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ONdrugDelivery Issue N° 149, June 19th, 2023

CONNECTING DRUG DELIVERY

This edition is one in the ONdrugDelivery series of publications. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

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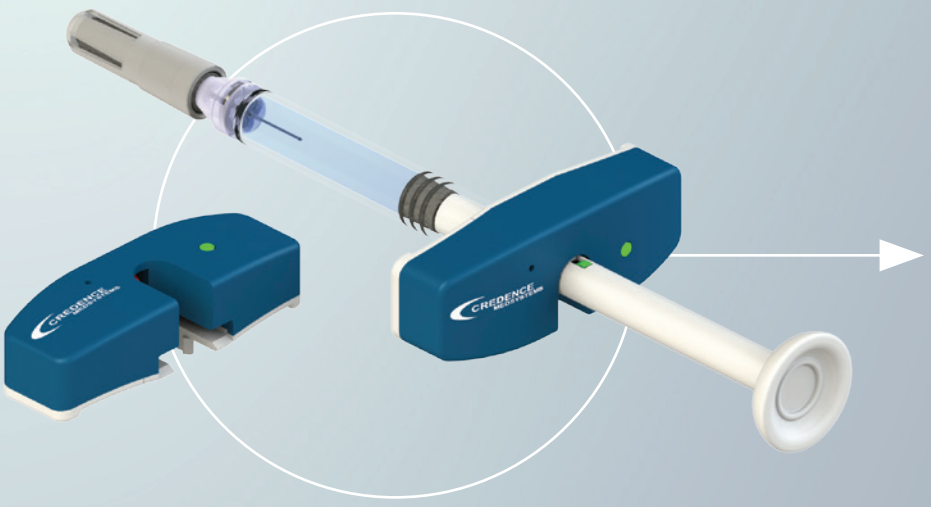

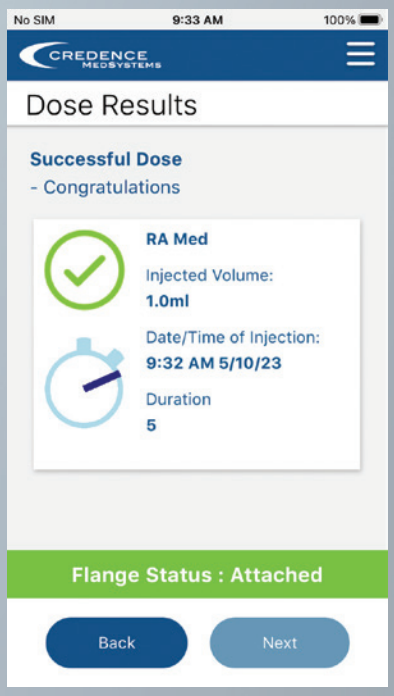

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CONNECTING PHARMA: INSIGHTS FROM AUTOMOTIVE INDUSTRY EXPERIENCE

– AN INTERVIEW WITH JIM McGOUGH, EDGEONE MEDICAL / EDGEONE VENTURE PARTNERS

In this exclusive interview, Jim McGough talks with ONdrugDelivery's Guy Furness about the current state and future of connectivity in drug delivery and pharma more broadly. In an enlightening discussion, Mr McGough shares insights from his time pioneering connectivity in the automotive industry at Volkswagen Group and how those lessons might apply to the pharmaceutical industry, as well as considering what might be holding pharma back from going full steam ahead on connectivity and how that might change over the next decade.

Jim McGough is a Co-Founder and a Board Member at EdgeOne Medical and a Managing Partner of EdgeOne Venture Partners. He was previously an investor and board member at several Big Data and AI ventures, as well as an impact investor, from 2007 to 2012. Prior to that, he held various executive and intrapreneurial leadership roles in marketing and digital at Motorola (2004–2007) where he was head of Global Digital, Audi of America (1998-2004) and Citigroup (1995–1998).

Mr McGough, as evidenced by his tech-forward corporate employers, likes to be on the bleeding edge of technological innovation – as Head of Marketing & eBusiness at Audi he championed and led the first integration of a smartphone with an automobile, the Palm Treo 650 with the Audi A6, via Bluetooth such that a call could seamlessly transfer from a device to the vehicle. Mr McGough studied International Business at the Thunderbird Global School of Management at Arizona State University (US) where he earned a master's degree in Management of Global Business, and has a bachelor's degree in History from the University of California at Berkeley (US).

Q What do you see as the current status of connectivity in drug delivery systems, and of digitisation in the wider pharma industry?

A When it comes to adopting and leveraging connectivity, pharma is in the second or third inning, to use a baseball analogy. We've moved on from the start, but we've still got a long way to go. For example, some in the industry have really invested in getting into outcomes-based health, most commonly in areas such as diabetes care and some neurodegenerative disorders where connectivity and data can be a critical differentiator in a highly competitive market. On the other hand, some areas are much more sceptical of connectivity, or at least slower on the uptake.

What's clear is that the situation is complex – it's a multifaceted business with a wide variety of stakeholders. A lot of people go into pharma early in their careers and spend upwards of 30 to 40 years here; traditionally, there hasn't been all that much migration between pharma and other industries. This means that, sometimes, there's a lack of an external perspective. On the other hand, those who do transfer in after they become experts in other fields, such as systems engineers from the automotive industry, are often not in a position at that stage in their careers to embrace and understand all the different stakeholders that pharma has to think about when they're developing what I call drug device and data therapy. There isn't really any other industry that faces this particular challenge.

> "Apple was trying to get Audi to integrate the iPod, offering us co-promotion and a strong marketing push."

The other issue that causes complexity for pharma when trying to make progress with connectivity is the heterogeneity of the different therapeutic categories – there are so many different unique categories of therapies, all of which are constantly changing, that it's difficult for any one person to have a strong grasp on what's going on in all of them at any one time. Because of this, it's hard for a big platform to get a foothold and grow to a scale where it can dominate the industry.

Taking these factors into account, it can take two or three times as long for pharma to adopt new technologies, such as connectivity, as it does for other industries. The people pushing for outcomes-based health have so many stakeholders – including pharma's infamously stringent and risk-averse regulatory bodies – and different therapeutic areas needing to be aligned that it's going to take a long time to get where they want to go. Unfortunately, there's not really a way around that; we're not going to see a sudden acceleration, except in specific cases where perhaps an outsider to the industry reaches escape velocity in terms of market cap.

The most recent example of this is Livongo (CA, US), which was an upstart from outside the industry. Their key innovation was in their business model, and in successfully making the case to self-paid insurers in the US that available diabetes management options weren't quite meeting their needs. Livongo really focused

on those companies and, in doing so, they achieved significant traction and growth, which gave them a fairly large market cap. Their connected device for diabetes management wasn't necessarily ten times better than anything else on the market, but it was good enough. Ultimately, they were acquired by Teladoc (NY, US). That's how you attract pharma's attention. There could be a company on the horizon with just the right combination of technology, usability and business model to cause a real stir that leaves pharma alert, so to speak.

That is not to say pharma itself is doing nothing in digital. To the contrary, for a while now, several big pharma companies have been making investments into connectivity for the long term, and we're starting to see some of the fruits of this. Three years ago, it was hard for pharma to acquire the talent, whereas people from the tech industry with the expertise pharma needs are now considering pharma as a serious option. However, as I mentioned before, the issue these folks have is that, while they're world class in what they do, it's going to take them years to figure out the ins and outs of all the stakeholders and sectors that are key to pharma development.

To summarise, it's a long game and most companies are playing it that way. Some companies are really investing in accelerating connectivity and bringing it about now, but they're up against the barrier that, at present, it can't be more than an optional feature. It's seen as too high-risk to commercialise something that's all-in on connectivity, so franchise leaders won't go there. Unsurprisingly, pharma is taking it slow and steady.

Q Although there's not a huge amount of migration into pharma from other industries, you are one of those who came in later in their careers, specifically from the automotive industry. Can you tell us your story in terms of career history, your role at Volkswagen Group and what you achieved there in terms of connectivity in automobiles?

A I had the great privilege of working for Volkswagen Group from 1998 to 2004. With respect to digitalisation, that was the first wave – the dotcom era. At the time, automotive original equipment manufacturers (OEMs) were frightened about being disintermediated by internet-based services, such as Autobytel and CarsDirect.com, which had started to emerge and garner fairly significant valuations. Volkswagen Group, seeing this starting in the US, felt that they needed to keep on top of what was going on there as there was a good chance it would happen in Europe as well.

> "People from the tech industry with the expertise pharma needs are now considering pharma as a serious option."

As for where I fit in, I was the one of the young Internet kids – I was previously at Citibank – leading their internet banking. Volkswagen Group saw me as somebody from outside of the industry who could help them get set up for the Internet age. That's what you see pharma doing nowadays; they go to industries that are further advanced and look to pull in talent from there. Initially, I was more on the marketing and commercial side, but after a year or so I moved to look at the overall system, seeing where we could create competitive advantage by leveraging data and the Internet.

About five or so years into this, we realised that mobile devices were going to be critical in terms of being the pathway to connecting to other services. At this point, I had the opportunity to evaluate a couple of options. One was the Palm Treo 650, which, back in 2003, was probably the first proto-smartphone that had 'over-the-air' software updates. For context, we're talking about an era when uploads and downloads were only in the kilobytes, but the promise of it was huge and we knew that our users were some of the most Internet-savvy connected people out there. So we made a proactive strategic move to be the first to integrate a mobile phone such that you could seamlessly get into your car, turn it on and your calls would natively come through the car's speakers.

At the same time, Apple was trying to get Audi to integrate the iPod, offering us co-promotion and a strong marketing push if we went with them. However, they had already done a big marketing push with BMW the previous year, who were obviously our main rival. So, we felt that Palm was the better option at the time – they were a publicly traded company and we thought their product would resonate more with our customer base. We initially got some good publicity with the Palm programme but within two or three years they were almost delisted from Nasdaq. They just didn't make the right calls. With hindsight, we should have swallowed our pride a bit and gone with Apple. Looking to the future, there are certainly lessons to be learned from these experiences that can be applied to pharma.

Q There are a range of attitudes towards connectivity in the pharma industry, what's your experience with how different players in the industry are reacting to connectivity?

A There's absolutely a range of opinion. On the one hand, you have folks who are really sold on the potential and are convinced that it's going to be a huge part of the industry, even universal, within years. However, I think that's an overly-optimistic outlook, especially since the people really evangelising for connectivity don't tend to be the ones making the big decisions – the C-level executives. In pharma, at the C-level, there tends to be a lot of traditional 'if it ain't broke don't fix it' thinking, the playbook doesn't change from one generation to the next without serious effort.

One of the big factors fuelling scepticism of connectivity is that there's no real incentive to take risk, and fully embracing connectivity right now would be a big risk. No one wants to be a casualty of moving too fast or making overly bold claims, so they take it slow and steady – pharma very rarely moves faster than you think it will. So, even if some top executives would like to really push connectivity, they often just keep it to themselves and stick to the tried-and-tested playbook instead.

> "It can take two or three times as long for pharma to adopt new technologies, such as connectivity, as it does for other industries."

Personally, I think the right attitude is somewhere between these two extremes. There's benefit in the industry pushing harder than it currently is, but pharma isn't a 'move fast and break things' sort of industry, so rushing headlong into it is asking for trouble. For now, everyone seems to be working on their own connectivity projects internally, with a lot of them choosing to focus on applications in clinical trials for the time being. For example, Roche had a really exciting development when they established a 95th percentile stride velocity with the right authorities in Europe as an alternative endpoint for Duchenne muscular dystrophy. Because of that, they can power their studies with around only a tenth of the number of participants usually required. Those are the kinds of folks who are on the vanguard for connectivity – clinical trials applications are getting a lot of attention internally from the industry, and there is a lot of activity here.

Another group that are resistant to embracing connectivity is hospitals, particularly in the US. I recently attended the JP Morgan Conference and spoke with some friends who are CEOs of hospital systems, and they told me that they've been losing money. In fact, they feel that their whole business model is under attack from the push towards a hospital-at-home model of care, which connectivity is a big part of. Also, hospital systems are struggling with cybersecurity issues, both from the perspective of having to be cybersecure to prevent breaches, such as ransomware attacks, and from the investment that's required to put that security in place. This is a major new expense that's directly related to connectivity.

"Hospital systems are struggling with cybersecurity issues, both from the perspective of having to be cybersecure to prevent breaches, such as ransomware attacks, and from the investment that's required to put that security in place."

In response to this, medtech needs to de-risk their devices and systems so that hospitals feel like they're not going increase their cybersecurity risk. Faced with this cybersecurity concern, a number of big decision-makers in pharma have a reaction of "We don't really understand this all that well, so unless we absolutely need to engage with it, let's just avoid the problem". I think this is actually one of the factors that has really slowed the development and uptake of connected drug delivery – there's a lot of trepidation and concern there.

Yet another factor fuelling scepticism at the upper levels is total cost of ownership of connected devices. Some pharma executives look at connectivity and think that, once they consider lifecycle management, including software upgrades, security patches and so forth, it's adding an unnecessary extra layer of expense. Therefore, many of them would prefer to keep things simple and leave the question of connectivity to someone else.

So, connectivity has its supporters and it is happening, but activity is focused in the digital medicines and clinical trials areas for now. But for commercialised drug delivery products on the market? There are only a few successful examples so far. Diabetes management is one area where connectivity has taken off and there's an expectation for digital features – you need to be taking steps towards connectivity there if you want to remain competitive. As such, diabetes is the most advanced sector of pharma in terms of connected drug delivery.

Q It's often said that, in pharma, everybody wants to be second (and nobody wants to be first). Would you say that the industry is waiting for one big success to open the floodgates or will the progress of connectivity be more incremental?

A What is going to be needed is a combination of both technical innovation and business model innovation. Right now, pharma is paying attention to outsiders looking to break into the sector, wondering if there's a company out there with a revolutionary idea that's going to turn everything on its head. On the other hand, a big push for change might also come from inside the industry if one of the smaller players in a therapeutic category, most likely a mid-size pharma company in combination with a willing group of payers, feels like they've got no other option to improve their market share. However, these players are still pharma industry insiders, so there's a baseline level of risk aversion there. Either way, I don't think that this sort of change is going to come from a number one or number two player.

"Another thing to consider is the slow, almost inevitable, encroachment of Apple into the healthcare sector."

Another thing to consider is the slow, almost inevitable, encroachment of Apple into the healthcare sector. They're very much bringing in an outside perspective, but they're not interested in taking big, brazen risks; they know that up to a third, or even half, of their value ten years from now could very well come implicitly or explicitly from products relating to healthcare due to factors such as the ageing population. They don't want to jeopardise their reputation in the sector, so they're not going to move too quickly and take risks that could violate the implicit trust that they've built up from offering a very private closed system. However, once they start getting more data on digital biomarkers and behavioural health in combination with big pharma, then things are probably going to start to move faster on that front.

There might be some reticence from big pharma to work with Apple on this, but I think that could be a mistake. To take an example from the automotive industry, in the early days of satellite navigation one of the big players was Garmin, who decided to develop a closed system – they had their own devices, their own software and no interoperability with other devices from the likes of Apple or Google. They were doing some pretty interesting things, but this lack of interoperability led them to be siloed off in their own niche as far as market share goes. Don't get me wrong, Garmin is still around and is doing reasonably well, but they're not huge like some of the other players. I think there will be companies in pharma that go that way, but the ones that take a more open approach will be the big winners here.

Q To what extent do you think brining in top talent, expertise and lessons learned from other industries is going to be key in pharma and drug delivery's progress towards widespread functional connectivity?

A I've actually done a few talks over the last few years on this topic. A few years ago at PODD (Boston) I essentially said that talent is the real challenge for pharma when it comes to connectivity. In hindsight, I may have been a little harsh, but I said that the stereotype of the talent pharma was pulling in was, rather than true top talent, simply capable people who were seeking a safe role – pharma wasn't about to suddenly go out of business in a year or two, whereas that's not uncommon for companies in the tech sector.

Because of this, you had a couple of types of situation when it came to pharma's connectivity projects. One that was common in big pharma was that they would someone who had come up the management development track entirely within the industry and was going to stick around for a long time, and they'd assign them to a post in digital. This manager would learn some of the ropes and then move on up the career ladder or get poached for their insider knowledge by an external venture capital-backed company looking to break into pharma. That's largely what's been happening over the past five years or so.

Another situation was that, if a digital project got underway, it would start pulling in people from other sectors and, within a year, there'd start to be a cultural of misalignment. What would happen is the digital talent would look at the situation and see pharma treating their project as the lowest priority in the whole corporation, way down below what they saw as their actual business. So the digital talent would only remain for a time, before bouncing back out to an industry where they felt more valued.

That was a real issue – it's been hard for a pharma to retain the real top-flight talent. Those who it did retain weren't at all bad at what they do, quite the contrary, but they were not really those movers and shakers capable of shifting the paradigm.

However, things are changing. Over the last couple of years, other industries that were hyper-competitive for recruiting that top-flight talent have been offering fewer and fewer opportunities, and pharma has become more eager to, so pharma now has much more of a chance to pull these people in. Some of the big players like Roche, Genentech and AstraZeneca have really been making a push to attract and retain more of these very high-calibre people. It's expensive, but companies like these can see the how digital medicine and connectivity will grow in importance substantially in future, and their profitability and their core franchises allow them to make that push.

> "Big pharma companies must support their digital departments and really make them feel like a valued part of their businesses, rather than having a culture where digital is treated as optional, which still seems to be pervasive through some of the large companies."

It's worth noting that even within pharma there's competition for digital talent. One of the really interesting things going on inside pharma right now is the development of computational drug discovery. There's a lot of buzz about how generative AI might be applied in that area, and it's taking up a lot of focus internally. Unfortunately, this might come at the expense of connected drug delivery for now.

There's ample opportunity for digital talent in pharma, and it's increasing, but it's a very fragmented landscape at the moment – there's not really a cohesive community around connectivity just yet. Right now, pharma is leaning heavily on their drug delivery platform partners and other digital partners, which is where my company, EdgeOne Medical, is. We act as a central point that helps pharma compliantly develop these multi-component systems. Increasingly, pharma companies have their own people, but they need external expertise from trusted long-term partners like EdgeOne Medical to help them navigate the digital ecosystem, including all the additional regulation connectivity entails and the wide variety of solutions and technologies on offer.

I'm bullish that digital talent is increasingly going to come into pharma, but you have to be aware that the very best talent is going to be hard to hang on to. Big pharma companies must support their digital departments and really make them feel like a valued part of their businesses, rather than having a culture where digital is treated as optional, which still seems to be pervasive through some of the large companies.

Q How else do you think the pharma industry will need to adapt to bring about the significant changes embracing connectivity will require?

A Pharma has the lobbying power and clout to work with payers to make big changes but, generally speaking, pharma isn't all that interested in rushing towards any big change because the current system has been pretty successful. However, things do change. The world is changing. There are some legislative headwinds with the Inflation Reduction Act in the US, and some patents could be shortened. This means that we could see a permanent diminishing of some of the profit profile for traditional drug programmes. Increasingly, pharma companies are starting to understand that there is a real need to think differently.

There's a potential lesson from automotive here where, around 15 to 20 years ago, Volkswagen Group pioneered a shared playbook with associated brands to try to close the gap with Toyota. Volkswagen Group was able to close in on being the number one global manufacturer by units sold in large part due to four brands, Volkswagen, Audi, SEAT and Skoda, having a common shared architecture of certain components and so forth. So, one way I can see pharma changing

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"There could be a pharma company that develops common services or common architecture with its peers, which closes the gap on some of the big tech blockbusters."

to adapt to digital is that there could be a pharma company that develops common services or common architecture with its peers, which closes the gap on some of the big tech blockbusters.

This Volkswagen Group approach could allow a group of companies, possibly across different therapeutic areas, to share some common operations and reduce their individual operating costs. This is especially relevant for the lifecycle management and software side of digital development, which can be very difficult for traditional business models to pivot to. There may be some people who say that the various therapeutic areas are all very different, but I think there will still be common components that could benefit from this model, such as patient pathways, wet biomarkers and digital biomarkers, for example. It's a potential area of development I'm excited to keep my eye on.

Another important point I'd like to make here is about diagnostics. I've been hearing that companies that have developed capabilities in, or kept a hand in, diagnostics over the past ten years are going to have a noticeable advantage over other pharma companies both generally and, specifically, in adapting to digital. It's a matter of translation – how the different groups understand each other and work together; having internal diagnostics people who are able to effectively communicate and work with the molecule team, the drug delivery team and the therapeutic franchise, as well as the tech and digital side, is going to be a big benefit in getting digital programmes off the ground.

In an industry where outcomes-based therapeutics is rapidly coming to the fore, and precision medicine is emerging, it is self-evident when you think about it that the ability to analyse, measure and monitor patients, their disease metrics and their responses to treatments will be at the core. And that's diagnostics.

I've been an investor in some digital therapeutics and so forth, and something that really interests me is the applications around adherence and responsiveness to therapies. This is actually an area where some of the science is already proven, such as being able to use digital therapeutics to tell if a patient is a non-responder to a certain pain medication. Imagine if we were to look closely at some of the highest valued franchises in pain medication and it became clear that, for example, 20% of the prescribed users were unknowingly non-responsive. Payers are going to want to know that information. Doctors are going to want to know that information. When digital therapeutics take off in a more significant way, the data is going to start to show not only which patients adherent and compliant, but also who is getting the therapeutic benefit, which may or may not perfectly correlate.

Q **Can you offer any additional insights on why the process of developing connectivity is taking so long, and initiatives that might accelerate it?**

A We've already discussed the issues around bringing in and retaining digital talent, as well as the huge variety of stakeholders all with different opinions and priorities, and it's the latter I can elaborate on. In the US, there's something of a battle going on with everyone trying to push their own ideas, including pharma companies and academic institutions, who each have their own patents for digital and mechanical systems. These ideas don't necessarily amount to a complete solution

"Payers need to evaluate what's efficacious, what's safe and what they should add to their formularies."

on their own, but they're all jostling for a place in the overall care pathway. This is a process that takes time to play out.

There's an open question of how digital formularies can be established. Pharma has already been through an arduous struggle here with combination products, establishing pen injectors and autoinjectors in formularies alongside traditional therapeutics. And now we have a similar challenge ahead with digital formularies, which would codify how and in what circumstances digital therapeutics and digital diagnostics should be prescribed. Payers need to evaluate what's efficacious, what's safe and what they should add to their formularies. Of course, hospitals also have their own, and so they're exerting influence, and, sometimes, the big academic hospitals are also developing their own digital projects that they want to try out. It's a hypercompetitive landscape and, again, we're at the start of a process that will take time to play out. It will likely take years for a set of agreed-upon ways of prescribing these products to emerge.

As for initiatives that could accelerate the development of connected and digital therapeutics, in a few markets around the world, such as Scandinavia, Singapore and Germany, there are public health bodies conducting case studies that might conclude that digital approaches are really working – that is to say that digitisation and connectivity are lowering the cost of care and the overall public health burden – and that might push things forwards in those countries in a way that could strongly influence what happens elsewhere. It's going to be really interesting seeing how this unfolds over the next five to ten years.

Q Do you have any final thoughts that you'd like to share with our readers?

A The last point I'll make is for perhaps younger readers, or readers with digital experience outside pharma, who are considering a move into this industry.

You need to remember that most of the people at the top, the chief executives, have been in pharma for most of their careers – we're talking thirty-plus years here. All of that time, they've been working from essentially the same playbook, and it's done well for them for all that time. With that in mind, it's easy to understand why they might approach a huge shake-up like digital with hesitancy. There would have to be an immediate and very significant reason for them to take that kind of risk at that point in their careers. It's the next generation of top decision makers, those who are a couple of rungs down the ladder right now but will be C-Suite in five to ten years' time, who are going to be in the opposite situation, where not taking the plunge on digital will be the big risk. So I think it will be in the next five to ten years that we're really going to start to see some changes.

As I said before, the industry is highly fragmented, and with the widespread adoption of digital therapeutics there's scope for dozens of new classifications of drug delivery systems intersecting with data collection, processing and analysis, and they're going to be big markets. If you're starting out in your career, or have experience in another sector and are considering moving into digital pharma, the heterogenous nature of the industry means there's going to be a huge number of digital opportunities across a wide variety of sectors, from oncology to diabetes to mental health. You'll have unbelievable opportunities to affect global public health in the next ten years. So, I'm genuinely very excited for anyone considering getting into the industry. Whether you work at a drug delivery system provider or you're at a big pharma company or with another type of player, this is a wonderful place to be.

"The heterogenous nature of the industry means there's going to be a huge number of digital opportunities across a wide variety of sectors, from oncology to diabetes to mental health. You'll have unbelievable opportunities to affect global public health in the next ten years."

ABOUT THE COMPANY

EdgeOne Medical is a global contract device development organisation that supports the compliant device development and testing of combination products. Since 2012, EdgeOne Medical has been elevating medical device and combination product development teams including in over half of the global top 20 biopharma companies.

EdgeOne Medical has a unique combination of multi-disciplinary product development experts combined with in-house ISO 13485 certified Testing Labs. These capabilities, known as Edgineering, and EdgeOne Labs provide clients with the peace of mind that they have complemented their teams with a partner with a successful track-record of de-risking, navigating, and accelerating device development programs.

EdgeOne Venture Partners provides more than device development and testing services. A device development team sometimes needs something extra, including access to emerging complex combination product and system development knowledge based on real development programmes; access to strategically interested big pharma, emerging pharma/biotech, medtech and digital health firms for partnerships and syndicates; access to funding opportunities for emerging firms and co-investment opportunities for larger firms; and the capacity and capability offered by adding a turbocharging best-in-class device/system development testing team and priority access to EdgeOne Labs. EdgeOne believes that nobody should have to develop complex combination products/systems by themselves.

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THE IRONIES OF AUTOMATION: LESSONS FOR REMOTE PATIENT MONITORING

In this article, Dan Lock, Principal Consultant in Psychology and Human Factors at TTP, considers how to overcome potential pitfalls and make the most of remote patient monitoring for the benefit of both patient care and clinical trials.

The basic idea of remote patient monitoring (RPM) is that a subject or patient uses a digital interface at home, such as a mobile app, to collect regular data relating to their health that is then accessible to their healthcare provider. Depending on the indication, the system may be augmented with a wearable device, such as a blood pressure monitor or connected glucose monitor. Their healthcare provider can then be notified of any concerns arising from the data and can access an analysis of data trends through a digital interface in their clinic, such as web portal.

The hope is that more and better data, along with algorithm-generated analysis of that data, will produce significantly better health outcomes, enabling healthcare professionals to make better decisions about ongoing care, for example, for the treatment of conditions such as cancer or end-stage renal disease. RPM could also help patients feel more engaged with their care as the app may provide them with insights into their progress, and provide personalised advice and content tailored to their immediate needs.

In healthcare settings, clinicians could be made aware of potential problems as soon as they arise, allowing them to intervene accordingly, rather than waiting weeks between appointments to discover a concern and then relying on patients to remember the frequency and intensity of symptoms.

Intervening early could make it easier and cheaper to handle any problems. For example, a home haemodialysis patient with increasing potassium levels could be advised on dietary changes or given medication, rather than requiring an urgent – and expensive – hospital admission if it is not detected until it is too late.

Early detection may also mitigate risks with cutting-edge treatments where there are serious side effects in a small percentage of patients. Knowing that complications can be reliably detected and dealt with before they escalate would give clinicians confidence to use new therapies with a wider range of patients.

This widening of the net is also valuable when it comes to clinical trials of new drugs and treatments as the remote aspect can enable clinical trials to include more diverse patients. A more diverse set of patients will improve the quality of collected data.

Unsurprisingly, then, interest in RPM during the drug development process is increasing. It gives researchers valuable data and analysis in real time, often speeding up the process, as well as enabling a wider spread in terms of both geography and risk profile.

If the drug delivery industry is to make the most of this technology and ensure its successful adoption, it needs to ensure that clinicians and patients alike understand both

Figure 1: Can we trust "drivers" who are used to being passengers to act decisively when needed?

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its potential and its limitations. The industry also needs to avoid the twin dangers of overreliance on automation and excessive scepticism about it. The former could lead to a de-skilling of clinicians, while the latter could result in the technology merely alienating patients, as their doctors may be unable to explain the benefits.

THE PSYCHOLOGY OF AUTOMATION

Human factors researchers have long been interested in how automation affects the thinking and behaviour of the human beings tasked with overseeing it. From autopilot in planes to safety systems in nuclear power, the danger is that operators take automated systems for granted. It is not just that they start failing to pay due attention as they get used to the automation handling everything, but that over time they experience "skill fade" as their expertise wanes from lack of use.

In 1983, the University College London (UK) psychologist Lisanne Bainbridge coined the term "ironies of automation" to describe the fact that "the more advanced a control system is, so the more crucial may be the contribution of the human operator".[1] When standard operations are automated under normal conditions, humans only become involved in trickier, "edge cases". If they lack the skill to diagnose the situation and act accordingly, it can lead to disaster.

Since the advent of the digital age in the 1980s – and especially with machine learning and AI – the relevance of these ironies of automation has only grown. Self-driving cars are the most obvious example – can we trust "drivers" who are used to being passengers to act decisively when needed? (Figure 1). A potential de-skilling of clinicians accustomed to automated systems is just as concerning. And, of course, the other human factor when it comes to RPM is the patients. The industry needs not only to determine how the technology will be used but also how its implementation will impact patients' perceptions of their treatment.

UNDER-TRUST AND OVER-TRUST

There are two scenarios in which RPM could fail to meet its potential, both in healthcare and clinical trial contexts – namely, if there is under-trust in the system, or if there is over-trust.

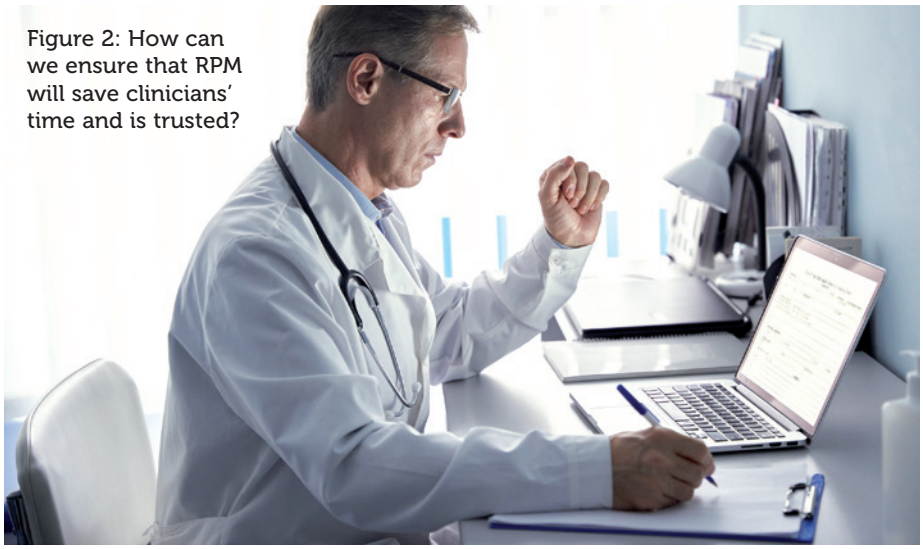

Figure 2: How can we ensure that RPM will save clinicians' time and is trusted?

Clinicians may under-trust the system precisely because they are highly skilled and accredited professionals. They may be sceptical of an automated system that can supposedly "do their job" for them, especially if the system comes to conclusions that differ from their own.

Under-trust could be a particular problem if the algorithm used by the system to interpret data is too complex for the clinician to understand, at least without specialist training. They are unlikely to trust the system's conclusions without at least a rough understanding of how it came to them. This is known as "explainability". Clinicians could put any "differences of opinion" down to the system's lack of nuance or completeness. For example, the clinician might know about some aspect of the patient's situation and assume the algorithm has failed to address it (which might or might not be correct).

Clinicians might also fear that RPM introduces unnecessary complexity to patient care, adding yet more factors that could go wrong. Relatedly, they may be reluctant to acquire the new skills needed to make the most of the system, or even to recognise a false alarm. This is particularly the case if clinicians feel that using the system involves a loss of autonomy. If, instead of entering into a dialogue with the system, everything is one-way traffic, they can understandably feel they are being de-skilled rather than empowered.

Whatever the causes of under-trust, the consequence is that the intended benefits are lost. Instead of greater effectiveness and efficiency – and a reduced workload for clinicians – there will be unnecessary duplication of work and over-complication of patient care.

The flipside of under-trust is over-trust. Potentially, clinicians could come to trust the system too quickly. Precisely because the algorithm "works" most of the time, it may be tempting to take its reliability for granted rather than checking its results. At worst, users could become as "automated" as the system itself, developing an unquestioning, habitual response to any given prompt. In a healthcare system increasingly under pressure to meet targets, there could be a temptation to let the algorithm "check" data, so clinicians do not have to.

If the system is effectively making decisions on the clinician's behalf, their situational awareness will decline, leading to a vicious circle of declining performance. Then there is the simple fact that skills fade from lack of practice. Moreover, a system that can be used by a less skilful operator is more likely to be used inappropriately. For example, not all data should be shared with patients or less qualified healthcare staff (Figure 2).

REMOTE PATIENT MONITORING 2.0

At TTP, we have conducted research to understand how the ironies of automation apply to RPM and how to mitigate their effects. Some high-level findings are shared here.

One finding was that patients want frequent reassurance that the system is producing valuable results, even if there is no cause for concern. If they get the feeling their data is just disappearing "into the ether", some will disengage. Medico-legal concerns may be a barrier to an RPM system that provides patients with reassurance that all is well in terms of their own treatment, which is likely to frustrate them. This is especially important

"There is a difficult balance between providing patients with enough information to keep them engaged and giving them a false sense of being qualified to make significant decisions about their treatment."

when it comes to clinical trials, given the costs and inconvenience should an unhappy subject withdraw from the study.

It was also found that patients do not always trust clinicians to monitor their data and act accordingly, for example, because they appreciate how over-worked some healthcare professionals are. Consequently, most patients have no qualms about calling if they see an unusual reading. Even if the RPM algorithm is working perfectly, this could cause RPM to actually increase clinicians' workload; an additional "irony of automation".

The study also showed that, for their part, clinicians tend to focus on the data points that they have been trained to interpret and understand, neglecting the system's more sophisticated, bespoke analytical insights. This is a classic example of under-trust and means clinicians may not always make the most of the system's potential. This is another facet of "explainability" – even if the system is right, if you do not understand why it is right, it is hard to trust it.

Clinicians are also wary of patients getting or inferring information directly through an app and making uninformed decisions. There is a difficult balance between providing patients with enough information to keep them engaged and giving them a false sense of being qualified to make significant decisions about their treatment. New research is needed that goes beyond "ease of use" concerns to shed light on how patients understand and relate to this technology. This would pave the way for a better informed and more nuanced application of RPM, ensuring that both clinicians and patients understand its benefits and limitations.

These findings indicate that over-trust is currently much less of a problem. However, it may be accelerated if RPM starts being administered by less qualified professionals. This has never been the intention, but it should be guarded against, as some in managerial positions may view RPM as offering an opportunity to make savings on clinical budgets by deferring responsibilities to cheaper, less-qualified personnel.

If anything, even highly qualified clinicians would benefit from a certain amount of further training in the technology and algorithms behind RPM. Precedents do exist – for example, anaesthetists today typically have advanced training in how ventilators work so they can spot functional issues quickly and act accordingly.

The goal should be a level of trust that is finely calibrated to the actual reliability of the system. One way of achieving this could be ensuring that users have accurate and up-to-date data about topics such as false alarms and false negatives so that they know what to look out for. Those developing RPM need to ensure that clinicians understand what considerations are not included in the algorithm's workings so that they can integrate their own clinical judgement into the analysis and derive a complete and holistic picture. Ideally, clinicians should learn to interrogate the system regarding its level of certainty, just as they would do with a fellow professional. Manufacturers should facilitate this by ensuring their systems are able to explain their decision-making process.

LOOKING TO THE FUTURE

All this is to say that the true benefits of RPM do not come from the technology itself but from its careful and intelligent application – with due consideration to the psychological tendencies of its users.

Those benefits are numerous, however, including reducing unnecessary appointments, reducing the likelihood of unplanned hospital admissions and facilitating better care of less mobile patients. Indeed, by reducing the salience of geographical location, RPM can also make treatments requiring closer monitoring available to a wider spread of potential patients. Moreover, because it can reduce the need for travel, as well as hospital visits and all the disposable accessories those involve, RPM could also be far more environmentally sustainable than the traditional way of working.

RPM is a very promising technology that is likely to become more widely used. However, it could easily become a victim of its own success, becoming popular with administrators but less so with clinicians, who will tend to distrust it (sometimes rightly), and with patients, who will be reluctant to agree to use RPM if they cannot see any benefits. With better implementation driven by user-centred design, testing based on human factors principles and risk planning, the ironies of automation may be mitigated, increasing the benefits of RPM for clinicians, patients and pharmaceutical companies.

ABOUT THE COMPANY

TTP is an independent technology company. Its unrivalled combination of science and engineering means that it has the know-how to help solve the toughest challenges. TTP can help clients get world-class technology to market – fast. The company's teams find better solutions faster because its consultants are uniquely empowered to collaborate with clients – and each other – in a truly agile way. This has been a cornerstone of the company's success for over 30 years, allowing TTP to develop and deliver thousands of pioneering products and services. From start-ups to blue chip organisations, what unites TTP's clients is their desire to make brilliant things happen.

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Dan Lock is a human factors specialist, psychologist and a chartered member of the Institute of Ergonomics and Human Factors (C.ErgHF). Mr Lock has 20 years' experience conducting user research at all stages of the design lifecycle from opportunity discovery, to conceptual design, formative and summative evaluations. Mr Lock's current areas of interest include how models from behavioural science can be applied to design to motivate and promote positive behaviour among product users, especially in the area of adherence to medication regimes, and how large language models like ChatGPT might impact digital healthcare.

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LESSONS FROM MARKETED MEDICAL DEVICES TO ENHANCE CONNECTED DRUG DELIVERY

In this article, Fallyn Flaherty-Earp, Global Marketing and Consumer Segment Leader at Celanese, looks at what medical device manufacturers can learn from connected devices already on the market and discusses the opportunities electronic inks can provide for the development of innovative therapies for the treatment of chronic diseases.

It is a testament to the seismic growth in interest surrounding connected drug delivery that the column inches dedicated to the topic continue to grow exponentially, too.

One particular aspect of that growth is attributable to the development of wearable devices, often referred to as on-body delivery systems (OBDSs). OBDS platforms can now deliver higher volumes of medicines that would otherwise need to be administered intravenously at a clinic under the supervision of a healthcare professional (HCP). This development follows an increasing demand for treatment away from clinical settings, enabling patients to realise greater choice and control over their disease management.

It is in this context that drug delivery partners can learn a great deal from medical device innovations, where there is already an established portfolio of customised, connected solutions available for different patient groups, across each key stage of the human lifecycle – from prenatal monitoring to elderly and palliative care.

MARKET TRENDS IN MONITORING AND PERSONALISATION

As the OBDS market is expected to grow, so too is the remote patient monitoring market, which is set to reach US$175 billion (£141 billion) by 2027, growing at a compound annual growth rate (CAGR) of 26.7%.[1] The narrative behind this trend is the same as in OBDS – HCPs and patients continue to prioritise at-home care over visits to healthcare facilities in the post-pandemic era.

> "With better quality data and insight comes greater personalisation in treatment regimens enabling individualised sensors and tools shaped to the needs of the patient."

And that is not the only comparison between trends in medical devices and drug delivery. There is growing demand for artificial intelligence (AI) to be incorporated into medical wearable devices to help with data analysis, interpretation and delivering insight that can help with diagnosis and treatment. This market is projected to expand at a CAGR of 29.8% from 2023 to 2030.[2]

With better quality data and insight comes greater personalisation in treatment regimens enabling individualised sensors and tools shaped to the needs of the patient. This personalisation includes integration with other devices, such as smartphones and smartwatches, that can provide patients with a more integrated and convenient healthcare experience.

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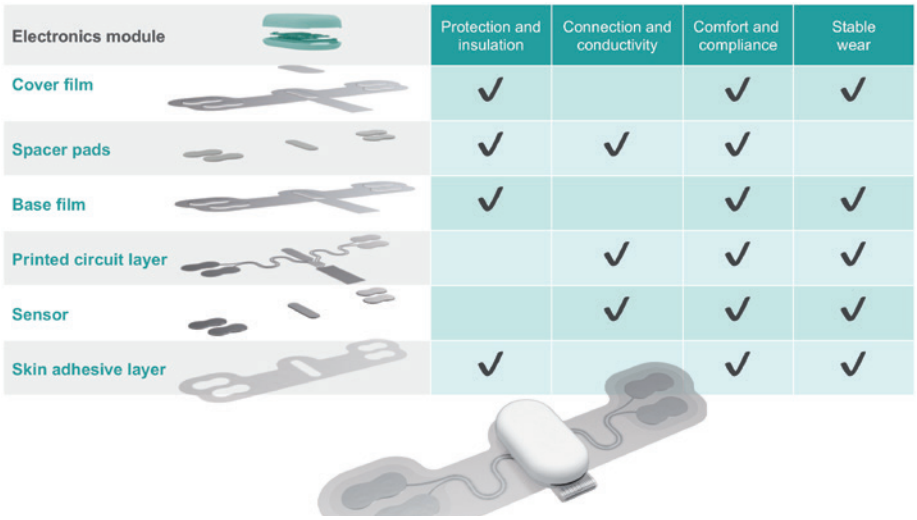

Figure 1: Anatomy of a wearable sensor – sensor technology for dry electrodes provides highly effective recording of biosignals when integrated into skin patches or textile devices.

The final trend we are witnessing is the continued development in non-invasive monitoring, such as heart rate and blood oxygen level monitoring, enabling patients to manage their own assessments and treatment more intuitively, simply and with less HCP intervention.

As everyone in the drug delivery ecosystem would recognise, improved patient outcomes, personalisation and at-home care are all key considerations for the development of next-generation devices.

OPPORTUNITIES WITH ELECTRONIC INKS FOR PRINTED SENSORS

To maximise the opportunities presented by these emerging trends, several enabling technologies are required – not least the use of electronic inks or conductive inks. These inks are used increasingly in the production of wearable medical devices due to their ability to create flexible and conformable electronic components (Figure 1).

Electronic inks, such as Micromax™ Biomedical Sensor Inks from Celanese, are used to print sensors onto wearable devices that can monitor various physiological parameters, such as heart rate, blood pressure and oxygen saturation. These sensors are typically made of conductive materials such as silver, silver/silver chloride or carbon, and are printed onto a flexible substrate, such as polymer film. The sensors can then be integrated into skin patches, garments, wristbands or other wearable devices, allowing for continuous monitoring of a patient's vital signs.

Electronic inks are often used in the production of electrodes for electroencephalography and electrocardiography monitoring. These electrodes are typically applied to the skin using a conductive gel or adhesive, which helps to ensure a stable electrical connection between the skin and the electrode. These gels and adhesives are also designed to be skin-friendly, minimising patient irritation or discomfort.

The make-up of the electronic inks is critical to the delivery of medications and accuracy in patient monitoring. Split into three main material types for medical purposes – conductive, dielectric and resistive – these inks are applied to achieve a range of functionalities.

Conductive materials are used to create conductive tracks, pathways and component terminations, including inner electrodes. Dielectric materials provide insulating (nonconductive) layers. They may be crossovers or multilayers with connections between layers. Resistive inks are partially conductive compositions that reduce electrical current. The quality of the ingredients and manufacturing of the electronic inks are crucial to how well the inks will transmit a signal. Electronic inks are typically developed for specific healthcare applications to ensure that they meet the requirements of use, including resistivity, stretchability, washability, chemical resistance, etc.

One therapeutic area where electronic inks show real potential for effective drug delivery is in the treatment of cancer. Electronic inks can be used to deliver chemotherapy drugs directly to cancer cells, minimising the damage to healthy cells through electrochemical gradients and targeted release triggered by electrical signals. Another potential application is in the treatment of neurological disorders, such as Parkinson's disease and epilepsy, where electronic inks can be used to deliver drugs to specific areas of the brain, allowing for more precise treatment of conditions.

Electronic inks are being explored as a viable combination drug delivery/diagnostic option for the treatment of chronic diseases, such as diabetes. They can be used to create printable biosensors that monitor glucose levels in real time – information that can then be used to trigger the release of insulin in response to changes in glucose levels (Figure 2). Similarly, electronic inks can be used to create printable sensors that can detect the presence of bacteria that then trigger the release of antibiotics in response to bacterial growth.

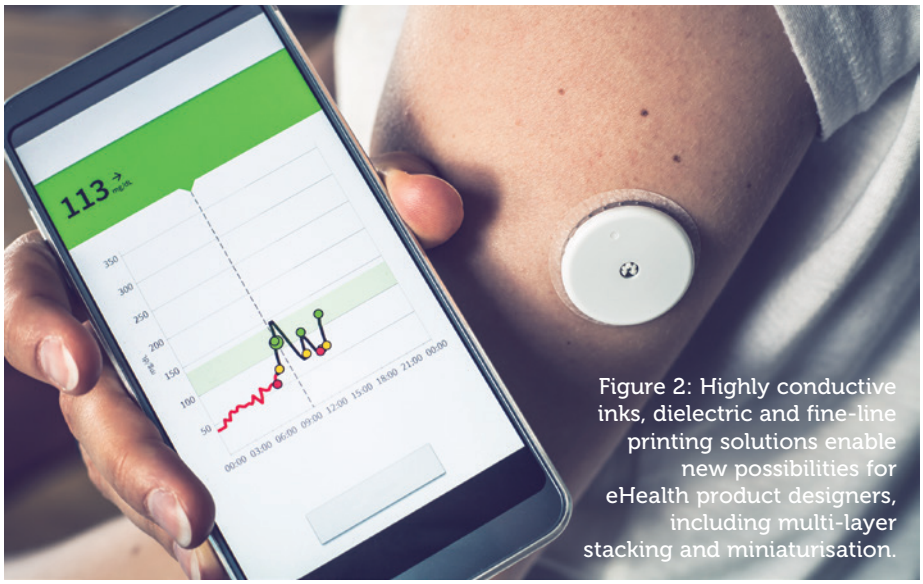

Figure 2: Highly conductive inks, dielectric and fine-line printing solutions enable new possibilities for eHealth product designers, including multi-layer stacking and miniaturisation.

WEARABILITY AND RELIABILITY: A CASE STUDY

The following case study reviews the development of an adhesive patch designed to deliver wearability and long-term comfort for patients, while reliably recording electrical signals for vital signs and physiological parameters.

The ability to effectively monitor an individual's health conditions – with electrical body signals, for example – and then deliver clinical-grade data for analysis without delay is revolutionising healthcare. To support fast market adoption of wearables at the original equipment manufacturer and patient levels, several design challenges must be overcome.

One challenge is to achieve long-term, accurate monitoring of biosignals with a device attached for a few days – or up to as many as 14 days. Currently available technology is limited by the battery lifetime, the electrode performance, and the device wearability on skin when exposed to sweat, humidity and bathing water. Also, skin contact patches potentially need to adapt to several skin types, based on age, gender and culture, and will require versatile patch adhesives.

Another significant design challenge is to improve the patient experience with a patch that is easily applied, comfortable and non-irritating, stays fixed in place for days during regular living activities and can be removed painlessly without causing trauma at the end of the procedure. The patch needs to allow typical body movements without impacting the signal quality or the reliability of the patch's adhesion to the skin. If the skin becomes irritated after a short period, this will typically disallow attaching another device to the irritated area, create patient discomfort and jeopardise patient compliance.

The smart adhesive patch concept for next-generation wearables relies on advanced materials that are being developed to provide improved electrode life, more data stability, better moisture control and increased patient comfort. Silicone elastomers, when extruded in films, offer tuneable wearability and excellent conformability, as well as stretchability, comfort and biocompatibility. Ergonomically, a smart patch should be so comfortable that the patient can forget they are wearing it in normal everyday life.

> "Ergonomically, a smart patch should be so comfortable that the patient can forget they are wearing it in normal everyday life."

Silver, silver/silver chloride and carbon-based electrically conductive inks and thermoplastic polyurethane (TPU) films also are used for signal transfer in medical device smart patches, as well as for smart, stretchable sports and fitness clothing.

The Nighthawk™ smart adhesive concept patch developed by Holst™ TNO (Eindhoven, the Netherlands) in conjunction with Celanese Intexar™ Inks and Films, and DuPont™ (DE, US) Liveo™ adhesives showcases the ability to provide a breathable, cushioning skin interface; dielectric insulation to protect signal quality; long-term wear with secure, skin-friendly, silicone-based adhesion; comfort and conformability with stretchable materials; and secure connections for biosignal reliability.

The patch maintains a minimum distance between sensing electrodes for data stability and accuracy. Also, the liner system is designed to effectively attach the patch to the body without losing control of the pliable design. The 20% stretchability of the shape is unmatched by any other design on the market, as are other patient-centric attributes of the Nighthawk™ concept patch.

CONCLUSION

There are numerous parallels to be drawn from connected, wearable medical and diagnostic devices and the current evolution of connected drug delivery devices. The demands from the entire ecosystem are consistent – to reduce HCP interventions, deliver more personalised care for patients, maximise the potential of the data from such devices and ensure greater patient adherence.

Electronic inks are critical to the performance of wearable and diagnostic devices. As a proven, robust and compliant technology, they offer drug delivery manufacturers real opportunities for the development of even more innovative systemic therapies for diseases such as cancer and neurological conditions such as Parkinson's, as well as chronic conditions such as diabetes.

The experience and expertise in wearable devices that resides in organisations such as Celanese can also enable drug delivery companies to develop more patient-friendly and comfortable wearable delivery systems that open the opportunity for further long-acting delivery applications.

ABOUT THE COMPANY

Celanese Corporation is a global chemical leader in the production of differentiated chemistry solutions and specialty materials used in most major industries and consumer applications. Its businesses use the full breadth of Celanese's global chemistry, technology and commercial expertise to create value for its customers, employees, shareholders and the corporation. As Celanese partners with its customers to solve their most critical business needs, the company strives to make a positive impact on its communities and the world through The Celanese Foundation. Based in Dallas (TX, US), Celanese employs approximately 13,000 employees worldwide and had 2022 net sales of $9.7 billion.

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EMPOWERING PATIENTS FOR SELF-CARE WITH NFC CONNECTIVITY

In this article, Sylvia Kaiser-Kershaw, Global Senior Principal Marketing Manager at NXP Semiconductors, looks at how near-field communication technology can be used to add connectivity to medical devices, empowering patients to self-administer medication.

Over the past several years, specialty pharmaceuticals and other biotech products aimed at treating the increasing occurrence of chronic diseases, such as diabetes, cardiovascular disease and chronic obstructive pulmonary disease, have dominated pharma profitability, new product filings and sales revenue.

At the same time, there has been an increased focus on self-care at home, with patients administering treatments themselves and – increasingly – receiving injectable and inhalable drugs directly, without having to visit a doctor's office or hospital.

Many of these self-administered drugs are supplied in connected drug delivery devices, which make it possible to create a valuable link between the patient and the medication, and between the healthcare provider and the patient. Digitisation can make drug delivery devices more intelligent, improve patient outcomes and offer clinicians a better remote-care relationship with patients. Smart injectors can prevent the use of expired, wrong or counterfeit drugs. Smart inhalers can send notifications to a smartphone to remind patients they have not taken their medicine for the day. Smart devices can track dosage and delivery time to ensure patients comply with their regime and even keep doctors informed. Intelligent digital solutions can thus provide a differentiation for pharma companies, improve the patient experience and therapy outcome, and assist clinicians in their daily work.

Connected drug delivery devices are available in single-use and reusable formats, and either integrate connectivity directly into the device or use connectivity as an add-on to a mechanical device. All these formats are evolving rapidly, and demand is projected to remain quite strong in the coming years. In its recent report on connected drug delivery devices, Mordor Intelligence[1] notes that the market is valued at US$659.54 million (£533.83 million) and, over the period 2023–2028 is projected to reach US$3,915.73 million, registering a compound annual growth rate of 35.13%.

ADDING CONNECTIVITY

Near-field communication (NFC) technology, a short-range wireless technology supplied by semiconductor

> "Digitisation can make drug delivery devices more intelligent, improve patient outcomes and offer clinicians a better remote-care relationship with patients."

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companies like NXP, makes it possible to deliver these kinds of services, creating secure patient experiences that are both beneficial and easy to use.

Perhaps best known as the wireless technology that makes contactless payments possible, NFC is readily available on most smartphones, and can be built into smart medical devices using a built-in NFC reader to automate processes.

NFC can be added to a medical device in a number of ways. If, for example, the device is already equipped with electronics and a power source, then an NFC reader frontend or NFC controller can be added to the design. Alternatively, if the medical device is purely mechanical, then passive NFC tags or connected NFC tags, which can harvest energy from the NFC field generated by the reader (e.g. a smartphone), can be used to add connectivity to the device without requiring other electronic components or a battery (Figure 1).

Connected devices can send data directly to a smartphone via Bluetooth, or can use one-tap NFC through patient interaction. Patients can then access a rich, interactive interface where data sets with corresponding timestamps can be stored or shared.

Figure 2: Smartphone-based patient support.

SMARTPHONE-BASED SUPPORT

The majority of patients in every age group already have an NFC-capable smartphone. Making use of this communication technology for medical devices empowers patients and lets them manage their health with a device that already feels like part of their identity (Figure 2).

With a simple tap of an NFC-enabled phone, patients have easy access to product information, can receive step-by-step application guidance (e.g. via a video), can check product authenticity or get a link into a helpful patient app to do things such as keeping a digital diary of their regime. Therapy adherence can be tracked more reliably with automated timestamps, and doses can be archived in a cloud-hosted database that records which batch of medication was administered when and to whom. This also brings obvious potential benefits for statistical analysis, since side-effect information can be captured directly in the patient app.

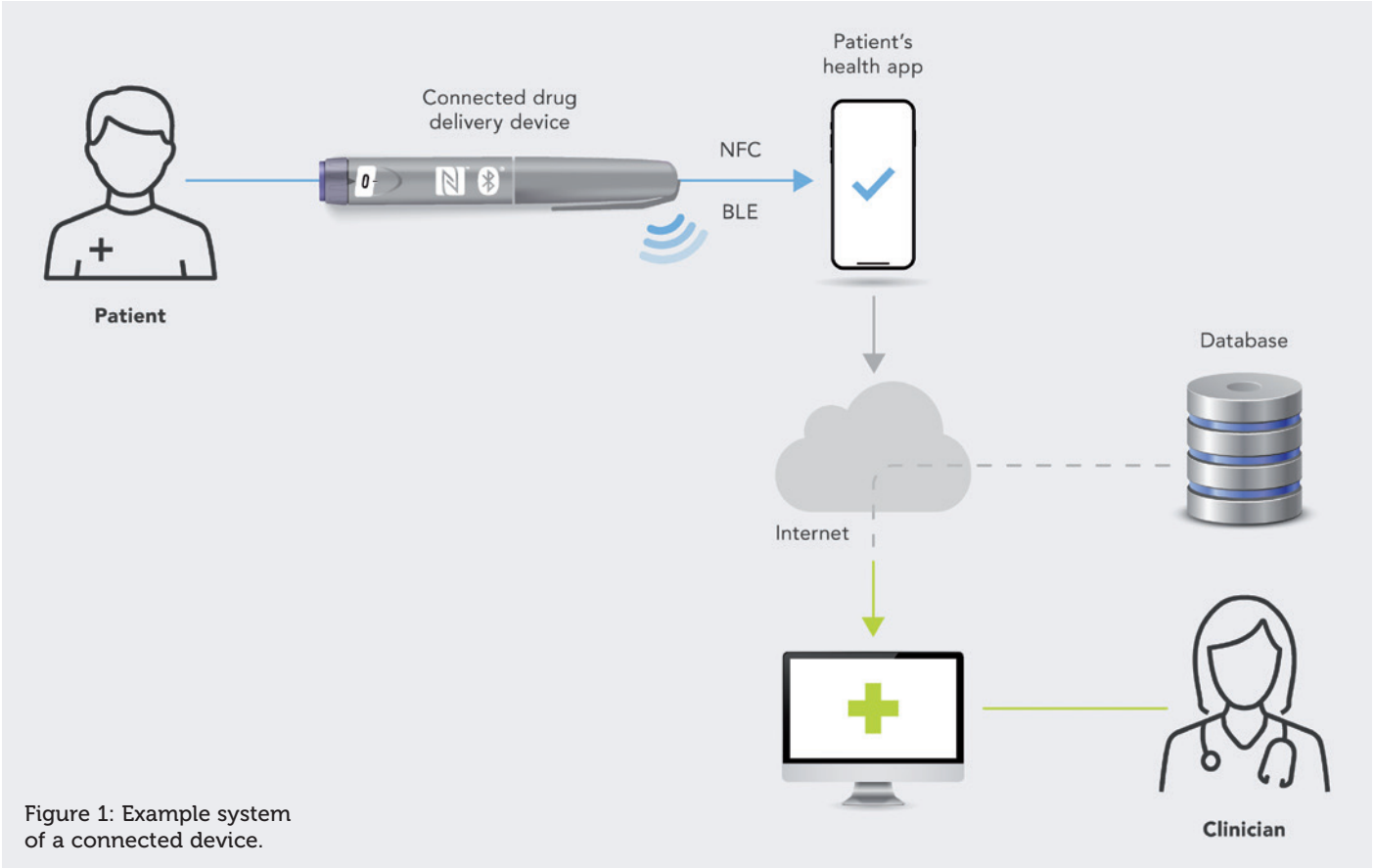

Figure 1: Example system of a connected device.

"Sensor-based feedback can confirm that medications are handled and dosed correctly."

Depending on the use case, patients may have to install an app on their smartphone before initiating an interaction, or they may be able to use existing internet connectivity – by tapping their smartphone to the device – to launch a website that then provides digital guidance. Some data processing can take place on a mobile app, to display information in real time to the patient, or data can be sent to the cloud for more complex analysis. Patients who also use a smartwatch for heart rate or sleep monitoring may even be able to directly measure and see the effect of the drug regime on their health, reinforcing their perceived empowerment and motivating them to continue treatment.

SMART-DEVICE/CONSUMABLE INTEGRATION

NFC can be used to automate communication between a reusable drug delivery device and a disposable drug container, such as a cartridge or prefilled syringe. In this case, the delivery device is equipped with an NFC reader, which communicates directly with a passive NFC tag in or on the container. The NFC transaction can be used to assure the originality of the consumable at the point of use, and to check that the drug is within its expiry date. The NFC communication can also confirm the type of drug and its batch number, and it can read out delivery parameters that might require an adjustment of device settings. Moreover, the NFC reader can register dosage events, even on the consumable's NFC tag, thereby preventing consumable reuse (Figure 3).

NFC tags can also be equipped with sensing capability, making it possible for the delivery device to play a greater role in supporting self-administration. Sensor-based feedback can confirm that medications are handled and dosed correctly. NFC tags that include a capacitive sensor structure can detect mechanical movement within the device or sense a change in the fill level of a drug container (e.g. full, empty or in-between states) to ensure dosages are administered fully and correctly.

CONNECTIVITY AND PATIENT ADHERENCE

The therapeutic efficacy of a drug depends not only on its pharmacology and bioavailability but also on patient compliance with the treatment regimen. However, many patients with chronic illnesses miss doses, take the wrong dose or stop treatment altogether. Reasons for poor dose adherence and compliance are often associated with symptomatic aspects of the disease, negative side effects of the drug, dose frequency, over-/under-dosing of a drug and usability of the delivery device. The result is poor health outcomes for patients.

With connected devices, patients can manage their condition while receiving immediate feedback to guide them through administration. Rather than manually recording data themselves, they can use automated features to effortlessly capture key information, such as injection dose, date and time. Also, notifications can help remind patients when their next dose is due and or send an alert when doses are missed.

Collected adherence data can also be uploaded to a cloud-hosted database through an active network connection, where more complex algorithms instruct data processing to extract patterns and inform therapy changes. It is also worth investigating how data could be further shared with existing healthcare systems, such as electronic patient records, or how information could keep patients' clinicians informed as part of automatic uploads or downloads in the doctor's office.

SECURITY AND PATIENT REASSURANCE

To reassure patients worried about the security of their drug delivery combination product, and to prevent the use of wrong or fake products, manufacturers should consider adding authentication and authorisation processes beyond mere identification. Unfortunately, counterfeit, adulterated, off-label and diverted products have become more and more widespread. The WHO describes counterfeits as "one of the urgent healthcare challenges of the decade", aggravated by the globalisation of supply chains and a growing share of e-commerce.

Authentication verifies that a device or its medication is genuine, securing access to an application or its data. While identification validates serial numbers using online whitelists, NFC-based authentication performs enhanced checks based on an item's NFC tag data and credentials, using passwords or secure cryptographic functions. Authorisation can further check attributes of each tag, such as ensuring rightful access of users to their data or delivery system.

Figure 3: Communication between device and medication.

NXP SMART TECHNOLOGY SOLUTIONS

NXP is using its position as a leading semiconductor company with advanced solutions for wireless connectivity, sensors and microcontrollers to support connected devices for personal and clinical use that deliver excellent quality of care and security.

NXP offers a range of solutions for NFC and, to address concerns over the security of patient data and the possible presence of counterfeit products in the supply chain, offers multiple functions that safeguard access to user data and check the authenticity of devices and drug consumables.

Secure NFC Tags

NXP's **NFC security tags** combine standard-based AES-128 cryptography for tag and message authentication with enhanced functionality, such as status detection. The company offers products with independently certified security algorithms backed by Common Criteria security certification. An optional scheme for mutual authentication ensures both reader and tag share the same secret or key, so the tag releases data only to an authenticated reader, thereby protecting it against unauthorised access or malicious modification attempts.

NXP NFC tags include the popular **NTAG® DNA** (ISO 14443/Type 2 or 4 Tag) and **ICODE® DNA** (ISO 15693/Type 5 Tag), which support a range of operating distances and form-factor dimensions. NXP's certified **NTAG 22x** and **42x DNA** tags come with Advanced Encryption Standard (AES)-128 cryptography and web-based secure, unique NFC (SUN) message authentication for dynamic, secured NFC messages on every NFC phone readout to prevent mass copying. For an automated offline authentication in a device, a mutual authentication mechanism can ensure only an authenticated reader in a device can access sensitive tag data, protecting such data from unauthorised access or malicious modification.

NXP's latest **NTAG 22x DNA StatusDetect** (ISO1443/Type 2 Tag) combines security with innovative status sensing using capacitance. When interrogated, the tags can capture a capacitance variation, resulting from a change in condition, and these variations can be interpreted with a software application. This feature can be used to measure the fill level of liquid drug containers or to capture mechanical movements in medical devices.

Connected NFC Tags

Connected NFC tags are devices that, in addition to their regular contactless communication functions, can harvest electrical energy and communicate through a wired interface. Connected NFC tags can provide power to an external sensor or a microcontroller, or to LEDs or switches. In medical devices, they can help measure temperature to make sure an injectable drug is within the expected temperature window, and they can measure pressure to help control an inhalation device or measure if a mechanical function is complete. Results can be stored locally but can also be made available for download to the user's NFC smartphone.

> "A mutual authentication mechanism can ensure only an authenticated reader in a device can access sensitive tag data, protecting such data from unauthorised access or malicious modification."

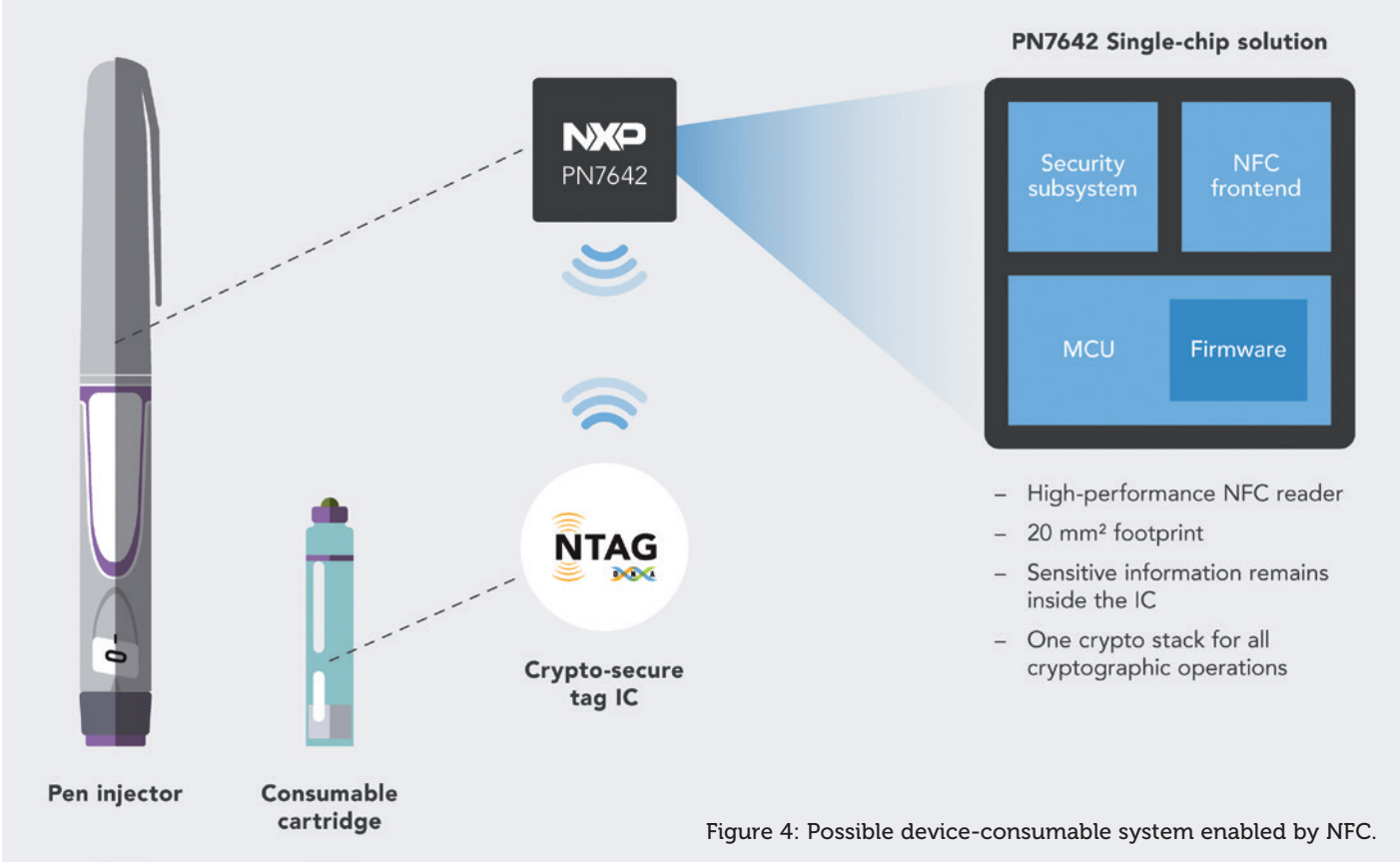

Figure 4: Possible device-consumable system enabled by NFC.

The **NTAG 5** (ISO 15693/Type 5 Tag) and **NTAG I2C Plus** (ISO14443/Type 2 Tag) are versatile connected NFC tag solutions for use in or on a system with an electrical system interface to connect to, for example, a microprocessor or sensor in a device via an I²C bus, and support memory data protection with segmented access rights management.

Single-Chip NFC Microcontroller

NXP's **single-chip NFC microcontroller PN7642**, released in March 2023, offers the highest integration level and the smallest footprint for adding NFC reader functionality, processing and security, even in small drug delivery devices. The PN7642 embeds a high-performance NFC frontend, delivering up to 2W output power and optimised for battery-powered application, an Arm Cortex M33-based microcontroller with 180 kB customisable flash memory and a full security toolbox supporting cryptographic authentication with internal key storage. The PN7642 is SESIP Level 2 security certified to resist software attacks (Figure 4). For devices requiring protection against more sophisticated hardware attacks, NXP offers Secure Elements (SEs) and Secure Access Modules (SAMs) for enhanced key protection.

LOOKING AHEAD

Connectivity will continue to play an important role in maximising the quality of healthcare for patients, especially those with chronic conditions. NXP is building on its reputation as an innovation leader to deliver high-quality, reliable solutions for connected drug delivery devices. The company's extensive partner network, supported by a comprehensive ecosystem of development resources, helps companies develop their next generation of drug delivery solutions.

ABOUT THE COMPANY

NXP Semiconductors brings together bright minds to create breakthrough technologies that make the connected world better, safer and more secure. As a world leader in secure connectivity solutions for embedded applications, NXP is pushing boundaries in the industrial and internet of things (IoT), mobile, communication infrastructure and automotive markets, while delivering solutions that advance a more sustainable future. Built on more than 60 years of combined experience and expertise, the company has approximately 34,500 team members in more than 30 countries and posted revenue of $13.21 billion in 2022.

ABOUT THE AUTHOR

Sylvia Kaiser-Kershaw is a Global Senior Principal Marketing Manager in the Connectivity & Security business line at NXP Semiconductors. She is in charge of product marketing for NFC tags as well as healthcare market segment development. As part of her role, she helps develop smart solutions to optimise processes, simplify medication application and enhance patient safety. Ms Kaiser-Kershaw has over 20 years of experience in strategic and operational marketing, working across a variety of industries, including personal care, healthcare and insurances. She is based in Austria.

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Essential Connectivity Solutions to Help Advance Medical Devices

From concept to commercial production, NXP is your strategic partner for connected medical devices. We accelerate NFC-RFID technologies that advance security, seamless connectivity, precise sensing and intuitive user experiences.

Enhance your devices with smart capabilities to optimize processes, simplify medication application and enhance patient safety.

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SECURE CONNECTIONS
FOR A SMARTER WORLD

INTERVIEW

In this exclusive interview with ONdrugDelivery, Arnaud Guillet and Fanny Sellier talk with Guy Furness about how Biocorp has become a key player in the field of connected drug delivery, discuss the current landscape for connectivity in drug delivery and update us on its two major parenteral products – Mallya and Injay – as well as looking forward to the launch of the company's next generation of connected drug delivery solutions.

Note: This interview took place before the announcement on June 5th, 2023, that Novo Nordisk had entered exclusive negotiations to acquire a controlling stake in Biocorp from its main shareholder, BIO JAG, followed by a mandatory simplified tender offer for all remaining outstanding Biocorp shares.

ARNAUD GUILLET, VICE-PRESIDENT, BUSINESS DEVELOPMENT

Arnaud Guillet is Vice-President, Business Development at Biocorp, in charge of finding partnerships and licence opportunities for Biocorp's range of connected devices. Previously, Mr Guillet worked for a healthcare consulting firm with a strong focus on connected health strategies for pharma and insurance companies and has additional experience in the pharmaceutical industry (with Sanofi) and the insurance industry (with AXA). He graduated from HEC Paris, a major European business school.

FANNY SELLIER, VICE-PRESIDENT, STRATEGIC MARKETING & ALLIANCE MANAGEMENT

Fanny Sellier is Vice-President, Strategic Marketing & Alliance Management at Biocorp, with responsibility for managing collaborations with its key partners as a main focus. She joined the company in 2021. Having graduated from the ISEG business school in Strasbourg (France) and Instituts Universitaires de Technologie (IUT) de Chimie (chemical sciences), Mrs Sellier worked at Rhodia (now Solvay), in the US, for seven years in marketing, lean enterprise and business development. She also spent eight years with Nemera in charge of ophthalmic products, promoting the company's preservative-free technology.

Figure 1: Mallya – Biocorp's connected smart cap for injection devices.

Q Biocorp was one of the first companies to see the potential of connected drug delivery devices; can you describe how your prescient early move into the connectivity space gives the company a strong position as an established key player, while many other companies are just entering the space.

AG Entering into the connected drug delivery space was a key intention of our founder, who saw many unmet needs and issues in the field of pharma engineering and drug delivery – in particular, the lack of treatment management support for patients with chronic conditions, poor adherence to treatments among those patients and a lack of objective data and feedback for healthcare providers (HCPs). He was convinced that connected technology was relevant and mature enough to tackle these issues, and so he decided to structure Biocorp with the objective of developing this technology in mind.

In the very early days, around 2013, he decided to merge Biocorp's historical device development and R&D capabilities with a company specialised in software developments. This gave Biocorp the necessary expertise – including mechanical, electronic, hardware, firmware and software – to develop its connected device programmes. I believe this is what makes Biocorp unique in this space because, for a relatively little company of only around 80 people, we have all this concentrated expertise inside. So, right from 2013, we were able to launch our first connected programme, DataPen, which was a motor-driven pen injector featuring Bluetooth Low Energy connectivity. A couple of months after that, we launched the Mallya programme of smart injectors, which is currently one of Biocorp's strongest assets (Figure 1).

Since those initial launches, we've worked on dozens of connected device programmes, mainly in the field of

"We've achieved significant milestones, including the regulatory clearance of several drug delivery devices and the signing of major partnerships with pharma companies."

injectables. We've learned a lot from these programmes, including how to build a solution that is easy to implement for our partners and easy to use for patients. This means a design that doesn't include too many functions or stimuli, and with an optimised form factor.

We've also improved our efficiency with respect to energy and resources, while also increasing our capacity for industrialising electronic devices. Furthermore, we've focused on the quality and regulatory departments, which are critical to getting products on the market. Thanks to these efforts, I believe we have become a reference point in the connectivity field for the drug delivery industry. We've achieved significant milestones, including the regulatory clearance of several drug delivery devices and the signing of major partnerships with pharma companies. We're excited about launching with these partners and completing the product development journey.

When it comes to other companies potentially entering the connectivity field, I think that's a good thing because we see that people need education and awareness around connected devices. More companies helping to build the awareness has the potential to be a real benefit to the field. There's room for many players here – there are many different angles to tackle. We're happy to see the community that is building around connectivity.

Q One of the key questions occupying the connected drug delivery space at the moment is that of interoperability. What are your thoughts on how best to facilitate interoperability with apps and ensure that data flows are secure?

FS We cannot sell a device without apps, so for us it is key to have this interoperability with software partners. Of course, it is also very important to secure the communication between the device and the software. This is what Mallya brings – secure and safe transfer of data and the ability to handle various use cases that can happen with the device.

Interoperability is important for accelerating integration so that we reach the market as quickly as possible. To this end, we've developed an integration process and have been steadily improving it in order to shorten the integration period with software providers. This means more apps, and the more apps, the better, because we want to reach as many patients as possible – one app does not fit all, so we need to have many different integrations to cover the different specifics, such as geographies, type of patients, etc.

In order to simplify this, we are also currently working on developing a software development kit (SDK) to standardise the process. The SDK will help our software and pharma partners to simplify development and reduce development time and costs on their end by relieving a lot of the coding burden – they will only have to develop the user interface and user experience. Our goal is to simplify as much as possible by doing the work once and enabling everyone to benefit. We're aiming to have the SDK ready by the end of this year.

AG In the context of a worldwide product launch with a pharma company, we've realised that a one-size-fits-all approach does not work. For example, some companies initially considered launching one single ecosystem together with their connected device but, in practice, this approach clearly doesn't match up with differing local requirements. So, we've had to find a way to multiply the number of integrations in the fastest and most secure way possible, which, for us, is the Biocorp SDK.

Q The new generation of Mallya, Biocorp's flagship connected device, is currently being launched. Can you talk about the launch plan in diabetes? Is there activity in other fields? What's improved with the latest version?

FS The big difference is that the first generation of Mallya had two pieces whereas the new generation is a one-piece device. This makes it much easier for patients to attach it to their injector pen. Additionally, the new generation does not need to be recalibrated in the way previous generations did. Overall, the new generation has been designed to be easier to use and more patient friendly. Also, because the new generation is a single-piece device, it is a little bit less costly as well compared with its predecessors. It's a win-win for everyone.

Figure 2: A next-generation Biocorp connected device.

With respect to launching the new generation of Mallya, our aim is to launch in most worldwide markets this year. For example, the new generation will be launched in Asia and Europe this year for insulin. You may have seen that the new Mallya has already launched in Japan, in March of this year. Outside of Mallya, we also have some next-generation devices (Figure 2), such as SoloSmart, which we designed for Sanofi, that should be launched soon in different countries.

Our launches this year are primarily for insulin. However, we also have upcoming launches for growth hormone treatments, which also will be launched in 2023.

We're excited about these launches because all patients dealing with a chronic illness, anyone who uses an injector pen, can get meaningful benefit from a smart device like Mallya. For example, with

"We're excited about these launches because all patients dealing with a chronic illness, anyone who uses an injector pen, can get real benefit from a smart device like Mallya."

insulin, it's great to have Mallya to keep track of the details of each injection to make it easier for a patient to look at their injection history and how their treatment is going. It also facilitates good communication with HCPs, giving them objective data to discuss with their patients and much better evidence of how the treatment is going.

This is true for much more than just insulin and diabetes, of course. For example, fertility is another field we're exploring where Mallya could provide patients with real reassurance. It allows patients to follow along with and feel more comfortable about their treatment and lets their HCP see that they are taking their treatment seriously. It's very important with fertility treatments to administer the drugs at certain times and dates, so it's important to use the best available technology to track these injections.

Q Please could you explain why digital ecosystems are so important in diabetes and how Biocorp is driving the technology forward in this area?

FS With diabetes, there is a very high treatment management burden on patients, so they need the fullest support available. For example, it's better for patients to have their glucose monitoring in the same app as their insulin tracking to make it as easy as possible for them to keep on top of everything. This is a key driver behind our partnership with Health2Sync (Taipei City, Taiwan), as part of which we've signed a partnership with them for Mallya's launch in Japan.

A next step to take in this is developing semi-loop systems. So, on top of having glucose monitoring and insulin tracking, we can also include an insulin titration algorithm that can calculate the amount of insulin that the patient needs to inject. In this area, we've signed a partnership with Diabeloop (Grenoble, France) to take one step further into this system.

A key benefit of using connected technology with diabetes is that it makes it much, much easier to conceptualise the insulin data. By doing so, it's possible to maximise the value of the treatment in a simple, safe and accurate way, and of course accuracy is incredibly important in diabetes. A good software partner can also put the data into the context of the patient's daily life, such as their glucose level, activity level, carbs intake and a whole host of things like that. Putting all of this information together is key for the patient, and that's what digital ecosystems excel at.

> "Injay is a very simple and very cost-effective way to monitor the adherence of medicines delivered with prefilled syringes."

Q Considering the current interest in artificial intelligence (AI), is Biocorp investigating the use of AI in the context of connected drug delivery?

AG Yes, it's certainly something that we're exploring. For diabetes, I think there are a numerous good algorithms in the AI area being developed by software companies, so our current approach is to partner with them and make use of their expertise. For now, Biocorp's key strength is collecting insulin data in a very safe, robust and accurate way – that's the piece of the puzzle we want to provide. If we can do that, then the larger digital ecosystem will be able to build on it and maximise the benefit for patients. We're currently considering taking on a bigger role in the field and perhaps developing proprietary software in the future, which could absolutely include AI-driven capabilities for recommendations and advice for patients to bring about more positive clinical outcomes.

There are two real and very exciting developments that will apply to drug delivery in the future: AI and behavioural science. The potential combination of these two trends is very interesting, because AI is based on using and analysing the data you acquire to better understand the condition of a patient based on their specific clinical conditions, whereas behavioural science is based on how a specific individual thinks and acts in both broad and specific terms, which is key to tackling low adherence – it's not only about your condition, it's about who you are, your personal belief regarding your disease and the way you behave as a person. If we're able to provide better for patients based on who they are, we might see some real improvements in terms of adherence.

I think for diabetes, the digital ecosystem is mainly focused on glucose and insulin data collection – that's the most critical part. However, outside of diabetes, in chronic conditions where there are less frequent injections and less frequent requirements for patients, the focus can shift to finding the right driver to keep patients taking their medication in a consistent way and seeing better health outcomes. I think this is somewhere behavioural science could really play a big role.

Q Biocorp's other major connected add-on in the parenteral sector is Injay, which is compatible with various sizes of conventional prefilled syringes (PFSs). Please could you give an overview of Injay's features and benefits, as well as its utility for the delivery of biosimilars?

AG Injay is a smart solution to track injection data on PFSs, composed of a near-field communication chip, the main purpose of which is to recall product information, and an activator to confirm complete injections. These components are directly installed by the pharma company onto the syringe, which is then delivered and ready to use by patients or HCPs. Once the PFS is used, the chip can be scanned to retrieve product information and confirm the complete injection together with a timestamp.

As such, Injay is a very simple and very cost-effective way to monitor the adherence of medicines delivered with PFSs (Figure 3). Additionally, Injay has limited environmental impact because there are no active electronic components installed on the syringe, making it freely disposable. Biocorp has developed one version that is applicable to naked PFSs in various sizes, including 0.5 and 1 mL – both long and short – and 2.25 mL.

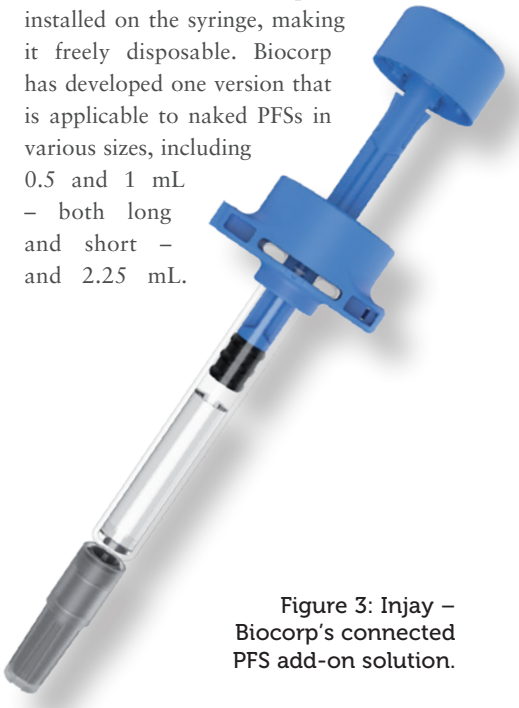

Figure 3: Injay – Biocorp's connected PFS add-on solution.

> "It tends to be assumed that, if you're participating in a clinical trial, you'll be adherent – but that's not always true."

Also, we've partnered with BD to develop a specific version that is compatible with the BD UltraSafe device.

A key use case for Injay is for monitoring drug delivery in the context of clinical trials. Here, the primary benefit is the ability for the study operators to monitor patients' adherence. This is critical, because we've found that between 30% and 50% of patients are non-adherent in clinical trials, which is often overlooked because it tends to be assumed that, if you're participating in a clinical trial, you'll be adherent – but that's not always true. This, of course, then has a significant impact the results of the trial. This is where Injay comes in, because it enables the detection of non-adherence, the trial operators can act on that information and intervene with non-adherent patients, saving time and guaranteeing the quality of trial outcomes. It also facilitates efficient and accurate automatic data collection, which increases the quality of the data over traditional patient self-reporting by eliminating human error, as well as enabling hybrid and decentralised trials, which are currently increasing in number.

The other primary use case is with commercial drugs. In this instance, we're talking about very expensive biologics, often in fields such as rheumatoid arthritis, dermatitic arthritis, psoriasis and multiple sclerosis. In these areas, a patient will have weekly injections, so Injay is a tool that can be used in combination with patient support programmes to keep a record of injection data. It can also provide HCPs with objective data on drug intake and the patient engagement – whether they are taking their drug or not. As well as that, it can provide payers with proof of actual drug usage in a real-life setting, which can enable value-based assessments; this is more a consideration for the long term, but a shift towards a value-based model is going to happen at some point, and Injay is able to facilitate that.

Q Looking at the big picture for the large-scale adoption of Biocorp's connected drug delivery devices, can you map out some of the key milestones that you've already achieved and those you're still aiming to achieve? Additionally, do you think that a clear regulatory pathway is a prerequisite to widespread industry and patient acceptance?

FS We have achieved US FDA approval for the first generation of Mallya, which was finalised late in 2022. This was a huge milestone for us and something on which we've been working very hard. We were proud to get this 510(k) for Mallya. We have also secured the CE mark for most of our new-generation products, including the SoloSmart.We have received further certifications from other jurisdictions around the world, mostly in Latin America and Asia.

What's coming next is the internationalisation of all of our new-generation products, starting with the new Mallya platform. We're currently in the ramping-up phase, launching all these devices onto the market in different countries. As part of this, we and our customers are also doing some real-world evidence studies as well. That's the challenge we're taking on in the immediate future. Looking further ahead, we're continuously building on our clinical evidence and deploying market access strategies based on the specifics of each country to get reimbursement.

AG One way to think about it is that it's like different stages of a rocket. The first stage is the technical development, which we've achieved successfully. Next is the regulatory stage, which was quite challenging, but we've now achieved that one as well. The third stage will be the pinnacle, building the clinical evidence and opening new doors for reimbursement. I think we are in the middle of this phase, building these networks together with doctors, building clinical evidence and creating awareness of the benefits of connected drug delivery. It's an exciting moment for the company.

ABOUT THE COMPANY

Recognised for its expertise in the development and manufacture of medical devices and delivery systems, Biocorp has acquired a leading position in the connected medical device market thanks to its Mallya platform, an intelligent sensor for insulin injection pens that enables reliable monitoring of injected doses and thus offers better compliance in the treatment of diabetes. Available for sale since 2020, Mallya is the spearhead of Biocorp's product portfolio of innovative connected solutions.

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THE POTENTIAL OF CONNECTIVITY AND MONITORING IN MESH NEBULISERS

In this article, Carolina Dantas, MD, Manager of Medical and Scientific Affairs, and Ulf Krueger, Chief Executive Officer and Founder, both at Pulmotree Medical, review the current connectivity and remote monitoring capabilities in mesh nebulisers – and their potential to impact patients' healthcare journeys and the clinical development of inhaled therapies.

Worldwide, respiratory diseases affect millions of individuals and remain a leading cause of death and disability, imposing a significant burden on both patients and healthcare systems.[1] The morbidity associated with respiratory conditions is related to symptoms such as breathlessness or coughing, and consequently to a reduction of quality of life. Moreover, the burden of disease extends beyond the patients themselves, with healthcare systems facing increased costs, more hospital admissions and productivity losses. It highlights the importance of developing effective and innovative disease control strategies, which is where novel inhaled therapies and devices assume a promising role.

In the rapidly evolving area of respiratory drug delivery, technologies addressing adherence and inhalation technique offer the opportunity to enhance personalised care for patients.[2] With current nebulisation devices allowing enhanced transpulmonary drug delivery, the potential indications and benefits of the inhaled route go beyond respiratory conditions to broader areas such as cardiovascular or immune diseases.

Digital technologies in healthcare are an active area of research and development, but their long-term success will depend on identifying real needs and integrating the interests of the different parties involved.[3] In the context of mesh nebulisers, despite remarkable evolution of the devices, relevant unmet needs persist and have a distinct impact on clinicians, patients and the industry. While tackling those challenges, connectivity and remote monitoring technologies have emerged as promising tools to help improve patient care, reduce risks in clinical development and push progress in respiratory medicine.

This article reviews, from the perspective of a clinician who transitioned to the healthtech and medical devices industry, the current connectivity and remote monitoring capabilities in mesh nebulisers and their potential to impact patients' healthcare journeys and the clinical development of inhaled therapies.

UNMET NEEDS IN NEBULISED THERAPIES

While progress in nebuliser technology is notorious, there are still relevant challenges to address, particularly when considering the following three important perceptions.

For clinicians, the uncertainties surrounding lung deposition can lead to questioning the treatment efficiency and raise concerns about risks for patients. In clinical practice, there is often doubt about the actual fraction of the administered dose that each patient truly receives and its precise deposition site. It is crucial to understand whether treatment outcomes can be attributed, for example, to disease evolution, the nebulisation process or drug effectiveness. Also, considering that the breathing manoeuvre plays a considerable influence in lung deposition, focus should be put on achieving optimal inhalation during nebulised therapy. Despite efforts from healthcare professionals to train patients, real-life variability in breathing patterns during nebulisation still poses a challenge that needs to be addressed.

> "Connectivity and remote monitoring technologies have emerged as promising tools to help improve patient care, reduce risks in clinical development and push progress in respiratory medicine."

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> "The inability to monitor highly influential parameters in drug deposition during inhaled therapies adds difficulty and complexity to clinical trials."

For patients, there is a pressing need for nebulisers that are smaller, user friendly and easy to clean but, at the same time, "smarter", with the ability to guide and provide feedback about the therapy. It is essential to alleviate the burden of disease for patients, by simplifying their interaction with the devices and facilitating therapy adherence, while simultaneously finding a balance between treatment effectiveness and patient engagement.

For the industry, the main challenge still lies in the high risks associated with clinical development of inhaled drugs. The inability to monitor highly influential parameters in drug deposition during inhaled therapies adds difficulty and complexity to clinical trials. The considerable variability in results often leads to costly study repetitions for dose finding and safety evaluation, thereby increasing overall expenses.

Altogether, tackling these unmet needs would help optimise nebulised therapies, ensuring better treatment outcomes, an enhanced patient experience and safer clinical development. Solutions to these problems are offered by the synergy between emerging effective nebuliser technology, innovative connectivity and remote monitoring tools, and the ever-expanding scientific knowledge.

THE RISE OF CONNECTIVITY AND REMOTE MONITORING TECHNOLOGY IN MESH NEBULISERS

Connectivity and remote monitoring technology have gained exponential relevance in recent years, transforming the landscape of medical devices and global healthcare. The progress witnessed so far in the nebuliser industry and, in particular, with mesh nebulisers, is truly remarkable, while the most prominent innovations are still to come to clinical practice. There is transformative potential in integrating mesh nebulisers in digital platforms with connectivity features that enable real-time data capture, remote monitoring and adherence tracking.

Mesh Nebulisers as Part of a Connected Platform

Mesh nebulisers have evolved far beyond their traditional function as standalone devices for respiratory drug delivery. The addition of connectivity capabilities has integrated nebulisers into a connected system or platform. These connectivity features enable automated real-time data transfer by wireless networks to digital platforms such as cloud storage or mobile apps. Detailed data about the inhalation process, flow rate, volume, time of nebulisation and adherence, as well as device status, are collected by the nebuliser and integrated into a connected platform.

As a result, nebulisers have become essential elements within a networked ecosystem that integrates relevant information regarding the therapy and the patient, while also offering the option to combine it with other valuable monitoring tools.

Monitoring Tools for Both Healthcare Professionals and Patients

By incorporating connectivity into mesh nebulisers, both healthcare professionals and patients gain access to information related to the therapy. The ability to monitor and analyse the patient's inhalation parameters, medication adherence and usage patterns can be valuable for clinical teams. When smoothly incorporated in the clinical routine of specialised multidisciplinary teams (nurses, physiotherapist or clinicians), patient monitoring can allow prompt interventions, thereby optimising patient outcomes and minimising risks.

Simultaneously, through these monitoring tools, patients can choose to easily track their treatment progress and receive personalised feedback and guidance using mobile apps or interfaces to cloud-based platforms. This way, connectivity empowers patients by providing them with the possibility to control their own treatment and improve self-management skills, ultimately enhancing patient engagement, adherence and satisfaction.

Reducing Risks in Clinical Studies

It is within the scope of clinical development that the addition of connectivity and remote monitoring capabilities in mesh nebulisers seems to create a greater impact. The ability to capture real-time data from mesh nebulisers to digital platforms allows researchers to collect reliable information about medication adherence, treatment response and patient-reported outcomes. Therefore, there is a minimisation of factors that influence the results of clinical studies and potentially an improvement in the outcomes. Early identification of non-compliant participants allows interventions and re-adjustments in trial design – granting more robustness and higher statistical power to studies. Particularly relevant in respiratory drug delivery, this proactive approach can reduce the need for study repetitions, resulting in accelerated development of novel therapies with lower costs.

Regarding patient safety, connectivity and remote monitoring enable real-time surveillance of study participants. This facilitates early intervention in the case of exacerbations or adverse events, mitigating risks and enhancing patient safety during the clinical development process. Digital platforms connected to mesh nebulisers also centralise data management in clinical trials by automatically capturing, securely storing, organising and analysing information in real time. Essentially, this allows a reduction of the burden for all parties involved in clinical development through optimisation of resources and timelines.

LIMITATIONS AND CHALLENGES

While mesh nebulisers with connectivity and remote monitoring features hold great promise, it is vital to address the challenges that come with their implementation. When it comes to accessing more information, it is reasonable to question the likelihood of usage in real-life clinical practice. Here is where accessibility and usability of digital tools are key to ensure easy access among diverse contexts and platforms in different health systems. Clinical

> "While mesh nebulisers with connectivity and remote monitoring features hold great promise, it is vital to address the challenges that come with their implementation."

"By capturing real-time data on patients' breathing patterns, such as flow rate and volume, nebulisers could offer important inputs for lung deposition models."

development holds the greatest potential for connectivity and remote monitoring tools in mesh nebulisers, but concerns regarding patient data privacy and storage raise ethical and legal considerations. It is crucial to ensure robust security measures and compliance with data protection regulations. Overcoming these limitations and challenges will require collaborative efforts among stakeholders – including clinicians, researchers, technology developers and policymakers – to implement innovation while prioritising patient safety, data privacy and inclusive healthcare delivery.

FUTURE DIRECTIONS

Connectivity and remote monitoring capabilities can potentially revolutionise respiratory drug delivery by providing new patient-side parameters generated during nebulisation – unlocking new pathways for drug development. By capturing real-time data on patients' breathing patterns, such as flow rate and volume, nebulisers could offer important inputs for lung deposition models. This would enable the characterisation and display of each individual inhalation during drug delivery. Access to these previously unattainable parameters could mark a significant advancement in personalised respiratory medicine, fostering further knowledge and pushing evolution in inhaled therapies.

In conclusion, connectivity and remote monitoring features should be seen as a valuable improvement to an optimised mesh nebuliser device, rather than necessary requirements for the therapy. These tools come hand in hand with the technological advancements seen in the nebuliser industry, holding vast potential to help answer unmet needs and push progress in respiratory drug delivery.

ABOUT THE COMPANY

Pulmotree Medical specialises in the development of drug delivery systems with targeted deposition of drugs into specific areas of the lung. It supports pharma partners with comprehensive services around the product lifecycle of drug and device combinations.

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ABOUT THE AUTHORS

Carolina Dantas, MD, is a pulmonologist who adds to Pulmotree Medical the valuable insight of both physicians and patients. Specialising in respiratory infectious diseases and lung-related indications, such as cystic fibrosis and bronchiectasis, she has vast hands-on clinical experience with inhaled drug therapies. As Manager of Medical and Scientific Affairs, Ms Dantas's search for innovation in healthcare matches with Pulmotree Medical's forward-thinking approach to the evolution of respiratory therapies. Besides her knowledge in clinical research, Ms Dantas is an accomplished communicator in science, with published scientific papers, a book chapter and several original presentations at international conferences to her name. She holds a master's degree in Medicine and is a member of several international scientific societies.

Ulf Krueger has extensive experience in life sciences, which is the basis of Pulmotree Medical's business – particularly managing projects, programmes and portfolios in the field of inhaled drug delivery. Throughout his career, Mr Krueger has been particularly engaged in the development of pulmonary drug delivery devices and the targeted delivery of drugs to the lungs. In his former position as Director of Fox Nebuliser Programs at Vectura, he held responsibility for the entire sector of vibrating mesh nebulisers. Before that, he held various positions in the research and development department of PARI. He is a graduate biomedical engineer and a certified senior project manager (IPMA® Level B) and member of several scientific societies.

Aptar digital health

TAKING A PATIENT-CENTRIC APPROACH TO CANCER CARE THROUGH IMMUNOTHERAPY

Here, Corinne Fechant, MD, Director Global Medical Affairs, Oncology, and Laura Hilliquin, Solution and Services Design Manager, both at Aptar Digital Health, highlight the role digital health solutions can play in supporting patient self-administration for the increasing number of immunotherapies for cancer treatment.

Immunotherapy has transformed cancer care with immune checkpoint inhibitors, providing efficient stimulating agents that act on patients' own immune systems. The response to these treatments drives long-lived tumour destruction with significant benefits for patients who have made minimal progress, or even relapsed, when using more traditional treatment methods. At the same time, these immunotherapies can present self-administration challenges and come with side effects that other therapies do not have, which can make self-management of care difficult.

Overcoming these two obstacles requires a patient-centric approach that is enhanced by the use of digital technologies that work alongside immunotherapy. By helping patients self-manage their treatment through education and guided decision making, digital products can improve the effectiveness of immuno-oncology, which can lead to better clinical outcomes and quality of life for patients.

> "Immunotherapies can not only enable the immune system to remember what cancer cells look like but also adapt to changes in cancer cells."

THE BENEFITS OF IMMUNO-ONCOLOGY

The use of immunotherapies in cancer treatment is meant to help use the body's immune system to prevent, or even eliminate, cancer. Essentially, immunotherapies enable the immune system to recognise the difference between healthy cells and cancerous cells.

Patients with cancer benefit from immuno-oncology largely because treatments are targeted to the specific white blood cells (lymphocytes) that evoke an anti-tumour immune reaction. It is common for immunotherapies to be prescribed in combination with other treatments, such as surgery, radiation, chemotherapy and other targeted therapies.

Highly targeted therapies are proven to be more effective at treating certain types of cancer, with a reduced likelihood of relapse compared with traditional treatments, such as radiation or chemotherapy, on their own. Additionally, immunotherapies can not only enable the immune system to remember what cancer cells look like but also adapt to changes in cancer cells, which further contributes to the long-lasting effectiveness of immuno-oncology.[1–3]

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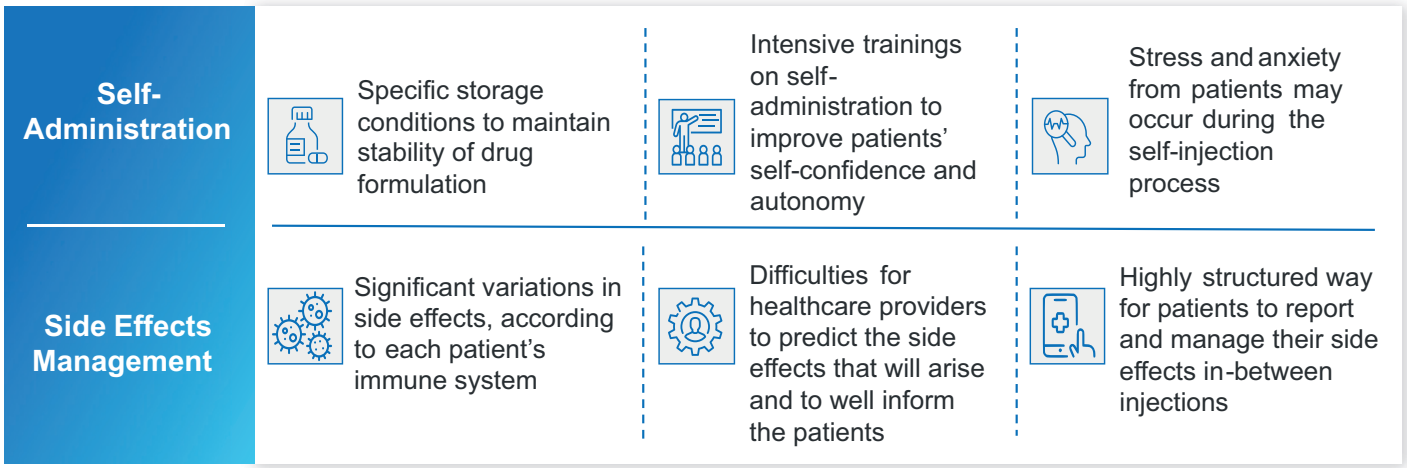

Figure 1: Real-world challenges for immuno-oncology treatments.

UNDERSTANDING THE PATIENT JOURNEY

Following an initial biopsy to confirm a cancer diagnosis, it is common for patients to be prescribed a generalised treatment to shrink a tumour prior to surgery or to avoid the risk of recurrence after surgery. Also, some patients fail to respond to traditional treatments. Others may see their symptoms persist or may suffer a relapse after an initial treatment appears to have succeeded. In these cases, an oncology care team may order an additional biopsy to determine if a patient has a biomarker for a particular antibody that could be targeted by targeted therapy or immunotherapy. If a biomarker such as PDL1 is present – or not, in some cases, as it is not required in some indications – then immunotherapy can be prescribed, and a new course of treatment can begin.

As immunotherapies continue to be brought to trial, approved and used more and more in real-world settings, and as access to genetic testing improves, it is hoped that these therapies will become more readily and widely available to patients for the early stages of treatment. This could help more patients receive the right treatment at the right time – improving both clinical outcomes and overall quality of life, while potentially contributing to lower care costs downstream.

SPECIFIC CHALLENGES FOR IMMUNO-ONCOLOGY

While immuno-oncology presents many clear benefits to patients with cancer, as well as their care teams, there are two areas where immunotherapies – and especially immune-checkpoint inhibitors such as CTLA-4 – pose challenges when compared with more traditional treatment methods (Figure 1).

Administration

Self-administration has been one of the most powerful advances in managing chronic conditions – and cancer is no exception. Patients who can administer therapies from the comfort of their homes save themselves a trip to the hospital or oncology clinic and all the challenges that may present, from scheduling and transportation to time away from family or work.

The same is true for immuno-oncology, but the nature of these therapies requires additional consideration for patients and their care teams. Immunotherapies tend to be made up of larger molecules than other treatments and need to be well distributed throughout the body. When appropriate formulations are homologated and given these characteristics, immunotherapies such as immune checkpoint inhibitors will require subcutaneous administration, typically in the abdomen or thigh.

> "Patients may need extensive training on self-administration to make sure that injections are done correctly and that they feel confident enough."

Self-administration devices must be developed accordingly, with appropriately sized needles and plungers. What's more, maintaining the stability of the formulation often requires storage at a specific temperature or humidity, which could be difficult for certain people, given their living conditions. As a result, patients may need extensive training on self-administration to make sure that injections are done correctly and that they feel confident enough. Patients should also be taught how to store the medication, remove it from the refrigerator to achieve room temperature, aseptic administration technique, along with education on what to expect as they are injecting a therapy to achieve success. Care teams must be prepared to make special accommodations as necessary.

Side Effects

Traditional treatment options, such as radiation and chemotherapy, tend to have predictable side effects – notably nausea and hair loss. Surgical procedures also typically have predictable recovery timelines and expectations for regaining mobility or recovering appetite, for example.

This is not the case for immunotherapies. Because the therapy reacts to the patient's immune system, side effects can vary significantly from one patient to another, depending on how their individual immune system responds. In fighting one type of cancerous cell, a therapy may activate the immune system and affect almost all tissues and organs with autoimmune disorders. For example, colitis was a common[4] – and unexpected – side effect of some of the first immunotherapies. Since care teams were initially unprepared to manage colitis, many patients struggled to manage their now-worsening health and could have faced difficult complications – leading to stopping treatment.

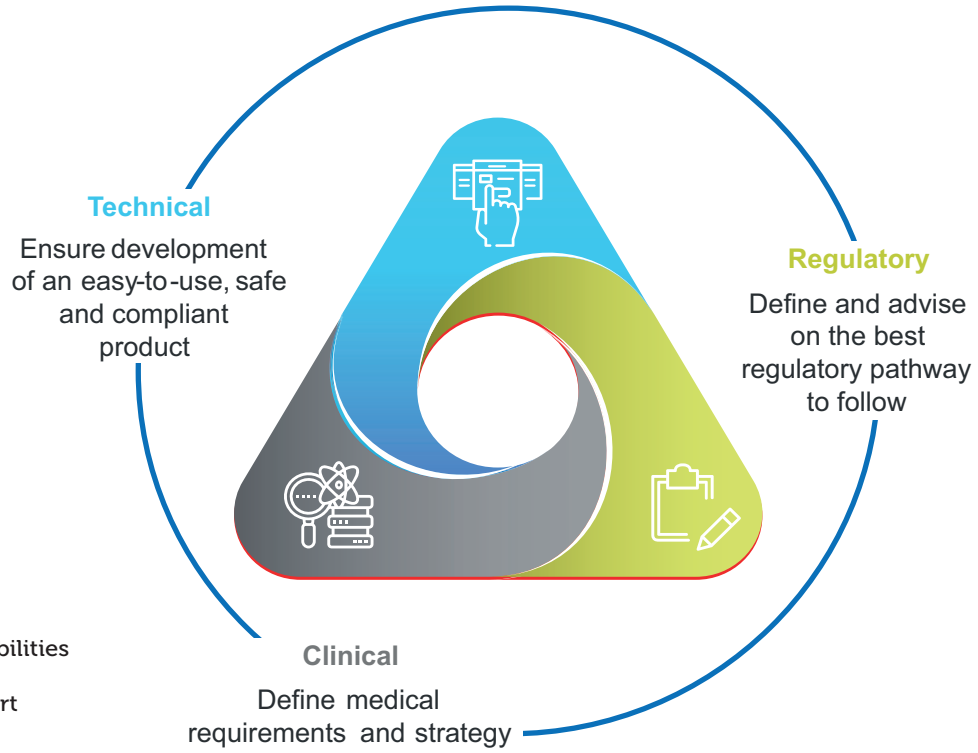

Figure 2: Team capabilities required to build technology to support immuno-oncology.

Because side effects can be difficult to predict, oncology care teams may find it hard to inform patients about what to expect as they begin treatment. Patients will also need a highly structured way to report and manage their side effects between treatment doses, especially if they are choosing to self-administer therapies and will have fewer in-person appointments. The unpredictable and potentially severe or delayed toxicities also suggest a clear need to help patients understand what to do if things appear to be getting worse.

> "Patients and care teams can clearly benefit from purpose-built digital health tools to help patients manage the administration of their therapies, monitor side effects and appropriately engage with their care teams between doses."

PURPOSE-BUILT TECHNOLOGY TO SUPPORT IMMUNO-ONCOLOGY

Given the challenges of immuno-oncology, patients and care teams can clearly benefit from purpose-built digital health tools to help patients manage the administration of their therapies, monitor side effects and appropriately engage with their care teams between doses. This growing market of digital health solutions emphasises an engaging user experience and personalised interventions based on tested and approved clinical pathways.

To create such a digital health tool, it is critical to bring together representatives from clinical, technical, pharmaceutical, medical device and regulatory and legal stakeholders from the beginning of the process (Figure 2). Patient input cannot be overlooked and should be gathered through both formative and summative studies; the former taking place throughout the design and development processes, with the latter functioning as a user test once a product is nearly finalised.

Creating such a multidisciplinary team brings some key advantages to the product development lifecycle. One is a collective understanding of the regulatory complexities that apply to digital health solutions. As these products are also held to different regulatory standards compared with traditional medical treatments, their value and safety can be demonstrated through randomised control trials (RCTs) and/or ongoing real-world evidence (RWE) generation. Applying this knowledge at the outset saves significant time in the long run, as issues are identified and addressed before significant redesigns are required.

Another advantage is the capability to test usability, efficacy and security throughout the product development lifecycle. Not only does this mirror best practices for software development, it also ensures that a product meets the needs of both patients and healthcare providers. Patients need an intuitive interface that is easy to navigate, while care teams should be spared a deluge of patient data and only receive notifications that require immediate attention, such as missed doses or worsening side effects.

With the right team in place, and with the right approach to design and development, a digital health solution can meet the needs of both patients and healthcare providers. In these situations, patients have the resources they need in a mobile app they can easily use, while clinical care teams receive the data and context they need to make the right care decisions on behalf of their patients.

PUTTING FORTH THE BEST PATIENT-FACING PRODUCT

It is critical that all patients can benefit from digital health support. This means designing products that present information viewable even to patients with limited vision, and to structure navigation menus and buttons to accommodate those with limited dexterity. At the same time, all digital solutions must strike a balance when it comes to sharing information with care teams. Too much information can be distracting, while too little leaves care teams uninformed about whether patients are making progress.

Organisations developing immuno-oncology digital products, such as Aptar Digital Health, need to account for the following factors.

Trustworthy Content: Patients are likely to have many questions about their immunotherapy, especially if it is their first time going through this type of treatment. Access to curated and approved resources will let patients educate themselves at their convenience, while giving care teams peace of mind that patients are only exposed to accurate and trustworthy information.

Self-Administration Guidance: Written resources alone may be insufficient to assist patients. Video tutorials work well to provide step-by-step instructions. Meanwhile, training devices can help patients get a feel for the proper angle and amount of pressure necessary for correct subcutaneous injection. They also allow for ongoing training in between doses, which helps patients build their confidence.

Self-Management Capabilities: Given the highly individualised nature of immuno-oncology, it is imperative that digital tools help patients monitor and measure their side effects. These capabilities should present information to patients in a familiar way, with an emphasis on clear language (and limited clinical terminology) and an ability to account for both physical and mental health.

Bidirectional Information Sharing: It is critical to keep care teams informed about a patient's progress. If they report certain symptoms, or if they are having difficulty using an injection device, then it may be necessary to modify a treatment plan. Effective digital tools can provide this information to care teams at the appropriate moments in their clinical workflows to minimise disruptions and distractions.

Patient-Facing Decision Support: As patients routinely review educational content, administer therapies and record side effects, they are increasingly empowered to manage their care. Digital tools can further this empowerment with evidence-based decision-support tools. This is especially valuable in providing guidance to help patients decide whether the symptoms they are experiencing require a visit to the emergency department or may be resolved in another manner.

These considerations show that the goal of digital health solutions in immuno-oncology is to reassure patients that they are not alone. Tools that provide access to reputable resources, enable self-management and keep care teams in the loop help to educate, support and empower patients are critical as patients go through a difficult and disruptive care journey.

CONCLUSION

Immuno-oncology is a growing and promising field for immune checkpoint inhibitors. Regulatory bodies in the US, EU, Japan and elsewhere continue to approve new therapies in this field, while life science organisations are ramping up the trial of existing therapies for new indications and new formulations. Both steps will help to bring more highly personalised and targeted treatments to more patients around the world.

Increased use of immunotherapies makes it all the more imperative for the industry to develop purpose-built digital health solutions that support patient self-management.When these products go through well-thought-out design and development lifecycles that account for patient and provider needs and involve all key stakeholders from the very beginning, the result is a product that is integrated into the clinical workflow and aims to improve clinical outcomes and quality of life while further demonstrating the efficacy of immuno-oncology – and encouraging additional developments.

For more information on Digital Therapeutics, visit: www.aptar.com/pharmaceutical/digital-health-enhanced-patient-experiences

ABOUT THE COMPANY

Aptar Digital Health is a division of Aptar Pharma, which is part of AptarGroup, Inc, a provider of design and manufacturing for a broad range of drug delivery, consumer product dispensing, and active material science solutions and services. Aptar Digital Health offers integrated health solutions and services with a mission to elevate patient experiences at every stage of their treatment journey. Its suite of end-to-end, patient-centric digital solutions leverages its extensive expertise and diverse, industry-leading product portfolio to deliver differentiating experiences and more positive outcomes.

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YPSOMED
SELFCARE SOLUTIONS

REAL-WORLD EVIDENCE IN THE AGE OF DIGITAL HEALTH – UNLOCKING VALUE FOR PHARMACEUTICAL COMPANIES

In this article, Ventsislav Dobrev, Digital Health Solutions Manager, Philippe Müller, Digital Health Solutions Manager, and Rafael Weiler, Technical Leader Innovation, all at Ypsomed, explore how real-world evidence in the age of digital health can help unlock value for pharmaceutical companies.

Digital health solutions have the potential to revolutionise the healthcare industry, providing opportunities for improved patient care, enhanced data collection and valuable real-world evidence (RWE). They enable the continuous monitoring of patients' health and progress regarding their treatment.

Wearable devices and mobile applications can track various parameters, such as heart rate, sleep patterns, physical activity and medication adherence. By collecting real-world data (RWD), healthcare providers can gain a comprehensive understanding of patients' health trajectories and make more informed clinical decisions. All these can contribute to personalised medicine, early detection of diseases and remote patient management – ultimately leading to improved patient outcomes.

In recent years, technological capabilities have expanded, and the use of person-generated digital health data has increased in importance. The recent trend for value-based and patient-centric care provides an opportunity for person-generated digital health data to play a fundamental role in the generation of RWE. RWE can be defined as "insights generated from RWD using appropriate scientific analytics with the intention to support a claim or belief, for which a hypothesis is usually formulated in advance".

> "In recent years, technological capabilities have expanded, and the use of person-generated digital health data has increased in importance."

RWD, from which RWE is derived, can be defined as follows: "Longitudinal patient-level data captured in the routine management of patients (for care, cost management or public health) which can be repurposed to study the impact of healthcare interventions".[1] This article explores the opportunities that RWE derived from Ypsomed's smart solutions can bring to pharmaceutical companies.

Digital health and RWE are linked as digital health facilitates the generation of RWE. RWE requirements and gaps demand data generation by new and innovative means. Despite the embrace in recent decades of evidence-based medicine, scientific evidence does not yet exist for the effectiveness of many clinical interventions, and the evidence that does exist is often surprisingly weak. Those two facts contribute to the so-called "evidence crisis".

Two important enablers are necessary to overcome this crisis – common digital standards and open digital platforms. They need to be developed for the routine capture, sharing and analysis of health outcomes and other relevant data across health systems. New analytical tools for research are necessary for translating the rapidly accumulating quantities of

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Figure 1: Ypsomed smart solutions.

> "New analytical tools for research are necessary for translating the rapidly accumulating quantities of standardised patient data into clinical guidelines."

standardised patient data into clinical guidelines for increasingly customised interventions, ever more precise care pathways and, ultimately, advanced decision-support tools to inform clinical practice and improve value for defined patient segments over time.[2]

YPSOMED SMART SOLUTIONS

Ypsomed smart solutions empower patients to improve health outcomes, connect stakeholders and support the generation of RWE (Figure 1). They represent an innovative digital ecosystem aimed at transforming therapy management for patients. The multicomponent system connects a patient-facing mobile app to manage therapy, a web portal and related cloud services for analytics and a connected injection device. The Ypsomed smart solutions platform provides a turnkey solution to continuously capture and analyse medication adherence data, drug and dosage data, patient-reported outcomes data and device data. As such, it collects a broad range of RWD, which can be leveraged by healthcare providers, regulators, insurance companies and pharmaceutical companies.

To deliver innovative therapy management solutions, Ypsomed has partnered with leading digital health players such as Sidekick Health (Reykjavik, Iceland) and S3 Connected Health (Dublin, Ireland). By combining their extensive knowledge in self-injection therapies with best-in-class digital capabilities, the companies reduce complexity and offer an integrated device and digital solution. While the therapy management solutions support the patient all along the treatment cycle, they also generate RWE by capturing adherence and dosage data from the connected injection device and patient-reported outcomes (PROs) such as symptoms and mental health status.

These data points are then processed into meaningful and easily accessible information for patients – for example, summarised in an injection logbook to see taken and upcoming doses, as well as previously used injection sites. Further, the PRO data show the treatment progress over time by summarising data from symptom tracking, adherence, wellbeing, sleep and further vital signals.

However, these data points are not only relevant for patients but also provide important information about treatment effectiveness, adherence and drug safety for healthcare professionals and pharmaceutical companies. For this purpose, the Ypsomed smart solutions ecosystem includes a web dashboard for pharmaceutical companies with aggregated adherence and PRO data, which can be leveraged for post-market surveillance and research and development.

By leveraging smart solutions, Ypsomed aims to set an industry standard for embedding connected devices into digital ecosystems. Its solutions are compliant with relevant industry standards and certified for medical device quality system regulations, ensuring seamless integration, improved therapy management and, ultimately, better patient outcomes. At the same time, Ypsomed smart solutions support the generation of RWE and PROs, which can serve all stakeholders in the healthcare system for better value-based healthcare.

The Value of RWE for Pharmaceutical Companies

Many industry reports and consultancy companies argue about the potential of RWE. A white paper from IQVIA[3] defines six areas that generate revenue growth and cost or productivity improvements throughout the product lifecycle. The white paper says the consensus is that RWE offers US$300–450 billion (£241–362 billion) in top-down opportunity for US healthcare alone. It says, at the same time, many life science companies are seeing ad hoc value from selected RWE case studies, often demonstrating as much as $100 million of bottom-up impact. The six value areas of RWE for pharmaceutical companies are as follows:

Improve Clinical Development, Clinical Trial Design and Patient Recruitment: By analysing RWD, pharmaceutical companies can gain insights into patient demographics, disease progression patterns and treatment use, which can aid in patient recruitment and trial planning. This can lead to more efficient and targeted clinical trials, reducing costs and time to market.

Better Market Access and Health Technology Assessments: RWE data is increasingly recognised and used by regulatory agencies and health technology assessment bodies. The result is that products may get to market faster.

Improving Launch Planning and Tracking: Digital health solutions can be used by pharmaceutical companies during the development and pre-launch phase, which allows the collection of the valuable insights needed for launch planning.

Optimising Commercial Spend Effectiveness: Pharmaceutical companies can improve their understanding of patient journeys and market dynamics through using digital health solutions that deliver patient insights and RWE. Marketing and sales departments of pharmaceutical companies can focus on specific points in the patient journey or physician's decision-making process.

Demonstrating Ongoing Safety and Value: Safety and value demonstration studies are the historical domain of RWE, and they drive numerous decisions. This is not just about downside avoidance, but also driving increased product use up to the late stages of a brand's lifecycle.

Increased Productivity and Cost Savings: RWE from digital health solutions may drive not only upside opportunities as outlined above but also significant advances in productivity and cost savings (Figure 2).

Case Study: Illustrating the Value from RWD/RWE Using Ypsomed Smart Solutions

A pharmaceutical company decides to use Ypsomed smart solutions for its cardiovascular drug in development. This allows it to collect precious patient insights such as:

Injection data: The connected autoinjector captures data related to the injection process, such as date, time, injection location, injection technique and factors that influence the proper injection practices. By tracking each injection versus dosing schemes, it allows monitoring and potentially influences therapy adherence.

Symptom tracking data: This feature of the therapy management app allows tracking of patient symptoms, disease flare-ups and changes in the disease condition, allowing timely intervention from the medical team.

PROs: The therapy management app can enable patients to complete PRO questionnaires or surveys that assess their quality of life, functional status or disease-specific outcomes. Collecting PRO data provides insights into treatment effectiveness and patient-reported benefits or limitations.

User feedback and preferences: The therapy management app can enable patients to provide feedback about their experience with the autoinjector, the quality of information delivered, etc. This feedback gives better understanding of the patient experience and helps improve it.

Other types of data agreed during the customisation phase: These can, for example, support different stakeholders involved in the therapy management cycle of the patient.

The pharmaceutical company uses Ypsomed smart solutions during its clinical trial phase, aiming to facilitate collecting longitudinal data from patients for the following purposes:

- Insights collected can guide the pharmaceutical company as to what kind of support to incorporate in its patient-support programmes at launch. This prevents investments in ineffective patient-support activities during the commercial phase.
- The pharmaceutical company can leverage the data to support the regulatory submission, demonstrate real-world effectiveness and safety, and provide additional evidence for the labelling claims. This approach accelerates market access and significantly improves the launch uptake curve.
- RWD and insights collected directly from patients reduce reliance on activities such as primary market research, which are often less scalable, more time consuming and less cost effective.
- Optimisation and customisation of Ypsomed smart solutions to be ready at drug launch to serve the target patient population in the best possible way.

The RWD and RWE delivered through Ypsomed smart solutions allows the pharmaceutical company to monitor the safety and efficacy of its product after it has been approved and launched in the market. By analysing the data, the pharmaceutical company could

Figure 2: Value of RWE for pharmaceutical companies.

"By leveraging RWE, pharmaceutical companies can enhance patient safety, improve treatment outcomes and make more informed decisions throughout the product lifecycle."

identify potential adverse events, drug interactions and long-term safety profiles. This information helps it proactively address any emerging safety concerns, make necessary product modifications and ensure patient safety.

CONCLUSION

Overall, RWE data from digital health solutions offers pharmaceutical companies a comprehensive understanding of how their products perform in real-world settings. This data can inform post-marketing surveillance, support market insights and commercialisation efforts, optimise clinical trial design, and facilitate regulatory submissions and health technology assessments. By leveraging RWE, pharmaceutical companies can enhance patient safety, improve treatment outcomes and make more informed decisions throughout the product lifecycle.

ABOUT THE COMPANY

Ypsomed's comprehensive drug delivery device platforms consist of autoinjectors for prefilled syringes in 1 and 2.25 mL formats, disposable pens for 3 and 1.5 mL cartridges, reusable pen injectors, ready-to-use prefilled wearable patch injectors and injection devices for drugs in dual-chamber cartridges. Unique click-on needles and infusion sets complement the broad self-injection systems product portfolio.

With over 35 years of experience in the development and manufacture of innovative injection systems, Ypsomed is well equipped to tackle digital healthcare challenges and has strategically invested in the development of connected solutions and therapy-agnostic digital device management services.

Anticipating the future needs of patients, pharmaceutical customers, payers and healthcare professionals, Ypsomed moves beyond manufacturing connected sensors. Ypsomed's smart device solutions strive to transform patients' lives by capturing therapy-relevant parameters, processing them to facilitate self-management of chronic diseases and integrating these insights with digital therapy management ecosystems.

The company leverages its in-house capabilities in electronics, software and connectivity for the development of new devices and digital product systems. Ypsomed is ISO 13485 certified and all its processes comply with design control and cGMP guidelines with operational QA/QC experts on-site at each location. Ypsomed's US FDA-registered manufacturing facilities are regularly inspected by pharma customers and regulatory agencies to supply devices for global markets, including the US, Europe, Japan, China and India.

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ABOUT THE AUTHORS

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REIMAGINING AUTOINJECTOR CONNECTIVITY

In this article, Kate Hudson-Farmer, PhD, Drug Delivery Expert, and Simon Hall, Digital Health Expert, both at PA Consulting, discuss a new smartphone-based connectivity solution for autoinjectors that requires no additional hardware and works with most autoinjectors and smartphones.

The rise in treating chronic diseases with biologics over the past 20 years has been significant. This has led to an increase in demand for self-administration of subcutaneous therapies – and a corresponding growth in the development and use of autoinjectors. In recent years, digital connectivity for autoinjectors and other self-administration devices has been seen as the future for improving patient engagement and outcomes.

However, despite this move towards connecting autoinjectors, many organisations fail to create a business case for such devices due to current constraints and risks. This leads to patients missing out on the benefits of a connected drug delivery environment, healthcare professionals missing out on insights into how patients are coping, and a missed learning opportunity for pharmaceutical and medical device companies and the wider science community.

There is a real opportunity for more sustainable, cost-effective, data-rich and device-agnostic connected solutions that support and liberate the pharmaceutical and healthcare sectors from current limitations but also empower and improve quality of life for patients and their carers.

CURRENT AUTOINJECTORS AND CONNECTING THEM

Autoinjectors were primarily devised as devices that help a patient self-administer a prefilled syringe safely and easily. To address ease of use, manufacturing, and industry models, the predominant autoinjector is a disposable, single-use, mechanical, two-step autoinjector. These autoinjectors provide relatively simple feedback to the patient in the form of visual signalling, mainly through the window to view the plunger moving, in addition to mechanical audible clicks to signal injection progress.

The majority of autoinjectors are composed of plastic and metal. In more recent years, connectivity has been achieved by adding on hardware-specific plastic and electronic components that capture data. The purpose of digital connectivity of autoinjectors is to help the patient use the device, record they have taken the

> "An alternative solution that addresses existing market challenges comes from a completely different way of connecting disposable mechanical devices."

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"Where current connected autoinjector solutions are expensive, device specific, introduce more plastic to the environment and only provide limited data, ARinject aims to achieve the exact opposite."

medication, remind them to take it, store a history of medication use and share information. These factors are aimed at ensuring the medication is taken properly and in line with the treatment and dosing regime in a non-clinical setting, primarily in the home environment.

Simplifying Connectivity, the Supply Chain and the Patient Experience

An alternative solution that addresses existing market challenges comes from a completely different way of connecting disposable mechanical devices. Developed by PA Consulting, ARinject™ is a smartphone-based connectivity solution for autoinjectors that requires no additional hardware and works with any type of autoinjector and smartphone. Where current connected autoinjector solutions are expensive, device specific, introduce more plastic to the environment and only provide limited data, ARinject aims to achieve the exact opposite (Table 1).

A patient-centric approach to home-based healthcare

ARinject uses sophisticated image processing, augmented reality techniques and machine learning to offer simple, real-time dosage guidance for patients and their carers. ARinject recognises the autoinjector type, label, cap on/off, autoinjector positioning on injection sites and dosing progression, and incorporates usage notifications and reminders. It also allows for front and rear camera use, eliminating the need to hold the phone, to enable two-handed injector use, if necessary.

ARinject not only captures injection and dosing information to increase patient confidence that they have taken the dose at the right time and day, and records this for future reference, but it also helps guide them through the injection process in real time (Figure 1, next page). This feature could provide both comfort and support to patients unsure of how to inject, in addition to carers gaining confidence – and provide support for more difficult dosing regimens, including during the early stage of a patient's treatment or in clinical trials.

MULTIPLE USE CASES ACCELERATE OPPORTUNITY

ARinject is currently at proof-of-concept stage, with early user studies showing that people can successfully perform a demonstration injection using ARinject. As ARinject is a platform for development, any company with an autoinjector could connect to it and, because no modifications to the autoinjector are required, this approach could be developed for any autoinjectors – whether they are on

	Existing Connected Devices	ARinject
Cost	Add-on devices are expensive to develop – each add-on is specific to a type of disposable autoinjector. Additional manufacturing, storage and distribution is required on top of the disposable autoinjector.	Involves software development only, meaning less cost than hardware and associated software development; no hardware manufacturing, storage and distribution costs. Works with existing commercial and research products and with most autoinjectors without modification.
Time	Regulatory development and manufacturing required to get approved and on market takes several years.	Faster development than hardware solutions; no manufacturing scale up and down; no logistics or component sourcing required.
Sustainability	Add-on devices are composed of plastic, electronics and metal so they deplete natural resources and are not easy to recycle.	Software based so no additional plastic, metal and electronics components to make or dispose of.
Usability	Adding a device to an autoinjector adds extra steps in the injection process. Patients have to store the add-on, remember where it is, add it to the injection device prior to injection, take it off and store it after injection and not accidently throw it away in the sharps bin with the disposable autoinjector.	Only requires a smartphone, no add-on devices to learn how to use and store. Suitable for patients using multiple injectable products – so will not need several different add-on devices. Simplifies usage guidance.
Evidence	Building business cases and return on investment models for connected health solutions relies on data from market examples, which are currently few and far between due to the cost and time to bring them to market. Many companies have also been expected to provide returns based on reimbursement for such connected offerings. However, gaining reimbursement is, again, a difficult proposition as there needs to be a proven example of success first – for example, increased patient outcomes data, such as that pertaining to adherence. Current business models also rely on these solutions being used by large numbers of patients over long periods of time.	Greater flexibility for patient numbers so more easily scalable to gather data to support market propositions.

Table 1: A comparison of ARinject and existing connected devices.

Figure 1: ARinject's image processing captures injection and dosing information and increases patient confidence.

the market in commercial use or in development. Use cases range, therefore, from clinical trials – to help guidance and training for autoinjector use – to on-market products where more training could help certain patient groups and adherence tracking, particularly with small patient groups needing greater support.

The versatility, lower cost and time, and low environmental impact of ARinject aims to revolutionise the way autoinjectors are connected, and the way training and guidance is offered to autoinjector users. By reimagining this market, PA Consulting aims to help open it up and make it faster, cheaper and available to the many rather than the few, so that the question of return on investment and business case are not as prohibitive. Everyone can then start to benefit from the data that comes from these approaches, and patients will have greater engagement opportunities and improved outcomes.

PA Consulting is looking to work with pharma or medical device partners to develop the ARinject in specific use cases for particular indications and autoinjectors. The company is open to discussions on how to proceed with such software developments to create customer specific variants.

ABOUT THE COMPANY

PA Consulting is a global innovation and transformation consultancy with more than 4,000 specialists – strategists, innovators, designers, consultants, digital experts, scientists, engineers and technologists. PA Consulting has over 45 years' experience in the design, development, characterisation and evaluation of drug delivery devices. PA Consulting has dedicated inhaled and parenteral drug delivery teams, covering both conventional and smart connected devices. Services include complete device design and development, human factors studies, device identification, selection and customisation, device strategy, product characterisation, combination product project support, development of custom test equipment, design verification programmes, manufacturing process innovation and transfer to manufacturing.

ABOUT THE AUTHORS

Kate Hudson-Farmer, PhD, has over 20 years' experience in consulting, business development, new product innovation and technology licensing in the pharmaceutical and medical technology industries. Her focus lies in developing solutions that improve patient engagement and outcomes, whilst strengthening competitiveness in the drug delivery market.

Simon Hall is PA Consulting's lead for connected drug devices, digital biomarkers and therapeutics. He has worked in digital healthcare for over 20 years, including healthcare provider, biotech, medtech and pharma sectors. Most of his projects are in neuroscience, oncology and rare disease therapeutic areas.

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COLLABORATIVE INNOVATION IN CONNECTED AUTOINJECTORS: CREATING HIGH-IMPACT ADHERENCE SOLUTIONS

Here, Chelsea Williams, Manager of Digital Healthcare, Nils Weber, Global Head of Emerging Technologies and Digital Health, and Gene Rhode Fuensalida Pantig, Senior Scientific Communications Specialist, all at SHL Medical, discuss the potential of collaborative innovation in connected drug delivery when it comes to creating high-impact, low-touch adherence solutions.

Stakeholder groups – including patients, healthcare providers and payers – all have unique demands and expectations. Patients seek greater convenience and improved quality of life when choosing a treatment modality. For healthcare providers, there is a deep desire to deliver higher quality and more personalised care that requires fewer resources. And for payers, it is critical that adherence levels improve patient outcomes and, in turn, mitigate the lifetime cost of care.

As we continue to witness an irreversible shift in the development of home-based medicines, there is also an increased demand for augmented devices that can monitor the efficacy of such home therapies. With a dramatically increasing number of drugs becoming available in autoinjectors for self-injections, it raises questions about how pharma and medtech can forge better partnerships to design connected therapeutics that aid in treatment adherence and improve patient outcomes. Equally important, such digitalisation should gravitate towards empowering the patient in treatment-related decisions.

DIGITAL HEALTH AND THE EVOLUTION INTO CONNECTED THERAPEUTICS

More than 30 years ago, the US FDA approved the EpiPen (Mylan, part of Viatris, PA, US) for the self-administration of adrenaline (epinephrine) to treat allergic anaphylactic reactions and, since then, autoinjection devices continue to improve the lives of millions of patients across the world. The popularity of autoinjectors for home use surged in the mid-2000s, driven by a dramatic increase in the number of frequently dosed biologics and the patient drive towards at-home care. Notable launches included AbbVie's Humira (adalimumab) and Immunex/Amgen's Enbrel (etanercept), both in 2006.[1]

Much of the success of autoinjectors comes down to a combination of safety, simplicity and convenience, which empowers patients and caregivers to self-administer essential therapies at their chosen time and location, reducing the burden on healthcare clinics and providers. Particularly for those suffering from chronic conditions, these qualities can avoid the need to continually attend healthcare clinics for treatment, liberating their time while also reducing the cost for payers and the burden on the healthcare professionals (HCPs) tasked with optimising the management of their patients' healthcare. Across the world, these factors have helped propel home-based self care to new heights in recent years.

While the pandemic forced a detachment between patients and HCPs, it could be said that it also accelerated the development and implementation of technologies that allow for remote care. For drug delivery

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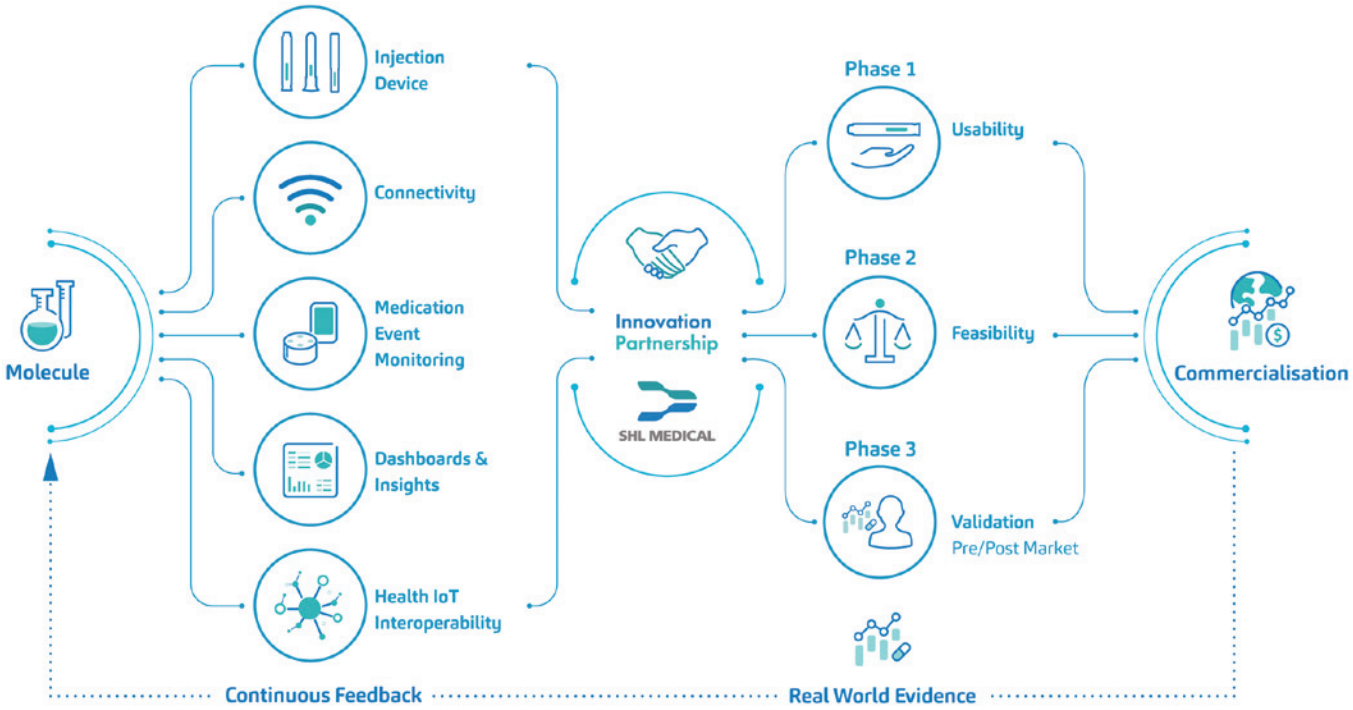

Figure 1: An overview of SHL Medical's Innovation Partnership.

> "The industry is at a crossroads to implement and scale connected solutions that harness the power of digital health."

devices, the use of connectivity is still being explored to uncover its potential. Digital health is complex and there is no one-size-fits-all approach to generating value from connecting and digitalising treatment modalities. However, the stride to health innovation will continue to drive the five Ps in healthcare (i.e. providers, payers, policymakers, pharma and the patient) to better understand the added value digitalisation brings to at-home treatments – and data will be key to this realisation.

With new developments in the space – e.g. more remote clinical visits, the introduction of digital therapeutics (DTx) and prescription DTx (PDT), and regulatory guidance on the implementation of decentralised clinical trials – the industry is at a crossroads to implement and scale connected solutions that harness the power of digital health.[2–4]

Transforming Concepts into Reality Through an Innovation Partnership Framework

To close the gap between conceptual testing and unleashing the real-world value of connected therapeutics, SHL Medical developed the Innovation Partnership Framework. This framework allows SHL and its partners to co-develop connected solutions and evaluate different use cases on a smaller scale through an agile approach (Figure 1). Key to realising this ambition is establishing a collaborative partnership with pharmaceutical and biotechnology partners while fostering knowledge sharing and challenging the status quo. For combination products, such an integrated process ensures that all aspects of a drug-device are considered in parallel, and that the resulting solution creates value that is relevant across the five Ps in healthcare.

Development of the Accompanying Digital and Connected Technology

An important element of SHL Medical's Innovation Partnership is the technology, and through SHL's application expertise, various emerging technologies have been in constant development in recent years. As early as 2016, SHL Medical presented an early connected autoinjector concept – a device featuring a recording unit that logs and transmits injection data.

Also, within the last decade, SHL Medical explored other technological initiatives and has been Innovation Zed's (Dublin, Ireland) official partner for connected pen injector solutions. Through active collaboration, SHL provided its technical expertise to Innovation Zed in the design and development of the InsulCheck family of devices – a range of connected add-on products that support the monitoring of disease management regimens.

One of the learnings from SHL's first connected autoinjector concept was that a suitable connected solution must come with the lowest possible impact on the device, through a so-called low-fidelity product refined through an incremental innovation model. This means that the solution should safeguard ease of use with no extra user steps, circumvent potential regulatory roadblocks for pharma and ensure manufacturability, as well as implement the principles of design for sustainability.

In this context, a clear opportunity for connectivity was identified, building upon the simplicity of SHL's market-proven Molly® modular platform. In particular, the addition of sensing technology and wireless communication would allow a digitally enhanced autoinjector platform to generate and transmit data on patient use and to support improved adherence to therapy regimens without further oversight from HCPs or the patient making additional clinic visits. The ensuing process gave rise to the Molly Connected Cap (Figure 2).

The Molly Connected Cap: Complex Problems Require Simple Solutions

The Molly Connected Cap is a compact, retrofittable autoinjector add-on that records and transmits data on patients' use of the device. Upon cap removal from the Molly device, the Connected Cap becomes active, allowing timestamped data to be relayed through a smart data transmission hub and to the cloud, which provides audio and visual cues to a patient on the timing

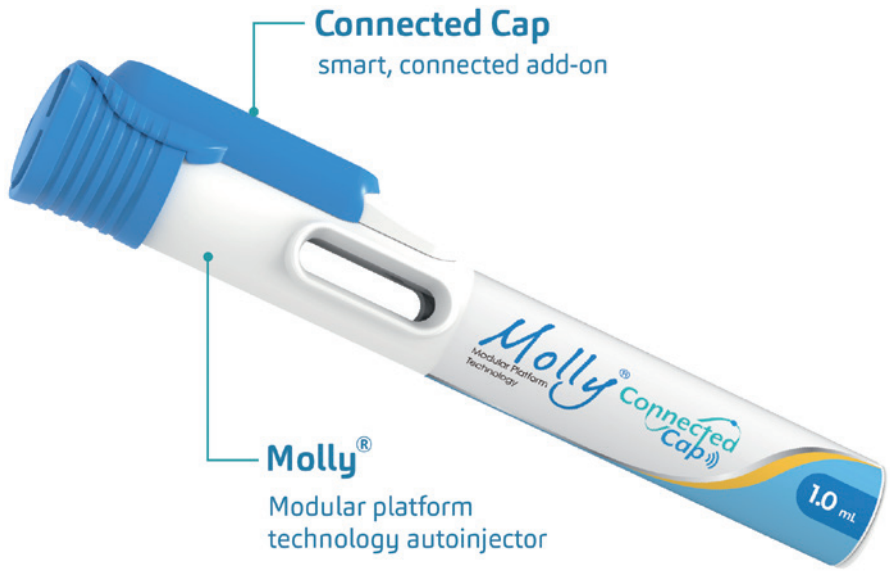

Figure 2: An overview of the Molly Connected Cap – a compact, retrofittable autoinjector add-on that records and transmits data on patients' use of the device.

"All elements were designed to provide patients with an autonomous platform for managing self-injections in line with their therapy regimen."

of forthcoming injections. Accompanying demonstration software, accessed via either a mobile app or web browser, was also developed to further provide patients with an assistive interface to their Molly autoinjector, providing patients with injection reminders, injection history and scheduled injection information.

SHL's Innovation Partnership and Molly Connected Cap in Action

With a strong use case for a connected autoinjector to benefit patients with chronic conditions, SHL Medical established an Innovation Partnership with one of its longstanding pharmaceutical partners, aimed at retrofitting connectivity to a version of its Molly-based autoinjector product in a different injection modality, complete with the associated data-management system and patient software interface. Taken together, all elements were designed to provide patients with an autonomous platform for managing self-injections in line with their therapy regimen.

Having completed the transition from early feasibility to proof of concept, a series of assessments was carried out to validate whether the Connected Cap would, in practice, deliver a user experience to the benefit of patients suffering from chronic neurological, as well as autoimmune and inflammatory, conditions.

A formative usability study, led by SHL Medical in close collaboration with its pharma partner, assessed users' overall interactions with the Connected Cap, with a particular focus on preference, safety and effectiveness. The study also evaluated the concept and design of the entire Connected Cap system for whether the injection reminder, injection recording and injection process satisfied users' needs.[5]

A Look into Real-World Evidence

In one of the studies explored with an Innovation Partner, 31 patients from a mixed age range, gender and disease severity – among other demographics – were recruited in the US Midwest, all of whom had experience with self-administering injections to manage a diagnosis of chronic neurological, as well as autoimmune and inflammatory, conditions. They were asked to perform multiple simulated injections in each of three separate scenarios: only using a Molly autoinjector (use scenario A); Molly + Connected Cap + mobile app platform (use scenario B); and Molly + Connected Cap + smart data transmission hub (use scenario C). Scenarios were counterbalanced to minimise instruction bias.

Putting the study design and primary test materials into context requires an explanation of the Molly Connected Cap architecture. The Molly Connected Cap implements a wireless mode of connection powered by a Bluetooth Low Energy beacon. Its proprietary firmware is programmed to facilitate the seamless, encrypted transfer of data from the Connected Cap, either to a smartphone or a smart data transmission hub. From the smartphone or the smart data transmission hub, a cascade of data transmission is triggered – using Long-Term Evolution wireless broadband communication – with an encryption algorithm in place. In real scenarios, this means that the usual injection process is unchanged and, in the case of using the smart data transmission hub, connecting the module to a power source is the only extra step prior to injection.

Taken together, it could be said that the confluence of the many relevant factors might have affected the turnout of usability data and overall patient preference. For one, the use of the mobile app and smart data transmission hub were accessories integrated into the simulated injection process experience. In detail, scenario B required patient interaction with the Connected Cap and the mobile app, where it could be assumed that the general population is accustomed to operating smartphones and apps. For scenario C, patients interacted with an entirely new accessory, wherein the light indicator on the smart data transmission hub would flash to signify an injection reminder. This feedback lighting is coupled with a text message reminder triggered by the two-way communication feature (bidirectional data transmission) of the hub.

As an extra layer, a post-task interview was designed to elicit subjective data based on the patient's experience of using the equipment. For the study, participants were provided with a set of prepared test materials to avoid any complications with software downloads or data transfer; they were also allowed to complete a training activity, which provided an opportunity to carry out a test injection using training equipment prior to the official simulation tasks. All the needle-based injection systems, in both the training and official tests, were activated on a pad; no self-injections were carried out as part of the project.

Each simulated injection was evaluated objectively and graded according to specific criteria. To simplify the analysis

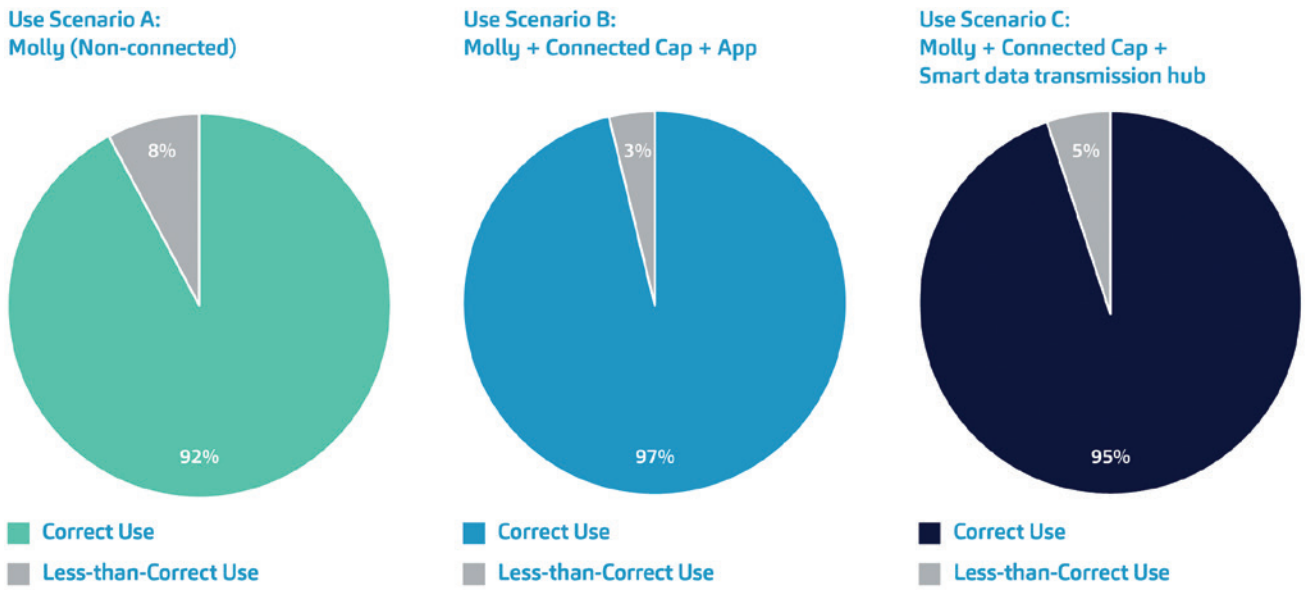

Figure 3: Summary of the formative usability study data. Users with chronic neurological, as well as autoimmune and inflammatory conditions were asked to simulate injections with the Molly autoinjector (use scenario A), Molly + Connected Cap + mobile app platform (use scenario B) and Molly + Connected Cap + smart data transmission hub (use scenario C).

(Figure 3), these criteria were grouped into either "correct use" or "less-than-correct use", with the latter incorporating instances defined as "user error". Across all three injection scenarios and all age ranges, participants used the equipment correctly in more than 92% of cases. This figure was highest (97%) for use scenario B. In total, recorded instances of less-than-correct use were 4.96% across all scenarios.

On the other hand, the subjective data (Figure 4) revealed no difference between concept-use scenarios A, B and C for ease of injection, with both Molly only (A) and all Molly + Connected Cap (B + C) scenarios registering 4.6 out of a possible 5. There was also a negligible difference recorded in the perceived force required to remove the device cap in each of these scenarios, with participants explaining that this action became easier over time as they became more familiar with the device. For many participants, this was their first interaction with a two-step autoinjector.

Overall, the Molly + Connected Cap + mobile app platform was the most preferred scenario (concept-use scenario B) among 48% of the study participants. Among the beneficial features cited were convenience, scheduling of reminders, automatic logging of injections and the ability to verify adherence. A total of 35% of the participants found the Molly-only scenario (concept-use scenario A) familiar and simple, while the Molly + Connected Cap + smart data transmission hub (concept-use scenario C) was the least preferred due to the requirement and potential burden of needing additional equipment.

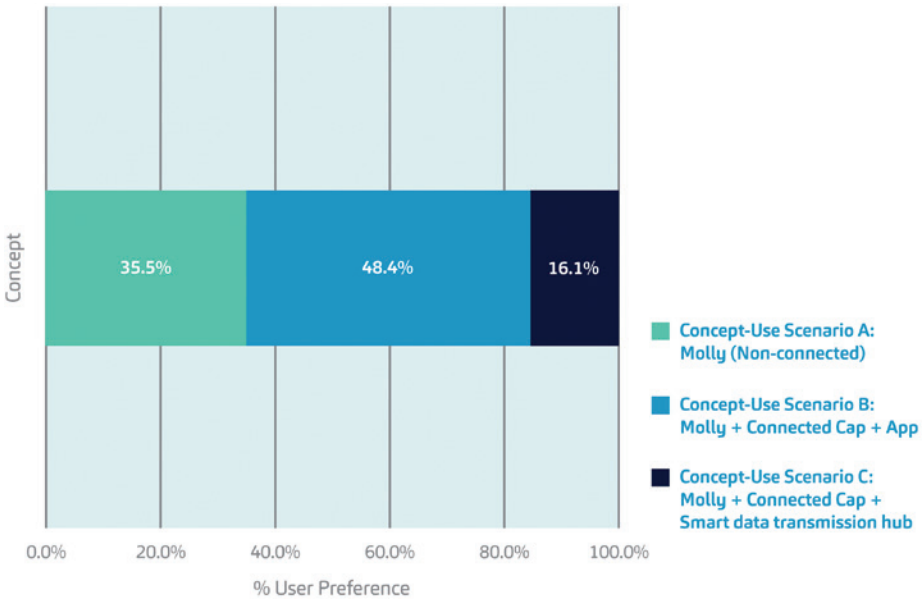

Figure 4: A readout of the overall preference rankings of the study participants for the concept-use scenarios employed in the formative usability study.

The Impact of Harnessing the Power of Data

The formative study results affirm the idea that the Molly Connected Cap offers key distinctive advantages. For one, it provides patients with a standalone solution for managing their self-injections, reducing the need for frequent clinic visits and empowering patients to take control of their treatment. The visual and reminder cues provided by the smart hub and mobile app help patients adhere to their therapy regimen and ensure they receive their injections at the right time.

As a connected therapeutics platform (i.e. the Molly autoinjector, together with the Connected Cap, the smart data transmission hub, the app and the cloud), it enables healthcare providers – among other stakeholders – to monitor patient adherence remotely and intervene when necessary. Also, care providers and contract research organisations (CROs) have the opportunity to review patients' injection histories, identify any deviations or missed doses, and provide timely support or adjustments to treatment plans. The platform improves the personalisation and efficiency of healthcare delivery, reduces the burden on HCPs, and produces a higher level of self-efficacy and engagement among patients.

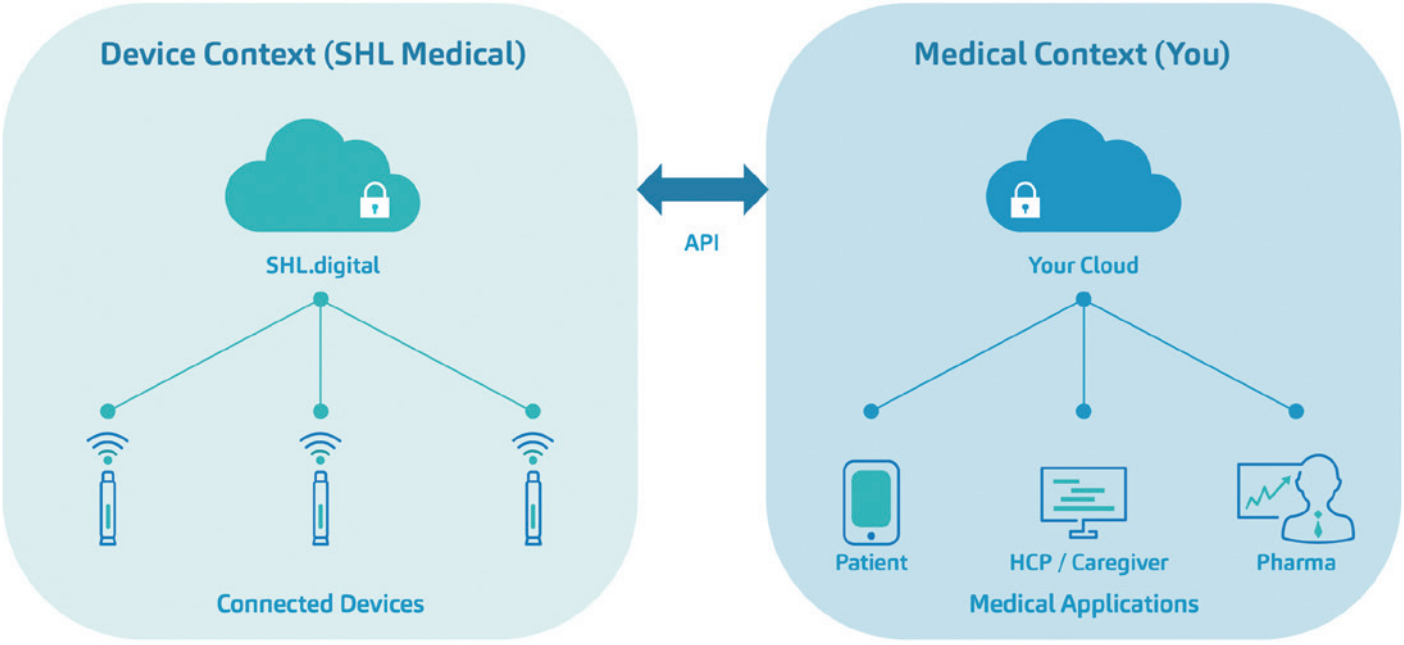

Figure 5: Device-driven solutions towards connected health – such as the Molly Connected Cap – facilitate the seamless integration of autoinjector combination products with an interoperable digital ecosystem.

The data collected by the Connected Cap opens up new possibilities for pharma and biotech companies to conduct real-world evidence studies and gather post-marketing insights. By analysing aggregated data on device use, medication use (e.g. Rx refills, drug shelf life and expiration), adherence rates, behavioural patterns and patient-reported outcomes, healthcare stakeholders can evaluate the effectiveness of therapies in real-world settings, identify areas for improvement, generate evidence to support reimbursement discussions with payors and identify potential hotspots for use patterns (e.g. looking into regions that suffer from minimal health literacy versus looking into health equity on a larger scale).

SHL's most recent Innovation Partnership demonstrates the power of collaboration between pharma and medtech in the development of connected combination products. The flux of expertise and resources from both sides is closing the gap in care, in turn addressing the unmet needs of therapy self-management. Partnering early on can help accelerate the development and eventual commercialisation of connected therapeutics.

A PRESENT SOLUTION TOWARDS A BETTER-CONNECTED FUTURE

Technology such as the Connected Cap has real potential to address patient-related issues, tackling poor adherence and filling the information void with valuable data on medicine use. Importantly, the success of these studies also highlights how digital solutions do not necessarily require pharmaceutical companies to pursue risk-laden product developments from the ground up. Instead, the ability to digitalise existing, proven technologies – augmenting them through connectivity and complementary data-management systems – can open up new opportunities comparatively rapidly and with lower risk.

A layered approach to exploring the potentials of digital health – such as through the SHL Innovation Partnership Framework and the Molly Connected Cap – serves as a compelling example of how connectivity can be integrated into existing devices to provide a wealth of valuable data. A supporting device ecosystem (Figure 5) can ease the transition to connected therapeutics. Of equal importance, the results of SHL's recent Innovation Partnership have also shown that collaborative frameworks can help generate meaningful data for pharmaceutical companies to better harness the power of digital health.

SHL is in active partnerships with pharma, clinical, R&D, HCP and patient groups to identify what the value of connectivity means for each segment. With an Innovation Partnership Framework designed to facilitate various connected therapeutics programmes in parallel, SHL will continue to support the success of connected device piloting programmes and exploratory studies as a low-commitment, high-data-generation approach to power through digital health and connected therapeutics.

ABOUT THE COMPANY

SHL Medical is a solutions provider in the design, development and manufacturing of advanced drug delivery devices, such as autoinjectors and pen injectors. The company also provides final assembly, labelling and packaging services for leading pharmaceutical and biotech companies across the globe. With locations in Switzerland, Taiwan, Sweden and the US, SHL Medical has successfully built a strong international team of experts that develops breakthrough drug delivery solutions for pharma and biotech customers. These include advanced reusable and disposable injection systems that can accommodate large-volume and high-viscosity formulations – and connected device technologies for next-generation healthcare.

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Chelsea Williams is a Manager of Digital Healthcare at SHL Medical, focusing on digital healthcare innovation and healthcare service delivery. She brings nearly a decade of experience in healthcare technology services, from both health IT and government contracting industries. Prior to joining SHL Medical, Ms Williams provided support for large-scale projects for the Centers for Medicare and Medicaid Services and the Office of Medicare Hearings and Appeals in the US. She gained a master's degree in Global Health Program Design, Monitoring and Evaluation from the George Washington University (Washington DC, US).

Nils Weber joined SHL Medical as its Global Head of Emerging Technologies and Digital Health. In assuming this new leadership role, he leads and manages various global teams that actively develop products outside the core business of autoinjectors. Mr Weber is entrusted with further developing the company's technological vision and strategy as well as managing the overall emerging technologies and digital health product and service portfolio. He holds a bachelor's degree in Microtechnics and a master's degree in Telecommunication from the EPFL Lausanne (Switzerland) and Eurecom (Biot, France). He also holds an MBA from the NYU Stern School of Business (New York, US).

Gene Rhode Fuensalida Pantig is a resident molecular biologist and pharmacist at SHL, most recently leading efforts in scientific communications and thought leadership. In his role in the growth organisation, he has been working with an expanding network of SMEs over the years to cement SHL's industry thought leadership. He is also an active member of PDA since 2021, where he leads the delivery of SHL's scientific communications at the PDA conferences along with other industry events. Prior to joining SHL, he worked as a full-time researcher in the Institute of Molecular Biology at Academia Sinica, Taiwan's national academy. He is trained in classic molecular biology techniques, having worked with Dr Sue Lin-Chao – whose mentor is Dr Stanley Norman Cohen, developer of genetic engineering methods still used today in the field of biologics.

gerresheimer

DIGITAL TWIN IN THE PHARMACEUTICAL SUPPLY CHAIN

In this article, Ali Badiei, Digital Solution Lead at Gerresheimer, explains the role of digital twin technology and its integration into the pharmaceutical supply chain, highlighting Gerresheimer's innovative approach to ensuring drug identity and quality.

The pharmaceutical supply chain has grown increasingly complex over time, necessitating strict adherence to safety and efficacy standards. As stakeholders in the healthcare industry search for innovative solutions to address these challenges, Gerresheimer, a leading provider of healthcare solutions and drug delivery systems, is pioneering the integration of digital twin technology into the pharmaceutical supply chain. Currently, the supply chain experiences data fragmentation, with information stored in isolated silos. However, modern digital technologies and innovative partner ecosystems have the potential to securely connect all supply chain participants, creating a cohesive and trustworthy supply network.

DIGITAL TWIN TECHNOLOGY IN THE PHARMACEUTICAL SUPPLY CHAIN

Gerresheimer is working to revolutionise its primary packaging by transforming it into a secure gateway to access digital twins. A digital twin is a virtual representation of a physical asset at a specific point in a process. By mirroring processes such as manufacturing steps and creating a virtual replica of an asset, like a syringe, it becomes possible to digitally trace an asset's journey from its inception to the end of its lifecycle. This approach enables multiple stakeholders along the value chain to securely track the product's current status and determine its true identity by digitally tracing its origin.

The benefits of digital twin technology include quality improvements throughout the supply chain and easy access to certifications issued at various stages of the process. Additionally, it helps combat counterfeiting in the highly sensitive pharmaceutical market, enabling secure and instant identification of drugs to be administered at the point of care. It also establishes a high-quality logistics chain where all items can be tracked. This enables faster root-cause analysis in the case of quality issues, as well as efficient limitation of a problem to the affected containers. A digital twin of the primary packaging will also support the prevention of mix-ups at filling operations by automatically comparing data from different production steps. This comprehensive list of benefits not only enhances the overall quality of future drug delivery but also reduces costs associated with cumbersome quality checks. It mitigates negative consequences, such as major recalls of expensive drugs or drug delivery systems.

> "The benefits of digital twin technology include quality improvements throughout the supply chain and easy access to certifications issued at various stages of the process."

This article will explore a concrete example of how digital twin technology can be applied from manufacturing prefilled syringes (PFSs) to administering high-quality medications. A traceability solution that demonstrates the benefits mentioned above will also be presented (Figure 1).

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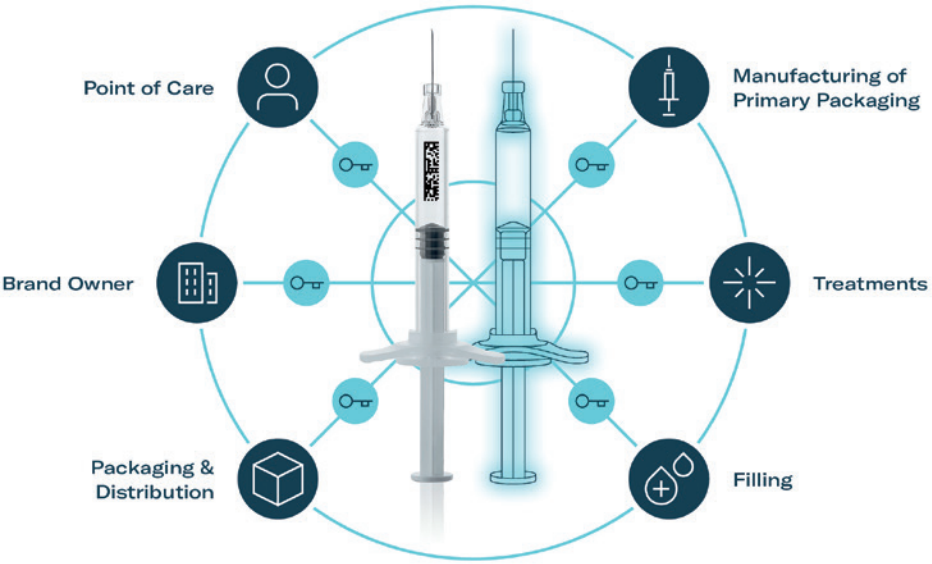


Figure 1: Digital twin in the centre of the pharmaceutical supply chain.

UNDERLYING TECHNOLOGIES FOR DIGITAL TWIN IMPLEMENTATION

To create a future-proof platform on which every company in the value chain can contribute data, Gerresheimer has partnered with Merck to develop a framework based on blockchain technology. This approach enables a zero-trust level of security for creating and adding virtual assets, eliminating the need for numerous intermediaries to control data flow. The resulting data, such as the identity of the medication or the specifications of the delivery system, serve as a "single source of truth" along the value chain.

Initially, selecting a physical asset in the supply chain and determining how it will be identified are crucial steps in creating digital twins. As illustrated in Figure 2, primary packaging, such as a prefilled syringe, is an ideal candidate for virtualisation as it is the only container that "travels" along the whole supply chain from production to the point of care. Unique identification is achieved through secure and tamper-proof marking of the asset, using methods like printed data matrices or embedded radio frequency identification (RFID) tags. The data matrix contains a unique identifier (UID), similar to serial numbers, which represents an individual physical asset or batch without revealing any details. Ensuring the authenticity of an asset's UID is also necessary, and a so-called crypto anchor is used to securely link the UID to a physical asset, preventing cloning or forgery and unauthorised transfer.

When an asset receives its UID and crypto anchor during the production process (e.g. through printing straight after forming the glass body), all relevant identity data, such as physical specifications or batch information, can be digitally connected with its virtual replica on the blockchain-based decentralised data platform. The digital twin of the asset is then officially created in the chain, thereby establishing a highly secure identity. As the physical asset, such as a syringe, moves to the next player in the chain (e.g. a pharmaceutical company filling the syringe), a new information block with relevant data can be added. The addition of blocks with enriched data by new stakeholders throughout the value chain contributes to overall benefits for all parties while increasing their accountability for managing their data.

A blockchain-based information management system offers several advantages. In comparison with other

Figure 2: Unique identification on primary packaging.

> "The decentralised nature of a blockchain allows members to have an exact copy of the chain."

technologies, blockchains offer high security, interoperability and easy scaling across many parties. In fact, the blocks (containing data) are immutable; it is only possible to create and add new blocks (data) to the chain. Each block's authenticity is secured through the so-called hash of the previous block, ensuring that the data chain cannot be tampered with. Traceability of information back to the creation of a block is possible, and data access depends on the authorisation rights of the stakeholder accessing the data, guaranteeing data integrity.

Additionally, the decentralised nature of a blockchain allows members to have an exact copy of the chain. Transactions within a blockchain are typically handled through tokens, which function as the chain's currency. Smart contracts facilitate self-executing transactions based on predefined rules and can be used to automate business transactions.

Due to its peer-to-peer and distributed network topology, blockchain technology offers a secure, efficient and fast means of data transaction in a decentralised manner without intermediaries that control the data flow of others. Permissioned or private blockchains, which are more common in

supply chain applications, enable simpler consensus mechanisms, allowing fewer known participants to add new data blocks compared with public blockchains. Private chains are often employed to increase throughput, reduce cost and increase privacy.

THE DIGITAL JOURNEY OF A PREFILLED SYRINGE

Gerresheimer, a leading manufacturer of prefillable syringes, conducted a field trial to explore the implementation of digital twin technology in the pharmaceutical supply chain. By using advanced data-marking techniques, a physical syringe was labelled with a UID using a data matrix code compliant with ISO/IEC 16022 standards. This label underwent rigorous testing to ensure it met pharmaceutical manufacturing requirements, including durability in extreme temperatures, resistance to chemical agents and tamper-proof properties. Additionally, an embedded security code (crypto anchor) was incorporated to enable identity verification.

At this stage, the physical syringe can be linked to its virtual replica, or digital twin, containing relevant manufacturing information, such as specifications and quality data, like the certificate of analysis. This initial information forms the first data block in the blockchain system, with Gerresheimer acting as the first manufacturer in the chain. Suppliers may contribute data or certificates in the future, and the information about the physical syringe, identifiable through its UID, can be securely accessed by new stakeholders in the chain.

In a preliminary use case, Merck developed an easy-to-use mobile application on the M2M Trust Framework. The application is based on decentralised blockchain technology and can read the syringe's UID and verify it by scanning the invisible crypto anchor. The app enables pharmaceutical firms that fill the syringe with medication to instantly confirm that all manufacturing and quality requirements have been met, significantly enhancing the efficiency of quality control and audits (Figure 3). Furthermore, pharmaceutical firms can promptly file complaints if irregularities are detected on the syringe, as the app provides the exact manufacturing specifications and batch information. This streamlined process reduces the effort required to identify the root cause of a complaint, enables faster feedback, helps avoid stockpiling batches with suspected quality issues and even prevents recalls.

Ongoing development of additional use cases and integration of advanced technologies, such as RFID for the UID in various drug delivery systems, continues to expand the digital twin ecosystem. As more partners and players join, the following benefits can be realised along the value chain:

- Improving overall quality, reducing complaint handling processes and minimising recalls
- Avoiding batch mix-ups of filled containers and enhancing batch segregation during and after the fill-finish process
- Increasing sustainability by enabling recycling and waste reduction, resulting in a positive environmental impact
- Contributing to a patient-centric pharmaceutical supply chain by allowing point-of-care facilities to instantly and securely identify the medication and support global anticounterfeiting efforts.

> "At this stage, the physical syringe can be linked to its virtual replica, or digital twin, containing relevant manufacturing information, such as specifications and quality data, like the certificate of analysis."

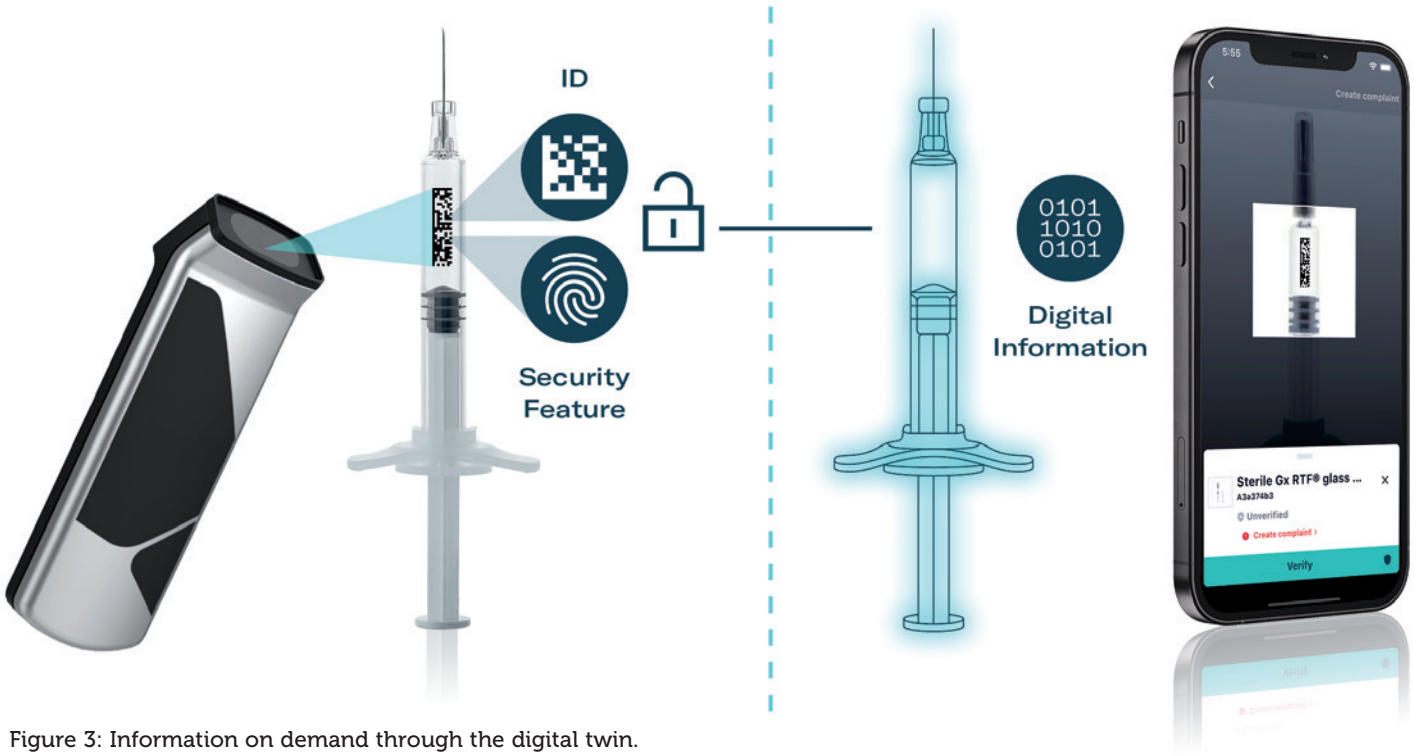


Figure 3: Information on demand through the digital twin.

FUTURE-PROOF PARTNER ECOSYSTEMS AND INNOVATIONS ON THE HORIZON

Partnerships are vital for success in creating digital ecosystems. Merck and Gerresheimer are collaborating to develop a digital twin solution that enhances traceability and trust in critical steps along the pharmaceutical supply chain. Gerresheimer is committed to contributing to a patient-centric and reliable pharmaceutical supply chain by driving digitalisation using advanced technology and trusted partnerships.

> "Gerresheimer is committed to contributing to a patient-centric and reliable pharmaceutical supply chain by driving digitalisation."

As a company known for offering one of the broadest product portfolios in the market, Gerresheimer also develops various technologies for identifying its products. The company believes that different products and use cases will require distinct marking technologies. Gerresheimer has a proven digital printing infrastructure ready for sample production and is working at full speed to implement RFID for selected products, such as prefillable syringes.

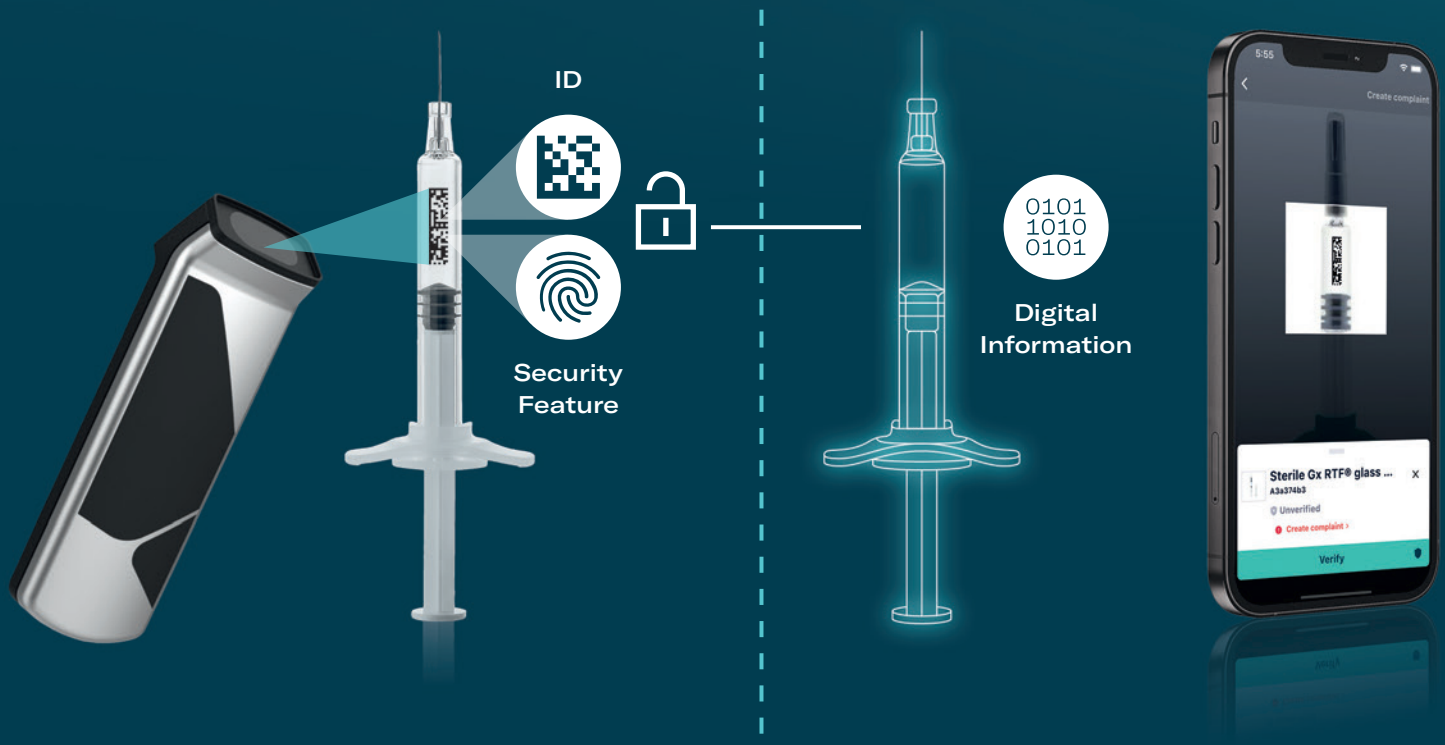
ABOUT THE COMPANY

Gerresheimer is the global partner for pharmaceutics, biotech, healthcare and cosmetics with a very broad product range of packaging solutions and drug delivery systems. The company is an innovative solution provider from concept to delivery of the end product. Gerresheimer achieves its ambitious goals through a high level of innovative strength, industrial competence and concentration on quality and customer focus. In developing innovative and sustainable solutions, Gerresheimer relies on a comprehensive international network with numerous innovation and production centres in Europe, America and Asia. Gerresheimer produces close to its customers worldwide with around 11,000 employees and generated annual revenues in 2022 of €1.82 billion (£1.6 billion). With its products and solutions, Gerresheimer plays an essential role in people's health and wellbeing.

ABOUT THE AUTHOR

Ali Badiei is a Digital Solution Lead at Gerresheimer's Digital Hub & Innovation. With passion and extensive experience around developing and managing digital products and services in different industries, he leads the traceability solution across different teams at Gerresheimer Group. He holds an MSc in Computer Science and Engineering and an MBA from SBS Swiss Business School (Kloten, Switzerland).

Primary packaging solution and its digital twin



Trustworthy information flow along the pharmaceutical supply chain

The Gerresheimer traceability concept ensures transparency throughout the value chain and greater safety for the patient in a secure way. By applying unique codes to our primary packaging and medical devices and utilizing our digital infrastructure, all authorized supply chain participants can share or add data to the digital twin of each individual item.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