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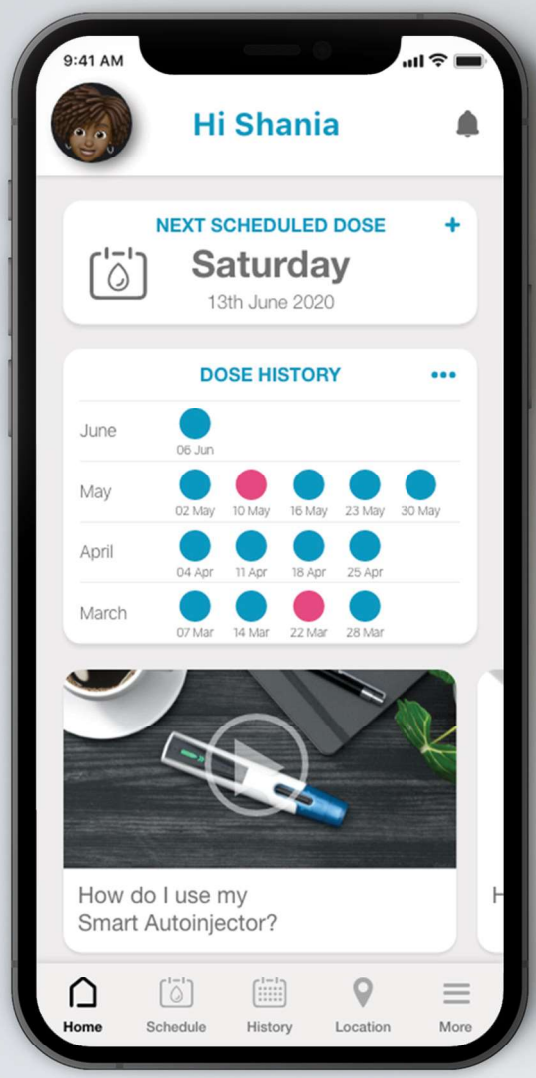

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The Future of Auto-Injectors

What's the current situation around auto-injectors in targeting chronic health conditions, and what more can be done to enable the safe self-administration of biologics?

Iain Simpson at Phillips-Medisize

The past 20 years have seen significant progress in the treatment of chronic diseases, with the development of disease-modifying biologic drugs to treat a wide range of autoimmune diseases, multiple sclerosis, and migraines, as well as hypercholesterolemia and atherosclerotic cardiovascular disease. Alongside the approval of new molecular entities, drug delivery device technology also plays a significant role in improving disease management in these indications. In particular, the use of auto-injectors has increased the opportunity for self-administration of these drugs and, since the introduction of the first devices around 15 years ago, more than 30 different drug-auto-injector combination products have entered the market. The approach brings benefits to key stakeholders:

- For patients, it offers the convenience of medication at home, avoiding the time and effort of a visit to a clinic. Although pre-filled systems can be used for self-administration, auto-injectors make administration easier and are particularly suited for higher viscosity drugs, which require higher injection forces than those that can be easily provided with a manual injection
- For pharmaceutical companies, it can provide a source of differentiation that can sustain or grow market share, or offer lifecycle management opportunities to reduce the threat of biosimilar competitors. Although difficult to prove, greater patient convenience may also lead to improved medication adherence (which reduces loss of revenue) and improved healthcare outcomes (which could facilitate value-based payments and/or higher reimbursement)
- For payers and providers, self-medication can reduce the healthcare costs associated with in-clinic treatment, and potentially improve outcomes due to better medication

adherence. Furthermore, the impact of the current global COVID-19 pandemic has increased the opportunity for auto-injectors, allowing patients to maintain medication regimens from home amid lockdowns. The acceleration to more and better remote healthcare is likely to continue beyond the current crisis

Single-use, disposable auto-injectors have dominated the market, and although several design variants exist, the most common form is a device that allows a needle, hidden behind a moveable needle shield, to be manually inserted into the skin. The movement of the shield triggers a spring-driven plunger to automatically empty the pre-filled syringe. At the end of injection, the patient lifts the device, withdrawing the needle, and allowing the shield to move back and lock in place over the needle, ensuring safety after use and in disposal. Such devices can provide good safety, as well as audible and visual feedback before, during, and after injection. In most situations, this design approach has appeared to offer the best trade-off between functionality, usability, and cost. Other spring-based disposable auto-injector designs exist that offer other features, such as better control of syringe engagement and drive mechanism, and automatic needle insertion and retraction, but these have tended only to be used in more niche applications or were early market entrants developed before the simpler, dominant design described above emerged. Although reusable mechanical and electronic auto-injectors exist, their uptake has been limited due to issues around ease of use, cost, and convenience.

In summary, although the current focus on simple, disposable mechanical auto-injectors has opened the self-injection market for biologics, there seems limited scope for further improvement of the technology. Current devices are increasingly seen as a basic requirement for

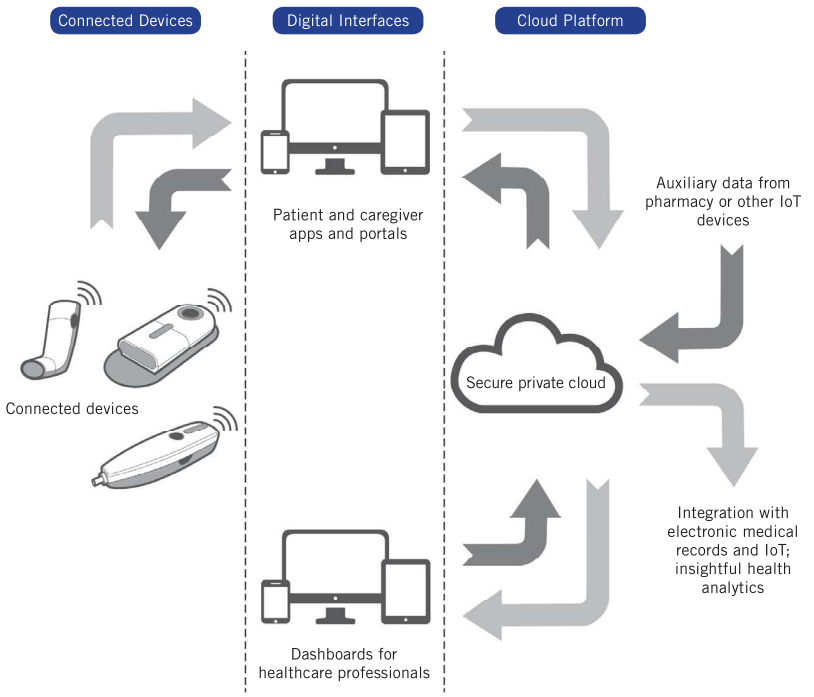

Figure 1: A connected health system consisting of connected devices, digital interfaces (apps and dashboards), and a cloud-based data system

market entry, rather than a means for differentiation. To make matters worse for innovator pharma companies, the maturity of current auto-injector technology means that it is becoming increasingly hard to use it as a means of lifecycle management.

The Rise of Biosimilars

Many biologic drugs that have transformed treatment of chronic diseases are subject to patient expiration, opening the market to the introduction of biosimilars, which is becoming an increasing area of activity within the pharma industry, with 59 biosimilars in the EU and 28 approved in the US (1). The biosimilar industry market can be segmented into autoimmune, multiple sclerosis, diabetes, and other therapies (2). Autoimmune and rheumatoid arthritis conditions accounted for the largest share of the market in 2020, and growth is expected in this segment due to increased prevalence of these chronic conditions in recent years, with the diabetes segment representing the second-largest disease population. According to Centers for Disease Control and Prevention data, within the US, approximately 26.5% (67.7 million people) of the total adult population are affected by severe joint pain due to arthritis (3).

Historically, developers of biosimilar drugs tended to replicate the delivery system used by the innovator product, or may even have considered a simpler presentation, in order to keep product cost down, in a market where price or low cost of manufacture have been sources of competitive advantage. However, biosimilars are now being launched in the same disposable devices used by innovator products, and there are increasing examples where the follower biosimilar products are utilising other innovations, such as switching from intravenous to subcutaneous delivery. For example, Celltrion Healthcare has developed and gained approval in Europe for Remsima®, a subcutaneous version of infliximab, a drug originally marketed under the brand name

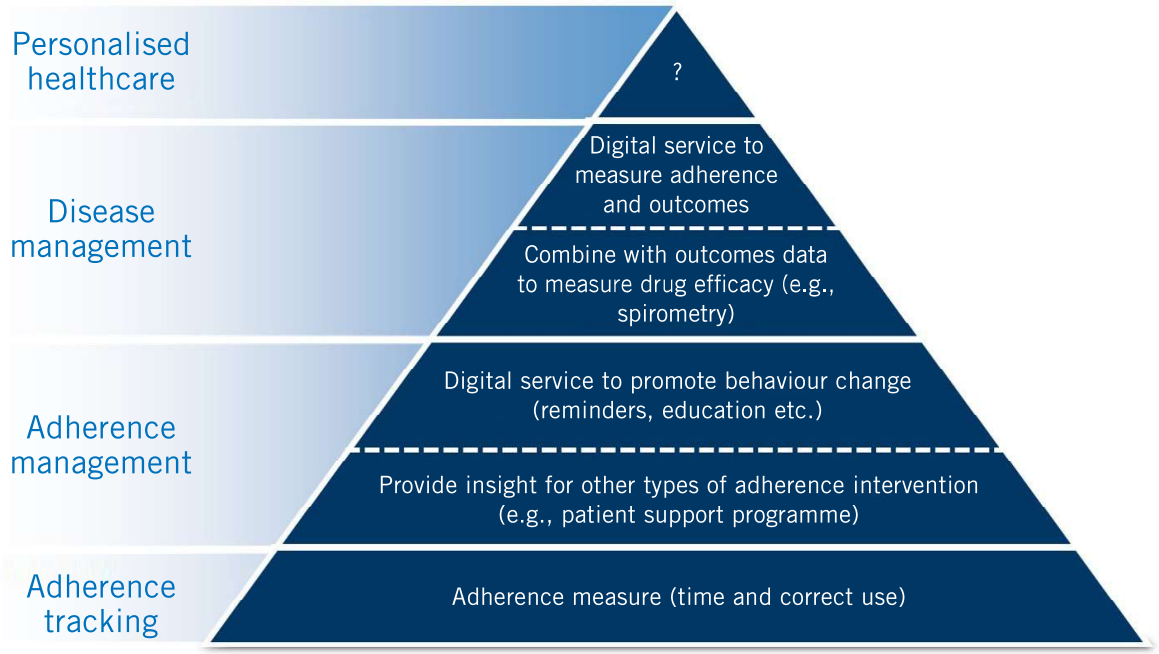

Figure 2: A hierarchy of healthcare opportunities built upon gathering 'digital' medication events

Remicade and only available as an IV infusion. Research in the UK suggests a saving of around £40 million per annum in reduced administration costs for Remsima compared to an infliximab IV infusion (4). Choice of device provides another opportunity for differentiation. For example, a survey conducted by Tischer and Mehl showed patient and nurse preference for one auto-injector over two other devices in the delivery of innovator and biosimilar drugs for the treatment of rheumatoid arthritis (5). However, as stated, the similarity of mechanical auto-injectors limits the ability for such preference to make a significant impact on market share. In the future, developers of biosimilars are likely to seek similar innovations around drug delivery device and formulation technologies, as have been used in the past for the lifecycle management of innovator biologics. As seen in Europe, multiple biosimilar products are often approved and enter the market at a similar time. Differentiation to increase market share for a biosimilar, therefore, becomes important, and device selection can create an opportunity to do this.

The Future of Auto-Injectors

Luckily, for companies seeking innovation around the use of auto-injectors, there are several emerging needs to consider, and novel technologies that can address them. In particular, emerging requirements range from increased sustainability to better patient support and feedback during device use. Additionally, the use of connectivity is beneficial in gathering use data in real time, and providing companion digital services. Moreover, there is rising demand to minimise the time and risk in modifying or configuring the technology for pharma companies looking to leverage device technologies across biologic drug portfolios containing multiple drug products, with varying viscosities, dose volumes, and injection frequencies (6). New auto-injector design can address these needs by introducing a reusable electronic drive unit and disposable cassette that contains the pre-filled syringe and provides needle safety, while optimising the use of new innovator drugs, the lifecycle management of existing drugs, as well as the introduction of new biosimilar versions of innovator drugs. Increased focus on connectivity is critical, as it enables the application of digital services to digitise medication data to facilitate better patient support around medication adherence.

Connected Health Applications for Auto-Injectors

WHO estimates that patients with chronic conditions have only a 50% adherence rate to medication regimens. Patient outcomes are negatively impacted by non-adherence, which also leads to significant, but avoidable, increases to the cost of medical care. Estimates of avoidable healthcare costs range up to $290 billion in the US and €125 billion in Europe (7). Pharma companies lose an estimated 36% in potential sales per drug on average (8). This adds up to approximately $188 billion in annual losses for the US pharma industry alone (9).

Patients do not take their medication for a variety of reasons. These include the intermittence of symptoms, perceptions about pharma efficacy, concerns about

real and perceived side effects, mixed messages or lack of regular guidance about therapies from different clinicians, high out-of-pocket costs, or simply forgetting to take the medication. Within the injectables market, when patients experience even one unsuccessful injection, or doubt whether it was administered correctly, the patient may develop concerns about future injections, which may have significant and detrimental effect on future medication adherence. Because of this, auto-injectors are strongly preferred to syringes, as they are less prone to use errors, such as incorrect dosing, misuse that can lead to injury, risk of needle stick injuries to the patient, and others (10). Although mechanical auto-injectors have addressed many of these use errors, they are still susceptible to errors such as lifting the device before delivery is complete or failure to check the expiry date of the drug in the device. 'Smart' electronic devices can provide better user guidance. For example, there is an audible progress tone throughout the injection process, including during any hold time required once the plunger has stopped to ensure the drug has been delivered. They can also detect if an expired drug is about to be used, or if the device is lifted too soon and provide feedback or a warning to the patient.

Beyond use errors, medication non-adherence is also a behavioural challenge that needs to be addressed using techniques that target factors that are causing non-adherent behaviour. As discussed in a previous article, digital services can provide a cost-effective means of supporting medication adherence, allowing information to be gathered using smartphones and apps, shared between patient, healthcare professionals, and caregivers, and digital interventions, such as reminders, diaries, and patient education to be implemented in a personalised manner (11). Furthermore, the addition of connectivity to a drug delivery device, such as an auto-injector, can enable reliable and timely monitoring of medication use. **Figure 1** (see page 27) illustrates how smart connected devices can interact with digital interfaces and secure cloud data systems to medication data in real time to healthcare provider dashboards, allowing physicians to monitor medication adherence and provide patient feedback and education.

By integrating connectivity into auto-injectors, it is possible to create a hierarchy of healthcare opportunities, as described in **Figure 2**. At the lowest level, devices can provide an accurate timestamp for when medication was taken, which, in itself, allows improved understanding of non-adherence based on quantitative data, including reliance on prescription fills as a means of estimating medication use. However, the situation for a particular patient can be improved only when this information is part of a feedback loop. One route to achieving this is to share the information with a healthcare professional who can identify which patients are struggling with adherence, prioritise those most in need for timely follow up, and provide support. Patient support programmes (PSPs) seek to improve patient engagement and adherence through interventions, such as training or education, and are already common in the pharma industry.

Digital technologies are starting to be used to improve the efficacy of these programmes. Usually, a PSP aims to increase adherence, and, as a result, medication sales. However, this business case limits the application of digital technologies to situations where a pharma company can earn an investment return through increased drug sales. Wider use in healthcare is limited to the ability of a healthcare provider, who is under tight time pressure to monitor patient data. Rather than relying on schedule-based support or patients initiating contact, connected health systems can ensure both more efficient use of expensive healthcare resources and a better patient service as they can target patients with the highest need, in a timely and proactive way.

Moving up the hierarchy, another possibility is to create a feedback loop in which digital services are used to change patients' behaviour to support adherence. This could be achieved via smartphone apps that provide reminders, medication diaries that allow for monitoring adherence, as well as educational support, such as device training and information to encourage medication use. All these activities focus essentially on medication management. A higher level in the hierarchy is the use of digital services to monitor symptoms and clinical outcomes, while providing lifestyle interventions that complement medication use. For

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example, collected usage data can be combined with other data to indicate patient risk of asthma attacks. Alerting the patient may nudge behaviour towards improving direct medication usage or seeking medical advice before an attack occurs. Digital services could also target behaviours that support better outcomes (e.g., exercise, diet). These types of interventions go beyond medication management to focus on disease management. Finally, at the top of the hierarchy is the opportunity to provide more personalised healthcare in which medication use and disease management are tailored to a patient's specific needs.

Connectivity can be integrated into existing disposable mechanical devices by adding electronic modules that incorporate sensors to detect device use. Although this approach has the benefit of not changing the user interaction, disposal of electronics after a single use has an adverse environmental sustainability impact. Consequently, add-on connectivity has been developed for disposable auto-injectors, pen injectors, and inhalers, but these have the disadvantage of requiring the user to transfer the add-on module from one disposable drug delivery device to another. They may forget to transfer and feel that the effort involved is not worth it. From an engineering standpoint, ensuring an add-on module can accurately detect that the host's disposable drug delivery device has been used is more challenging, and may result in unreliable monitoring of medication adherence. Reusable drug delivery devices offer the best of both worlds – the usability of an integrated connectivity solution, combined with the sustainability of a reusable system, as the environmental impact is shared across many doses.

Conclusions

Although existing disposable mechanical auto-injectors have facilitated a rapid growth in the self-injection market both for biologics and biosimilars, a new approach is required to address emerging needs around sustainability, flexibility for use with multiple drugs, improved patient feedback, and the introduction of companion digital services that can track and support medication use and adherence. Reusable electronic auto-injectors can address these needs in a cost-effective way, and without compromising the benefits offered by current disposable auto-injectors. As a result, this innovative approach is poised to increase market share, while paving the way to more effective use of digital services to improve patient support and medication adherence. The time is right for this innovative technology to drive the delivery of both innovator biologics and biosimilars entering the market.

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Iain Simpson is a Director of Front-End Innovation at **Phillips-Medisize**, a Molex company. He is part of a global team developing industry-leading solutions and platforms for drug delivery, digital medicine, and connected health.

He has more than 30 years' experience in multi-disciplinary technology and product development. He has a degree and PhD in Physics from University College London, UK, and an MBA in Technology Management from the Open University. He has published and presented at conferences on drug delivery, digital biomarkers, healthcare technology, and technology licensing. He is an associate lecturer at the University of Cambridge, UK, in Bioscience Enterprise.