BILL WELCH, PHILLIPS-MEDISIZE & JOHN PATTON, DANCE BIOPHARM

Bill Welch has over 25 years of contract design, development and manufacturing experience, primarily serving customers in the drug delivery, health technology and diagnostics markets. In his current capacity as Chief Technical Officer at Phillips-Medisize, he leads a global development, engineering, tooling, programme management and validation organisation of over 500 people, with more than 75 concurrent schemes. Mr Welch has been with Phillips-Medisize since 2002.

John Patton began Dance Biopharm in 2010 with a carefully selected core team. Previously, he was the co-founder of Inhale Therapeutics (now Nektar Therapeutics), where he helped lead the development and US FDA approval of the first inhaled insulin product. Prior to founding Inhale, Patton led the drug delivery group at Genentech from 1985-1990. Before that time, he was a tenured professor at the University of Georgia. Dr Patton was the founding investor in Halozyme Therapeutics, a co-founder of Incarda Therapeutics and has served as a member of the board of directors of Activaero.

In this exclusive interview with *ONdrugDelivery Magazine*, Bill Welch and John Patton discuss inhaled insulin, connectivity and their two companies' close partnership, under which Phillips-Medisize, a Molex Company, provides manufacturing and large-scale industrialisation services for Dance's inhaled insulin products, also encompassing, under a major expansion of the agreement in December 2017, the provision of connectivity. In October 2018, after this interview was conducted, the companies announced Phillips-Medisize Chief Executive Officer Matt Jennings' appointment to Dance's Board of Directors, thus deepening the relationship still further.

Q Cutting straight to the quick, Dance Biopharm's inhaled insulin delivery device, Dance-501, comes in the wake of the withdrawal of the (at the time) only approved inhaled insulin product, Exubera, back in October 2007. What is different with Dance-501? Do the same challenges that thwarted Exubera still exist, and how does Dance-501 overcome them?

JP Dance-501 (Figure 1) is very different from Exubera. Exubera was the star product of the company I first co-founded. It won many technical awards and the Wall Street Journal's medical innovation of the year in 2006, it was as reliable as injection. We were very proud of Exubera. It did have its drawbacks, however, and one of them was connected with the fact that the manufacturing and packaging of the powders was very expensive. One-of-a-kind manufacturing facilities had to be made. The moisture barrier for powders is very technically challenging. Putting it in small blister packs, we had to develop a whole suite of new technologies. Then, powders by their nature can induce cough. This wasn't a major problem with Exubera, but it was a side-effect.

The other thing was that the original device, which was approved, was a large device. It took a lot of abuse online, people called it "the bong", said it was the size of a tennis-ball can, and so forth. Patients didn't really mind it, and we had a much smaller second-generation device in development.

However, while we were developing this powder product we were looking at all of the other inhaled insulin possibilities – the other types of technology. We went to a CRO over in Germany called Profil that specialises in insulin PK/PD studies and asked: "You've tested all types of inhalers, MDIs, DPIs etc. Which type do patients like the best?" Without hesitation the reply was: "The vibrating mesh from Aerogen. It's a soft, gentle mist." That always stuck with me. Then after Exubera was recalled and my company decided not to pursue it, I founded Dance and licensed that vibrating mesh technology for insulin.

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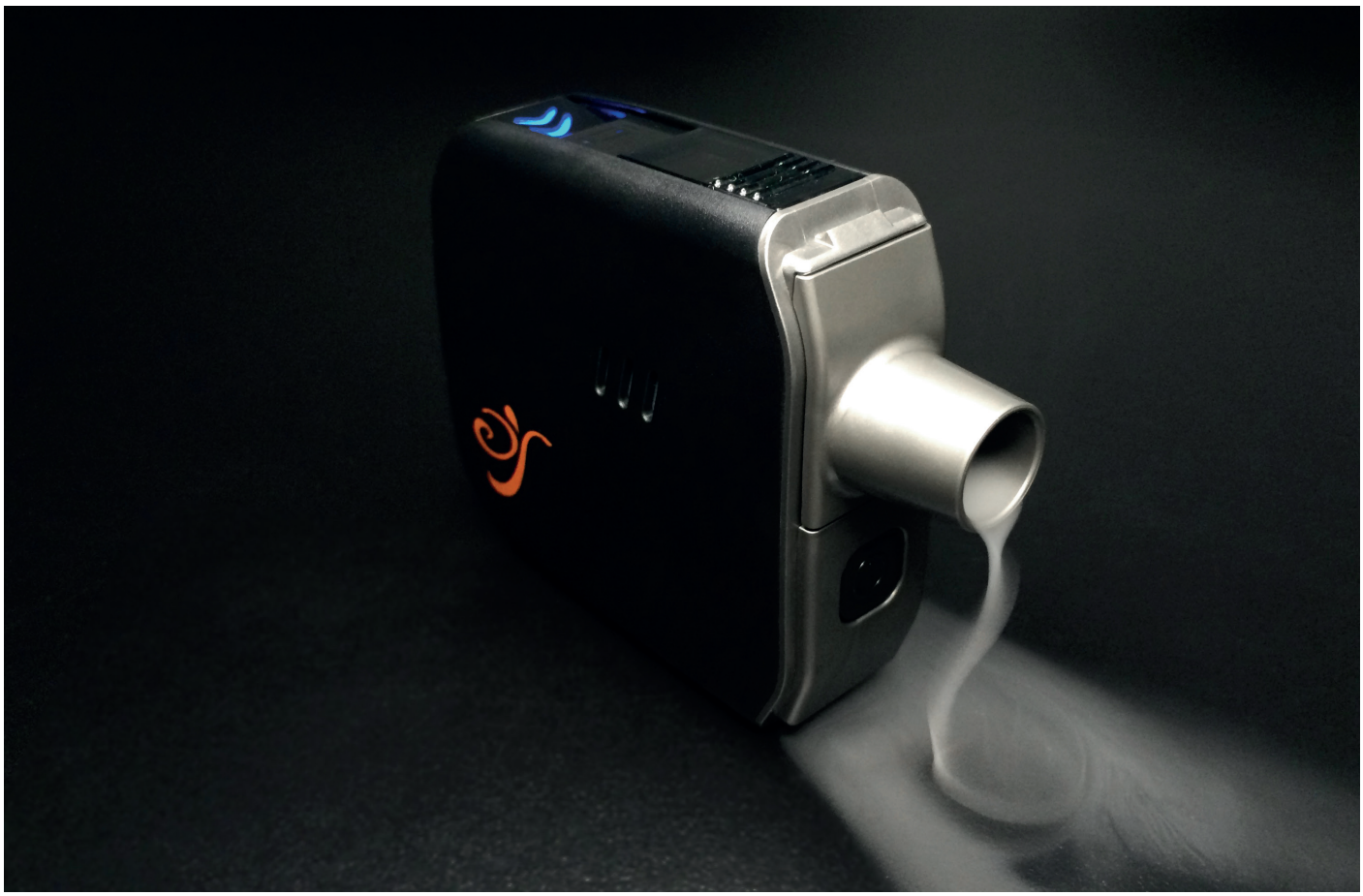

Figure 1: The Dance-501 insulin inhaler uses a vibrating mesh to create a soft mist.

Dance-501 generates a liquid, aqueous mist. The patient loads the inhaler from a sterile, preservative-free insulin dropper. It's a durable inhaler, manufactured for us by Phillips-Medisize.

We've spent a lot of time working on the formulation. We have two formulation chemists, Mei-chang Kuo, PhD, and Blaine Bueche, PhD, and these guys collectively have 37 years of insulin formulation experience, both dry powder and liquid. They've come up with this marvellous high-purity soft mist from which there's virtually no cough.

There was another product approved in addition to Exubera and that's the one that's on the market now – Mannkind's Afrezza. It's also a dry powder, and both Exubera and Afrezza need to be packaged in unit-dose blister packs or cartridges. That means, for most people, they often need to use multiple blister packs to get their dose. These powder devices are like single-shot guns. You have to load the gun (load the cartridge), cock it (puncture the blister pack), fire it (inhale the dose), take the spent cartridge out, put another in, and repeat that process in a serial way to achieve the required dose.

The device that we have is designed to last for at least a year and the patient adjusts their dose by adding the required number of drops of liquid insulin formulation from the drop dispenser into the inhaler (shown in Figure 1). The drops can be placed in a matter of seconds. So it's a much faster, easier device to load. It's silent and low cost. The six-month toxicology that we've looked at is squeaky clean and in preliminary tests in humans we are seeing virtually no cough.

Dance-501 is really very different. It's smaller, far easier to manufacture, and as lung-friendly as we can make it.

BW I see three main areas that devices have changed in the last couple of decades. First, the emergence of biologics has driven a need for more devices, including more therapy-specific solutions. This leads to the second area, which is that with more products out there, there's an increased need for innovation to differentiate from numerous other competitors. By this I mean using the device to help differentiate the drug and that really means looking to go beyond the original inhalation devices and patents the device industry has been based on. Third, and I see this as the most important, there is a drive towards smarter and more intuitive devices. That includes connectivity, merging the device aspects of connectivity with full solutions that include digital interfaces and cloud-based database management, with the full intent of driving patient engagement and improved adherence.

Pulling all this together, how does it relate to inhaled insulin today? There's a diabetes epidemic taking place worldwide, not just in Europe and North America. If we take a look at what's happening in Asia, the numbers are staggering. Having better delivery systems that can drive patient engagement and adherence is really going to be the key to improving outcomes for those patients.

JP Approximately half of all new medicines are new dosage forms, new delivery systems for old molecules. That's kind of amazing when you think about it, that there are so many different products you can get out of one molecule, using different types of delivery systems. As Bill said, the devices are becoming more sophisticated, connected, cooler I think.

"It's a different world now. It's a new day for inhaled insulin and we think we're very well positioned to take advantage of that."

The need for inhaled insulin remains enormous. Fundamentally, people just don't like sticking themselves with needles. There are a few who do, I guess, but the vast majority do not. They don't like it. Avoiding needles has always been the Holy Grail in drug delivery.

While you can use drug delivery systems to create numerous products with one molecule, what you cannot do is charge too much. You can't have an expensive drug delivery system for a previously less expensive drug, unless you improve efficacy significantly. This is a key element with Dance-501. We have got to be competitive with injection, the same price or lower, unless we can show that our product is so superior medically that it justifies a higher price. One of the reasons Pfizer stumbled and had a poor launch with Exubera was that they felt they could price at a premium, but really there was no justification for it. We take that off the board with Dance. This applies more generally too, thinking in terms of the future of drug delivery, you cannot add too much cost.

Some of the challenges we faced 25 years ago still exist, but others we have really put to bed. For example, the safety and efficacy of inhaled insulin has been studied exhaustively, not only by Pfizer in our Exubera programme but also by Novo Nordisk, Lilly and others. Collectively, the published scientific output from these numerous studies form a unified database on safety and efficacy, with more than 10000 patient years of exposure. We are not being asked to repeat all of that. We do have to show some significant safety data, but the amount of money, time and effort that has already been spent on very good science means we are standing on the shoulders of that. We're able to leverage all of the previous work primarily because we've not added new excipients to our formulation, and the small amounts of excipients we do have in our products are found naturally in the lungs and other inhaled products in large quantities, so there are fewer safety concerns about them. In our ongoing discussions with the EMA and US FDA about our development programme we do not need to repeat everything done before.

The other challenge is that three major pharma companies have dominated insulin product sales in all countries, whether it be with pumps, pens or the old-style vial and syringe, it's all still invasive injected insulin with them. They have considered inhaled insulin but remain resistant to it. But their dominance of the insulin market is crumbling under their feet. With price controls, no non-invasive insulins on the horizon except inhaled, patents expiring, the emergence of biosimilars and other players being able to come into the field, the dominant insulin players will be forced to consider inhaled insulin again or let their markets dwindle.

Overcoming that original challenge has been really hard. If you remember, as soon as Pfizer dropped out, Lily and Novo dropped their advanced inhaled insulin programmes like hot potatoes. The costs of goods in those programmes were not as good as with injections and integrating that into their business was going to be complicated. It's a shame that we have this history, as most patients clearly prefer inhaled insulin over injections. But it's a different world now. It's a new day for inhaled insulin and we think we're very well positioned to take advantage of that.

Q **Last December PMC and Dance entered into an exciting, major partnership. Please could you describe the scope and objectives of the deal itself and talk about how the agreement came about?**

JP This is really a marvellous deal that we've struck with Phillips-Medisize. We've been working with them for a number of years. Before partnering, we conducted a thorough diligence project on the other companies that are out there. They were all world class. We ended up with about ten we were talking with and Phillips-Medisize really won us over, hands-down. It wasn't like there were just two or three companies we had to decide upon.

The scope initially was fairly limited, sort of a starter manufacturing relationship, and they performed so well for us that we were very happy to broaden this to Phillips-Medisize being our partner not only for Dance-501 but for future devices, to be our industrialisation and large-scale manufacturing partner.

And now Phillips-Medisize has brought connectivity to us. We always wanted to connect our device but previously it just seemed like it was going to be very complicated and we should "keep it simple, stupid" as they say. We thought let's get the device out there and we'll connect it later. Now, this partnership gives us the opportunity to wade right into this new field. It's very exciting, there is a lot of potential. This is the best partnership we could have for our device and we're very happy.

I don't know how Phillips-Medisize does this but they don't get bogged down with bureaucracy and overdoing things. They just get the things done that need to be done. A lot of large organisations increase the service to try to increase the money that they can make. It sounds counter-intuitive but that's really going in the wrong direction and what you really want to do is keep things streamlined and simple. When you do that, things begin to flow. That's what we have with Phillips-Medisize.

BW We have had a strong partnership on the base device for several years with Dance Biopharm, and Phillips-Medisize has a world-leading position in connected devices, digital interfaces and connected health services. As a reference you can look at the ground-breaking approval of the Bayer Betaconnect device [Betaseron® (interferon beta-1b) for multiple sclerosis] last year.

So, given that existing partnership, and our experience in connected health, it made sense to expand our partnership in this way. We'll be working with Dance on any engineering changes for connectivity, clinical supply and higher-volume manufacturing when that time comes. Additionally we've made significant investments in our connected health offerings and we're very excited to partner with Dance to go beyond the innovative Dance device into digital services that will help Dance's patients.

Q **Thinking about the connected device that the partnership will develop, what are the major technical, regulatory and market challenges and requirements that this project will face?**

BW We can divide the technical challenges into two categories – the device itself and the digital interface / cloud-based data management.

On the device itself, we came up with a modular, easy-to-implement approach to adding connectivity to the device. We wanted to avoid impacting anything from a regulatory standpoint, and this requirement drives our approach to how we add connectivity to an existing device. We did not want to disrupt existing firmware or architecture that could cause additional regulatory concerns downstream, so working with Dance on that aspect is critical.

Regarding the the digital interface / cloud-based data management, Phillips-Medisize is at the forefront of this field and in fact we will be announcing a major new development in our offering later this year.

[As this issue was going to press, this announcement was made as Phillips-Medisize launched its third-generation Connected Health Platform (CHP). The CHP is built on technology from the world leader in health data interoperability and includes an advanced analytics package designed for connected drug delivery devices, biosensors and regulated Mobile Medical Applications (SaMD/MMA). This enables customers not only to quickly generate views of their data but also to create a data presentation layer for analytics. The CHP can integrate healthcare data from multiple sources thanks to the enterprise master patient index.]

JP In diabetes, it's a blood glucose challenge. Patients are managing their blood sugar. So our device will be measuring insulin use, and our connectivity challenge and opportunity is to send this information to people's phones and, with algorithms, integrate it with their glucose data to help them better manage their blood sugar. Glucose monitoring and recording technology is moving ahead and changing, there are different players. The big challenge in development is not to build something that is obsolete by the time you get approval. You build into your device the space and capabilities, including for sensors and signalling capability to send and receive data, but you don't build that into your clinical endpoint. You don't need to. The clinical development and the integration of connectivity are done in parallel.

We're building the hardware and capability in our device, and our app, to receive and potentially process glucose data but we haven't partnered with anyone yet. We are leaving that open. Meanwhile, the device we're making is going to have that capacity and the software can change as we wish and as the market dictates. So we're taking our device through the clinical programme. In parallel we're developing the connectivity and building the app and, ideally, they will both come to market as separate products but married to each other.

The other challenge that we have is handling the data. We at Dance are relative "babes in the wood" in this area, and climbing the learning curve, but this is such an enormous area now. New things are happening all the time. We're really grateful to be partnered with Phillips-Medisize, who are on the cutting edge.

A key element is giving doctors back their time. Right now there's an explosion of connectivity work and innovation. Coming soon in the future, the data from connected devices will be processed and brought back to the patients, doctors and other caregivers in such a way that their lives will be made easier and more rewarding. It's going to be a giant boon to the healthcare system, but there are a lot of growing pains. We are repeatedly told that and other healthcare providers don't know what to do with this avalanche of data. It has to be crunched, processed and synthesised into crisp, meaningful insights that make people better at doing their jobs.

Q **Please could you each talk about how this agreement fits within the broader context of your respective organisations' strategies?**

JP Dance has been exclusively focused on inhaled insulin – first, second and third generation products. Even though this is basically an insulin drug product, what everybody sees and everybody holds, the patient interface, is really the inhaler. This is an absolutely critical part of our overall business strategy.

Obviously our insulin partner – Dongbao [Shanghai, China] is our global insulin supplier, and development partner in China – is of strategic importance. As we go downstream we will be entering into marketing partnerships and pharma partnerships also.

In terms of how our relationship with Phillips-Medisize fits within this context, when we go to form any pharma sales and marketing / commercial partnerships we are much, much stronger with a partner like Phillips-Medisize, who we see as the premier medical device company in the world. Having them as our partner is ideal – this is just what we need to advance our business.

BW The relationship with Dance fits with our Smaller and Smarter strategy, and we've advanced our Smaller and Smarter thought processes into the areas of connected health and digital interfaces as well. We remain committed to being a contract development manufacturing organisation serving our customers, and our approach is to be an innovation engine that is going to enable differentiated devices for our customers' drugs and connected devices for their patients. The whole drive behind this, of course, is to bring a device and connected health system together to provide a full connected system to improve outcomes for patients and a leading market position for our customers.

One of the things that is really great about the Dance device is that its life will be one-year minimum. So once you've got an electronic-enabled device, meaning it needs power and a brain, a processor, in order to function, that is a natural platform on which to add on connectivity, to make it a connected device. So the device is a really natural fit for the way the world is headed.

Another interesting aside on this is that when you've got the electronic device, and it's going to be used for many, many doses, that changes the cost profile of how we evaluate the cost of connectivity. It's very difficult today to have a disposable device with electronics on it, just because of the cost of the electronics. To address this, we have a low-cost connectivity electronics solution in development. You've got to find a way to bring down the cost per dose delivered, as John mentioned earlier. Today, key to that is having a device that has a long lifetime, and in this case a long lifetime with electronics in it.

Q **Back at the start of this century the insulin pill was talked about a lot as the natural next step after inhaled insulin. The insulin pill hasn't materialised though and, although not impossible to connect an oral dosage form, it is very difficult. In terms of patient centricity, how does a connected insulin inhaler stack up against an insulin pill?**

JP The dislike of injection is deep and means a pill would be welcome. And you could connect a pill to

> "Especially for diabetes patients, and patients with other chronic diseases, the ability to take control – that empowerment – is the key."

a pill dispenser and it could show on your phone, so it could be a kind of connected system if you wanted it to be. Insulin is a special case though. A pill would be ideal if it could be made but the problem is you have to overcome some major laws of physics and biology in order to do it. These are virtually insurmountable. I spent sixteen years before working on inhalation studying oral drug delivery, particularly oral drug delivery of insoluble molecules and macromolecules. The barriers are formidable. I've spent the subsequent twenty years on inhalation because I know it works.

We're so excited about having our inhaler connected because it's just so much more engaging. My FitBit now analyses my sleep and tells me when I'm in deep sleep, REM sleep etc, for example. Connected devices allow you to get in touch with your body. This can be deeply gratifying, especially when you're managing your health. Clearly, having an insulin inhaler that is connected is much better than having an insulin inhaler that is not connected. Because of the great patient empowerment potential of a connected inhaler you have to connect it if you can. You're stupid if you don't.

BW Especially for diabetes patients, and patients with other chronic diseases, the ability to take control – that empowerment – is the key. This is how connectivity can drive patient engagement and hopefully improve outcomes.

Q **Finally, I wanted to get personal! Still thinking about the recent partnership between PMC and Dance, and the other recent developments and breakthroughs you've each been involved with, I wondered if you could talk about these as part of your drug delivery stories and careers?**

BW Fortunately from a personal standpoint I remain in excellent health and I've never actually needed a drug delivery device, and I'm very grateful for that. However, having family members and loved ones who need devices it does become part of my personal mission every day to figure out how to get better devices on the market.

As a company, we started in this field about ten years ago and we were largely a US-based company. We started expanding our development and electrical engineering expertise within Phillips-Medisize. Then in 2016 we acquired Medicom. That acquisition was made due to their expertise in electrical engineering, embedded software and connected health. Finally, we were acquired by Molex later in 2016 and that rounded us out because we added electronics manufacturing at scale with facilities in Ireland, Mexico and China, thereby providing excellent supply chain management covering three continents and most of the world's population.

JP I was hired by Genentech in the 1980s to find a way around the needle for large molecules that cannot go through the gut. At that point the product was growth hormone. That was when we discovered that the lungs were open, the only door that was open in the body to these large molecules. I worked on that project for five years at Genentech, doing all of the preclinical studies showing that it works, that it was safe, looking at formulation and final potency.

I could not convince them that the lung was a good way to go, so I left to found a company, whose principal molecule was insulin and we developed Exubera. I've been working on inhaled insulin for 28 years and it's still unfinished business! As for what the future holds, I want to get this across the goal line and make it stick.

You know, people are dying, because they don't like injections. They refuse or put off injections, they take less insulin than they need, the disease progresses and it's killing them. It genuinely upsets me that this thing is not widely available already with all the work that has been done, all the safety and efficacy studies.

I am involved in a lot of other drug delivery projects; there are many other drugs – indeed many other peptides – that could be inhaled to great advantage, and Dance is now starting to develop some of these and create a pipeline. But I will continue to champion inhaled insulin until it becomes widely accepted.

Returning if I may to our relationship with Phillips-Medisize and Molex, I feel that entering into this partnership really marked a point when the project turned the corner. Bill has believed in what we're doing and without Bill's support I certainly wouldn't have been talking to you today, and we might not have been able to get this thing going at all. Now, with the support we have from Phillips-Medisize, I think we've got a great shot. We're getting some fantastic new people working for the company – a great new CEO, in Anne Whitaker, board members, executives, advisors – we're getting close.

It's kind of a simple story – we have to make this happen.

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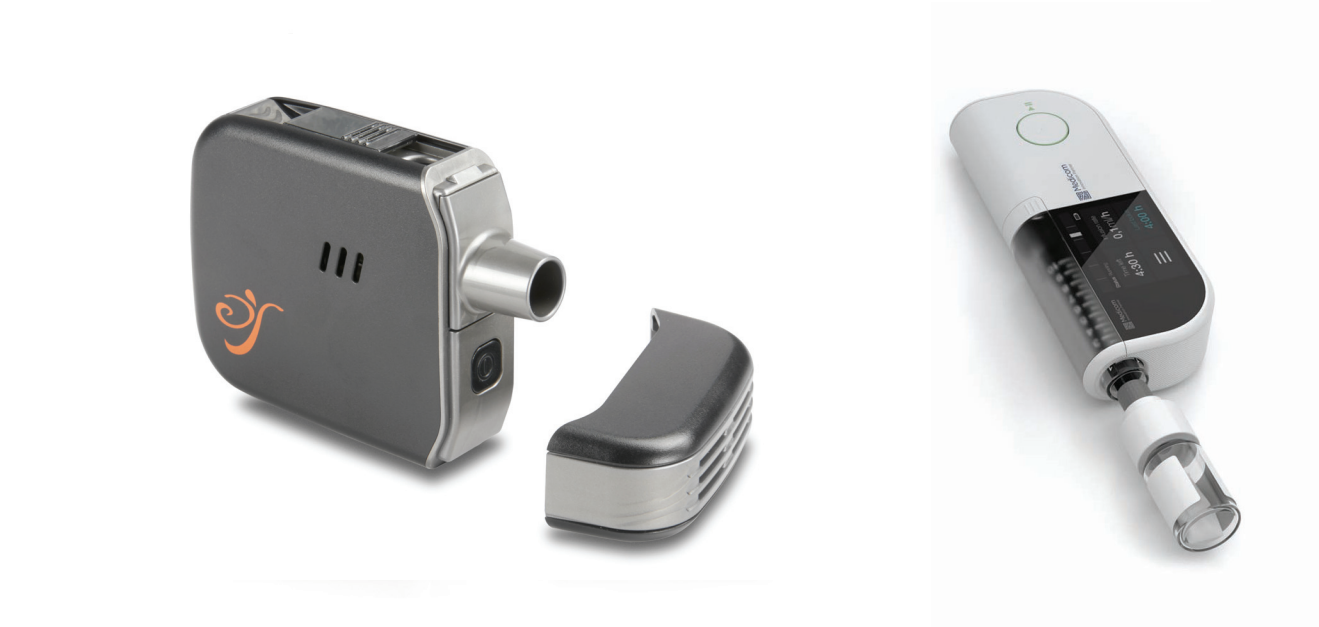
5 THINGS TO CONSIDER
WHEN MANUFACTURING CONNECTED DRUG DELIVERY DEVICES

The estimated number of connected drug delivery devices continues to increase and the impact of this trend could be significant, explains Phillips-Medisize, a Molex Company



While digital connectivity or connected health can improve the coordination and delivery of patient care, original equipment managers need to keep these five things in mind when creating connected drug delivery devices:

1. **Development strategy and design consideration**
2. **Situation analysis and patient compliance**
3. **Connectivity ecosystem**
4. **Wireless subsystem**
5. **Security of device and information**

As the Internet of Things continues to become an integral part of people's lives, the opportunity to use it within drug delivery device applications remains promising. The manufacturers and device designers must identify, investigate and overcome these challenges so that the implementation of wireless and other related smart technologies can be achieved. When done successfully, connected systems enable the patient and caregivers to have a 360° view of both the patient and the disease – not only to manage adherence, but to improve results by understanding the effect of the regimen.

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