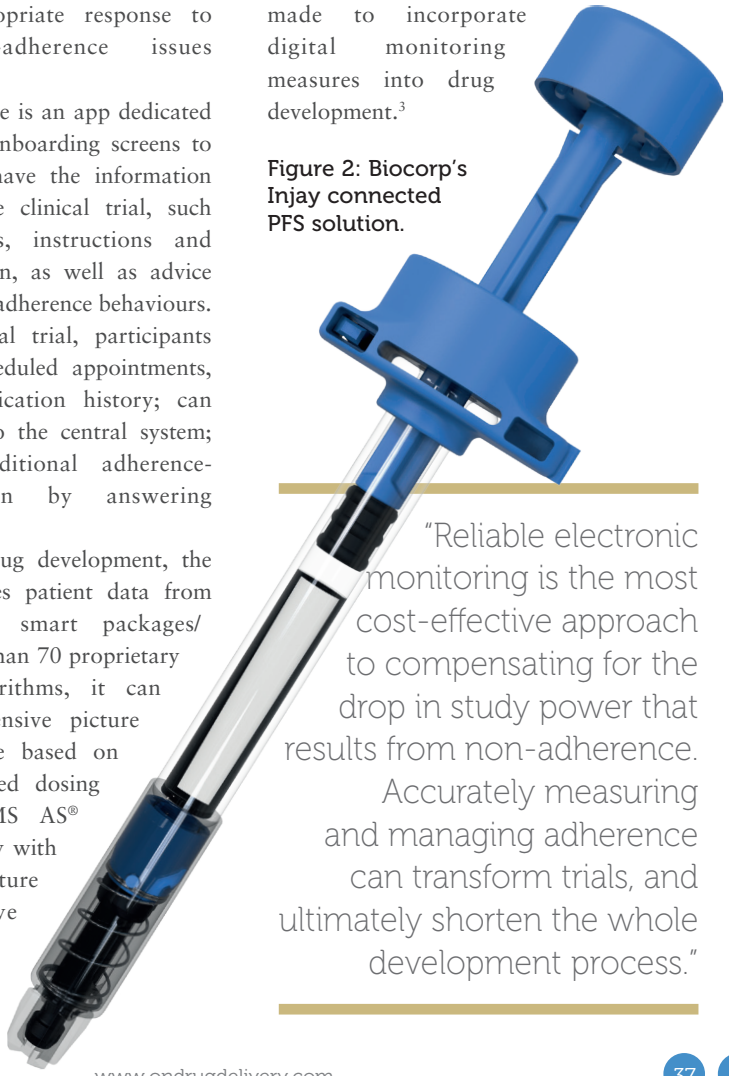

Figure 2: Biocorp's Injay connected PFS solution.

"Reliable electronic monitoring is the most cost-effective approach to compensating for the drop in study power that results from non-adherence. Accurately measuring and managing adherence can transform trials, and ultimately shorten the whole development process."

Optimising Adherence in Clinical Trials Yields Significant Benefits

Reliable electronic monitoring is the most cost-effective approach to compensating for the drop in study power that results from non-adherence. Accurately measuring and managing adherence can transform trials, and ultimately shorten the whole development process. Collecting this information during drug development informs evidence-based risk mitigation strategies and provides key patient behavioural data for a successful commercial strategy. This is demonstrated by MEMS AS®, which has been proven to improve medication adherence, data quality and integrity, and ensure high fidelity to the dosing regimen specified in the clinical trial protocols (Figure 3).

The partnership between Aardex and Biocorp offers a turnkey solution for pharma companies that are developing PFS injectable molecules and want to boost clinical trial efficacy and efficiency. What's more, this solution can be extended beyond the clinical phase, bringing significant benefits to commercialised daily practice.

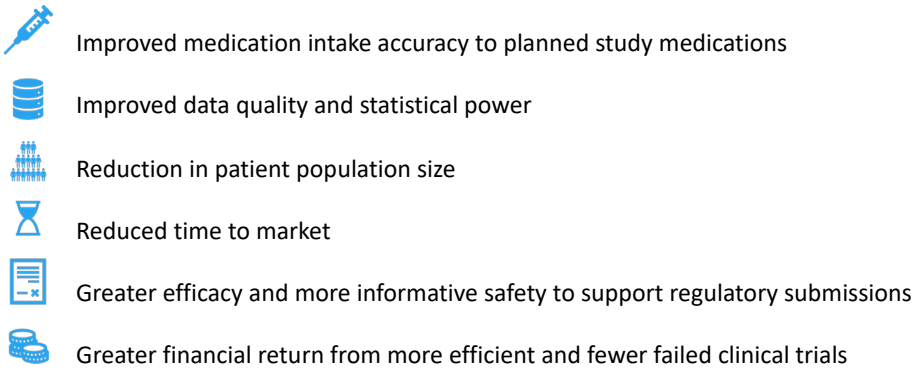

Figure 3: The clinical benefits of MEMS AS®. Source: FDA guidance on trials enrichment strategies and the ICH 9 (R1) addendum on estimands and sensitivity analysis in clinical trials.

USING THE INJAY MEMS AS® SOLUTION TO BOOST ADHERENCE FOR PFS-BASED COMMERCIALISED DRUGS: SPECIFIC USE CASE WITH RHEUMATOID ARTHRITIS TREATMENTS

In chronic diseases, adherence issues are even more prevalent than in clinical trials. People are usually left to manage their medication alone, without the benefit of a highly controlled environment and frequent support from healthcare professionals (HCPs). Some members of the industry have described this phenomenon as the "self management gap".[4] Traditional adherence rates for chronic diseases are around 50%[5] and this figure can significantly decrease over time, with a massive drop in medication refills after six months.[6] This calls for solutions to support and engage patients in the long run.

While these statistics hold true across delivery methods, injectable medicines present specific challenges. People need to learn how to use their injection devices properly, deal with the complexity of treatment protocols and maintain good technique over time. It's especially difficult for injectable treatments that are taken once a month or once a week, as the large gaps between injections often lead to patients forgetting good administration technique, or even forgetting to take their medication altogether.

This is typically the case in rheumatoid arthritis (RA). While some treatment options involve hospital administration, self-management is becoming the norm as various biologics are delivered via PFS as subcutaneous injections. Treatment protocols vary from a monthly or weekly injection for anti-TNF alpha products such as golimumab, certolizumab, adalimumab and etanercept, to daily administration, as with the anti-IL1 anankira or abatacept.

To ensure that their products are successful in real-life conditions, pharma companies commercialising biologics for RA need to design services that will boost treatment adherence and support effective delivery. To do so, they must leverage the available digital options and relevant tools.

USING THE MEMS AS® MOBILE APP AND INJAY TO SUPPORT ANTI-TNF TREATMENT MANAGEMENT

Using the example of an anti-TNF treatment, which is typically delivered by standard PFS every two weeks, we will illustrate how the Injay treatment delivery device combined with the MEMS AS® can support patients and HCPs, improve adherence and result in better clinical outcomes.

Treatment is delivered by the Injay-enabled PFS. This device is comprised of two components: a customised piston rod containing an NFC tag and a finger flange featuring an activator. Both Injay components have similar size and shape to regular PFS components. The Injay piston rod is installed by the pharma company on the assembly line after product filling, where the NFC tag is flashed with key product information. The Injay finger flange is assembled on the PFS after filling, and combines a backstop function. Injay does not add any new components to a traditional PFS package.

Patient onboarding is typically carried out in a hospital setting by a resident rheumatologist, who will offer the connected option, as well the opportunity to download the MEMS AS® Mobile app, and provide a prescription for the Injay-enabled PFS. A rheumatology HCP then would help the patient to install the app and teach them how to use the syringe.

Every two weeks, the MEMS AS® Mobile app will use push notifications to remind people to take their medicine. They will be prompted to open the app, where they will find a simplified treatment delivery guide, information about their treatment, including potential side effects, and motivational features. Guidance is critical to guarantee proper use of a PFS, yet recent studies have shown that many people struggle to follow all of the required steps outlined in instructions for use (IFU) documents.[7] Offering simplified, user-friendly guidance on the app is an effective way to address this issue.

Patients then use the Injay-enabled PFS and, when the piston rod reaches the stopping point, the system will detect a complete injection. They will then be able to timestamp their injection and transfer the product information stored on Injay's NFC tag, simply by placing the Injay device near their smartphone and enabling the app. The information is then stored in MEMS AS® Mobile app and becomes available in real time on the MEMS AS® web portal.

This extra step of transferring data to the smartphone could be considered a hurdle, but it is one that can be overcome by making sure the app is useful to the patient beyond data collection. In this configuration, the app is not merely a recording tool, it's a comprehensive way to engage patients, by providing reminders, injection guidance information and treatment information.

The MEMS AS® Mobile app can also be used to report side effects and monitor other patient factors.

All the information recorded by MEMS AS® is available to the referring physician in real time through the MEMS AS® web portal, which provides a detailed view of injection history, adherence rates and behaviour, potential issues reported and more. It can also be used as a means of communicating directly with patients, re-ordering prescriptions and even managing appointments.

To overworked HCPs, using connected solutions to monitor a pool of patients may be perceived as an additional burden. But this tool can actually help to optimise tasks by providing relevant analytics to identify at-risk patients, prioritise interventions within a multidisciplinary framework and adjust treatment plans. It also helps the care team to interact with patients remotely.

Finally, this approach has the potential to become an additional revenue stream. In many markets, reimbursement schemes are evolving to cover patient monitoring through connected solutions. For instance, in the US, Medicare and Medicaid released a new framework in November 2019 which extended access to reimbursement for certain acts (remote physiologic monitoring, chronic care management) and created new categories eligible for reimbursement (principal care management). These new reimbursement plans open new doors to engage HCPs, as well as compensate them for their time and service. Aardex and Biocorp are looking into these new schemes intensively, and designing the quality measures needed to make their common solution eligible for these reimbursements.

Beyond HCPs and monitoring reimbursements, this new, connected solution is an opportunity for pharma companies to enter into outcome-based contracts with public and private payers. Medication non-adherence is a significant cost burden on healthcare systems and individuals worldwide. There is a clear benefit to payers to look into solutions that target this specific issue and propose outcome-based deals. Interestingly, one of the most famous outcome-based contracts in the field of chronic disease management was signed in 2018 between Harvard Pilgrim and Amgen for Repatha® (evolocumab), a molecule targeting familial hypercholesterolemia, which is administered via PFS. Better adherence measurement and management could surely help towards achieving better outcomes in this specific case.

CONCLUSION

In clinical trials and clinical practice alike, patients not taking their medicine as prescribed presents huge health and economic challenges, impacting pharma companies and healthcare systems alike.

The collaboration between Biocorp and Aardex provides a unique opportunity to monitor patient adherence to PFS in clinical trials and medical practice, while driving up engagement. Injay is easy to use, and its MEMS AS® companion app provides patient support through education, notifications and behavioural advice. The solution provides HCPs will all the information they need to remotely monitor a patient's disease, and study teams with all the data they need to make risk-mitigation plans during clinical trials. And with outcome-based financial compensation moving into the mainstream, it's never been more important to take every opportunity to boost patients' wellbeing.

ABOUT THE COMPANIES

Biocorp is recognised for its expertise in the development and manufacture of medical devices and delivery systems. Today, Biocorp has acquired a leading position in the connected medical device market thanks to its Mallya technology. This intelligent sensor for insulin injection pens allows reliable monitoring of injected doses and thus offers better compliance in the treatment of diabetes. Available for sale from 2020, Mallya spearheads Biocorp's product portfolio of innovative connected solutions.

Aardex Group is a provider of digital solutions to measure and manage medication adherence. Located in Belgium, Switzerland and the US, Aardex develops and markets digital solutions for adherence-enhancing strategies in clinical trials, research settings and professional healthcare systems. Aardex is the central actor of a complete ecosystem that combines its MEMS AS® with a wide range of smart packages and devices that measure patient adherence across all routes of drug administration. The company's vision is to continuously innovate in data-driven

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medication adherence solutions to enhance digital therapeutics and patient empowerment. Aardex is ISO certified, compliant with HIPAA, FDA 21 CFR Part 11 and GDPR, and is regularly audited by pharmaceutical companies.

REFERENCES

1. *Blaschke TF et al, "Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories". Annu Rev Pharmacol Toxicol, 2012, Vol 52, pp 275–301.*
2. *Vrijens B, Urquhart J, "Methods for measuring, enhancing, and accounting for medication adherence in clinical trials". Clin Pharmacol Ther, 2014, Vol 95(6), pp 617–626.*
3. *Breckenridge A et al, "Poor medication adherence in clinical trials: consequences and solutions". Nat Rev Drug Discov, 2017, Vol 16(3), pp 149–150.*
4. *Williams C, Rafiei R, Howald R, "Digital Health Reformulation: from Hope to Hype to Health". ONdrugDelivery Magazine, Issue 108 (June 2020), pp 51–56.*
5. *Kleinsinger F, "The unmet challenge of medication nonadherence". Perm J, 2018, Vol 22(3), pp 83–85.*
6. *"Patient adherence: the next frontier in patient care. Vision and reality, 9th Edition". Research report, Capgemini, 2011.*
7. *Baker C, "Improving Patient Onboarding with Advancements in Medical Device Training". Drug Discovery & Development, Feb 2015.*

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