ROUNDTABLE: DISCUSSION ON ANTI-OBESITY TREATMENTS

In this roundtable discussion chaired by ONdrugDelivery's Guy Furness, Stephen M Perry and Mathias Romacker, Kymanox, and Andreas Schneider, PhD, Ypsomed, tackle the subject of GLP-1s and related obesity-targeted injectable therapeutics and the enormous impact they are having and are expected still to have on drug delivery and the wider pharmaceutical sector. The insightful and wide-ranging discussion touches on various aspects from the transformative potential these drugs could have on patients' lives, through the relative lack of digital connectivity in the GLP-1 pipeline, to the potential benefits, risks and pitfalls that the sheer scale of the GLP-1 and obesity market could pose to pharma.

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Stephen M Perry, Chief Executive Officer and Founder of Kymanox, is an accomplished life sciences business leader with nearly three decades of experience. Mr Perry has participated in the US FDA commercial approval of over two dozen unique drugs, devices, biologics and combination products. In 2004, he created Kymanox, a professional services firm specialising in the development and commercialisation of modern medicines. Prior to this, he held roles at M+W Group, Abbott Laboratories, FujiFilm Diosynth Biotechnologies and Human Genome Sciences. He holds a Bachelor's degree in chemical engineering from the University of Notre Dame (IN, US).

MATHIAS ROMACKER

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Mathias Romacker is a Kymanox Executive Advisor with more than 30 years of experience in the field of injectable drug delivery devices. He brings a deep understanding of prefilled syringes, handheld injection devices and on-body wearable devices, having been involved in multiple successful combination product launches. Mr Romacker was a co-chair for the PDA Universe of Pre-Filled Syringes and Injection Devices conference in 2013, 2017, 2019 and 2022, and received the PDA Edward Smith Packaging Science Award in 2018 for his contributions over the years.

ANDREAS SCHNEIDER

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Andreas Schneider, PhD, is Head of Innovation at Ypsomed Delivery Systems. He leads a group that drives innovation end to end, from insights to ideas to prototypes to proof-of-concept. The team's responsibilities range from market and technology intelligence to strategy and business development, engineering and technology, and digital innovation. Dr Schneider has published and presented extensively in the areas of innovation management and drug delivery. He holds a PhD in Innovation Management from ETH Zurich (Switzerland).

Q To kick us off, Stephen, can you follow up on how things have progressed with regard to GLP-1s since your keynote address at last year's PDA Universe of Pre-Filled Syringes conference?

SMP So, for that keynote, I outlined that we have US$125 billion (£95 billion) disruptor in the form of GLP-1s entering the market. This is unprecedented – we haven't seen any product or class of products like that before. At a minimum, we're going to need reusable dose delivery systems for it, particularly from the environmental, cost and convenience standpoints. And, building from the main theme of that keynote, we can draw a strong parallel here with between GLP-1s and diabetes treatment with insulin. The first insulin pen was vastly ahead of its time – it was a cartridge system, it was reusable and you could dial in the dose; GLP-1s will evolve to a similar platform, with a scale or impedance body scan acting as the diagnostic analogue to glucose monitoring.

One of the disruptions we've seen as a consequence of GLP-1s has been large pharma companies securing their own supply chain. The clearest example of this is the purchase of Catalent, specifically for a GLP-1 manufacturer's exclusive use.

Another thing that's been disruptive is the data that's regularly being released indicating that GLP-1s are actually bending the mortality curve – they're not only solving for obesity, they're potentially solving for cancer, heart disease and a myriad of other life-shortening indications. Orthopaedic surgeons are changing their forecasts for knee and hip replacements because so many more people who had to lose, say, 50 lb (23 kg) before it was safe to proceed with surgery are successfully achieving the weight loss;

in other cases, people are losing weight before joint damage accumulates to a point where surgery becomes necessary.

We've gone from a situation where patients were opting out of elective surgeries that could greatly improve their quality of life because their obesity means their odds of dying on the operating table are unacceptably high, to one where they can shed that weight with GLP-1s, something they might not be able to do any other way, so their surgery becomes feasible and they've got a real pathway to getting their lives back.

Going back to the diabetes comparison, there's also the digital health side of the equation – something diabetes has mastered. I think something similar is going to happen with GLP-1s. My anticipation is that we'll see advanced, connected dose delivery systems that intersect with the wellbeing industry because obesity goes beyond just treatment with the drug.

The next key point is how the supply chain impacts patients' lives. For example, I've spoken with one person who has several active prescriptions to ensure they have access; including getting the drug in a vial format. They then have to buy their own syringes and inject themselves manually. There's no autoinjector, which is a problem for needlestick injuries and a wide variety of failure modes.

However, it's important to appreciate just how transformative these drugs are. I've been speaking with about two dozen GLP-1 users, and the difference it's made to their lives is astonishing. It goes beyond just weight loss, it affects every aspect of their lives in a significant and positive way. I don't think the media or the people inside the life science industry really understand how big this is yet. I think it's so much bigger than people are estimating at present – when you stack all the benefits of GLP-1s, we are seeing the mortality curve bend in real-time and completely change the insurance actuary tables.

The last key thing to state up front is the scale of use. Morgan Stanley has predicted that, by 2035, nearly one in 10 Americans are going to be on a GLP-1. As things stand, that could bankrupt US healthcare, absent some changes. We're looking at a trillion-dollar hit on the healthcare system in that scenario, and I'm not convinced that we're prepared for that. All of this would have ramifications beyond healthcare. If you've got almost 10% of Americans on GLP-1s and their caloric intake goes from 3,000–4,000 calories a day down to 2,000 calories a day, that's going to have a massive impact on the food and beverage industry.

Q **Andreas, taking a step back and looking at the industry behind this, what's going on in terms of the obesity-targeted pharmaceutical pipelines for GLP-1s and beyond?**

AS In short, it's mind-blowing. We've done some systematic analysis into how many clinical-stage drug products are there and how the clinical trial landscape is looking. We estimate that there are well north of 100 drug candidates on the way, not counting biosimilars. While a significant number are, of course, injectables, we're seeing a number of formats, including intravenous infusions, implants and, of course, orals. The pipeline currently spans multiple different routes of administration.

I think what's also interesting to see is that it's not just the western big pharma companies driving innovation; many of these new drug candidates are coming from small biotechs and, also, from Chinese companies. It's very vibrant and it's exciting to see innovation coming from across the globe beyond the usual big pharma companies.

Right now, innovations are targeted at improving weight loss. So, if we're currently working with a 20–25% reduction in body weight in a year, the question is how quickly can we push it to 30%? It's about attaining higher potency in order to increase the effective weight loss and to reach higher efficacy at an earlier time point so that patients lose more weight more quickly. However, with rapid weight loss comes the question of whether we are losing the "right" weight – fat loss or muscle loss. For example, it is becoming increasingly important to limit muscle loss through concomitant treatments that promote muscle growth.

Secondly, I think innovators are investigating tolerability. There are side-effects of GLP-1s that could theoretically be overcome by adding certain additional drugs on top. For example, you can try to address the gastrointestinal and other side effects with amylin, glucagon or gastric inhibitory polypeptide receptors (GIPRs), among others.

Then, of course, there's improving convenience – there are companies trying to formulate an effective oral dosage, which are often seen as more convenient. However, we're also seeing developers looking to improve convenience by changing injection frequencies. For example, Amgen has a late-stage Phase II asset (AMG133, a dual GLP-1 agonist and GIPR antagonist) looking into monthly injections versus weekly – today's dominant dosing regimen – most likely in a convenient autoinjector format.

SMP To add to that, one of the things I think is notable by its absence is digital connectivity – there are several products in the pipeline and few to none of them are connected. Considering that one of the biggest issues facing healthcare right now is low adherence, and GLP-1s are the sort of drug where poor adherence can derail the entire therapy, you'd think that the benefits to adherence offered by connectivity would be a natural fit. We shouldn't be shocked by this. Humira's number one failure mode is non-adherence, and now we have a dozen generic competitors approved with none of them using a connected device to solve that problem. When you have to take a medicine for a certain number of months at a minimum to see an effect, you want to ensure that patients are taking it properly.

MR That's a good point. Personally, I think that connectivity is likely to come at some point but it's probably a little bit further out, after the sector has matured more. After all, to add to the adherence aspect, GLP-1s are expensive, so healthcare systems are going to want to hold patients accountable for taking the drug and ensuring that the cost pays off. How do you do that? Either you need to believe patient self-reporting or you need to have a tracking mechanism, which would almost certainly be digital.

Q **Mathias, Andreas mentioned that oral forms of GLP-1s are currently in the pipeline, do you think these are likely to pose a threat to the injectable share of the market?**

MR The big open question is what oral forms will be like when they arrive – whether they're a threat to the injectable share of the market will largely depend on whether they're a positive thing for patients. From my research on the situation, I'd say it's currently all over the place. The big factor is likely to be how fast the weight loss actually happens with oral formats compared with their injectable counterparts. That's important, because GLP-1s require lifestyle changes alongside the actual therapy. It's even on the label – exercise and dietary

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changes. From what I've seen so far, it seems that the weight loss takes quite a lot longer than with the injectables, although we're still very early on with the oral forms so that could change.

Beyond that, I think that we should question the common assumption that, if you have an oral dosage form, that it's automatically better in terms of adherence than an injectable. In my experience, if you have a monthly injection, you're probably going to remember it, but, if you have a daily or twice-daily pill, it's easier to forget when things are busy or something else demands your attention. In some cases missing a dose here and there isn't a big deal, but we don't know that for sure with GLP-1s. In my opinion, oral forms may not be the holy grail the industry sometimes thinks they are.

AS Going by the data that I'm aware of, injectables are comparing favourably with orals in terms of efficacy at present. Currently, the injectables are pushing towards 20–25% weight loss after a year, whereas the oral formats are in the range of 10–15% so far – we'll have to wait and see how they perform once we have data on longer timescales. Our estimate is that oral formats will take around 20–30% of the market in the mid- to long-term, meaning there's still a significant share for injectables. Add to that the expected growth in this sector, and I wouldn't describe injectables as losing out. Consider, for example, that oral formulations of GLP-1 peptides such as semaglutide require many times the amount of API compared with injectable formulations. Given the current shortage in the supply chain, going oral does not seem to be the most efficient way to serve the exploding market.

To add to Mathias's point, in a study on patient preferences for GLP-1s in Type 2 diabetes comparing a once-weekly injection with a once-daily oral alternative, patients clearly preferred oral over injectables initially but, once they studied the product-specific administration procedures in detail, the preference became much less clear-cut. I would expect the same pattern to emerge for GLP-1s in obesity, where you have one segment the market that is effectively managed with and/or prefers an oral dose over injectables and another where that's not the case. We also do not expect fundamental differences in pricing between injectable and oral forms; we currently assume a "price per day of therapy" – with increasing cost pressures for all forms of therapy.

Q **Earlier, Stephen pointed out that the GLP-1 market is set to be unprecedentedly large. Andreas, from the device side, how do you expect companies like Ypsomed to adapt to service the need for delivery devices suited to GLP-1s?**

AS In my opinion, the challenge is twofold. Firstly, how can we serve the market in terms of innovating and ramping up production capacity along the entire supply chain – including primary containers, fill-finish and final assembly – to meet demand? And secondly, how do we think the market is going to evolve and what device presentations are going to become the dominant ones?

That second challenge is especially interesting as, currently, GLP-1s are among the first products that are being commercialised in both syringe- and cartridge-based formats. That's going to create some additional trade-offs and decisions need to be made for the future with regard to which formats are going to serve which markets. There's also a question around sustainability and environmental impact – given the sheer size of the market, the number of devices being used is enormous. Today there are over a hundred million devices serving the market, and that's only going to multiply in the years to come, so we need to carefully consider the sustainability of any product we put out there; for example, the difference in sustainability between a single-dose syringe-based autoinjector and a prefilled cartridge-based pen injector containing four doses is significant – it really adds up at this scale.

SMP I have a vision on how the device aspect of GLP-1s should work, which I alluded to at the end of last year's keynote in Sweden. It could work just like insulin. With diabetes, patients have a cartridge-based pen injector where they can dial in their dose at the time that is most appropriate to them – it's essentially personalised medicine. Weight loss is incredibly hard, so giving patients a way to tune their dose to their needs seems to me to be the natural way to achieve the best therapeutic outcomes.

For example, if the label gives a dosage for a once-a-week injection, but a patient is finding that, on day five, the cookie on the counter is calling to them, that's the ideal opportunity for an app-controlled dosing level and frequency. Most GLP-1 patients quit their injections due to side effects in the first couple of weeks and months; by dialing in a dosing scheme for both the amount and schedule, those side effects could be greatly minimised. Empowering patients to deal with their individual situations will increase the overall efficacy of the product, optimising it for the individual and, ultimately, the plan sponsors who are authorising and paying for the drug access.

Q **Risk management is a huge part of the pharma and drug delivery industries. With a technology as disruptive to the market as GLP-1s, what do you consider to be the key pitfalls and risks that we need to watch out for?**

MR Obviously, there's a huge amount of enthusiasm for GLP-1s out there right now. One risk is that the industry may end up overinvesting in that space and, in effect, neglect other projects, potentially missing out on opportunities in other therapeutic areas. I think there are significant business development opportunities to be found in underserved disease areas and, if GLP-1s suck up all the oxygen in the room, pharma will be failing both itself and those patients.

There are also concerns around pricing. Considering just how widespread the use of GLP-1s is expected to be, I'd expect there to be a lot of pressure around this topic. I have wondered if,

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should GLP-1 pricing become a major topic of public debate, that pressure could then be extended into other therapeutic areas if legislators are forced to respond? It's only a possibility, but I think it's something that should be in the conversation.

SMP It's also important to consider that some GLP-1s are imminently about to come off patent, so we can expect to see a rapid transition to biosimilars to meet demand in many cases. And, when there are large populations taking a drug for long periods, there's always a risk that an unexpected side-effect could be detected that creates a concern about safety. Such a safety signal would change the dynamics significantly – it could completely change the public mood around these drugs.

We also have to be mindful of supply chain risks, taking macroeconomic and geopolitical risks that could significantly impact the market. We need to rely on networks of contract manufacturers and really make sure our supply chains are robust all the way down to the component suppliers just to be able to handle the fluctuations we expect to see in today's world. There's already a shortage problem and rationing going on, so these supply-chain disruptions will make a bad situation worse.

On top of that you have the risks around pricing we mentioned before. With the scale of GLP-1 use we're expecting, there will be political pressure to direct pricing, with the public putting pressure on governments to keep prices low, as happened with insulin in the US. There's also the issue of counterfeiting which can play into this. And, of course, if the price of the end product is pushed lower, that's going to have implications for the supply chain in turn. There are a lot of interconnected factors here that need to be carefully thought through by everyone in the space.

Q **Mathias, you're scheduled to deliver a talk on this topic at the PDA Universe of Pre-Filled Syringes conference in Phoenix later this month. Please could you give ONdrugDelivery's readers a sneak preview of what to expect?**

MR The title is, "*The Disruption Potential of New Injectable Anti-Obesity Therapies on Drug Delivery and Beyond*". We've already touched on quite a few of the aspects I'll be covering in this interview. Let's start with the expectation that we are going to have 30 million patients on those drugs in the US. That's a whopping 9% of the population. However, when looking at numbers for 2030, almost half of Americans are projected to be obese. So, this is a huge market but, even then, it's not reaching the majority of people who may potentially benefit from it.

What I also find fascinating is the impact we're expecting to see on other sectors. The potential impact on the food and beverage industries, for example. But it extends beyond that to things like restaurant dining, retailers and the wellness and fitness industry – exercise is on the label, so we can expect to see a knock-on effect in gyms, for example. I think a lot of other areas will be impacted by knock-on effects, including some we haven't thought of yet.

And then there's the drug delivery landscape. First of all, when you do the maths that 30 million patients in the US, if they're all taking an injectable, that's over a billion injections a year. That's a lot of prefilled syringes and autoinjectors that will be discarded. So, clearly, we have to talk about sustainability and the potential for reusable injectors. We should also consider multi-dose injectors, such as a cartridge-based device that can deliver four doses from one device. That topic on its own could be a whole second interview!

Q **Andreas, you're also presenting at PDA Universe, could you give us some insight into what you'll be discussing as well?**

AS One thing I want to discuss is how, in light of drug shortages and capacity ramp up, we've tended to neglect to explore what is it that the patients are asking for. A lot of the discussions happening in pharma are being driven by the supremacy of supply chain, with the primary concern being simply getting things onto the market. What we've done at Ypsomed is conduct an extensive online survey with over 400 patients, asking them about their preferences and perspectives on four delivery device archetypes – syringe-based versus cartridge-based and reusable versus prefilled.

With this survey we've looked into different geographies such as the US, UK, Germany and Switzerland and into different target populations, such as varying BMI, co-morbidities and injection experience. With that, we've tried to discern what patients would ask for if they had the choice. Considering the competitive pressure we're expecting in the GLP-1 space, understanding true patient preferences is going to be critical to success.

ABOUT THE COMPANIES

Kymanox is a life sciences professional services organisation that offers engineering, scientific and compliance support to companies exclusively in the biotechnology, pharmaceutical, medical device and combination product industries throughout the product lifecycle from early development to post-market.

Ypsomed is a developer and manufacturer of injection and infusion systems for self-medication, and a specialist in diabetes. The company's comprehensive self-injection device platforms consist of autoinjectors for prefilled syringes in 1 mL, 2.25 mL and 5.5 mL formats, disposable pens for 3 mL and 1.5 mL cartridges, reusable pen injectors and ready-to-use prefilled patch injectors for up to 10 mL volumes. The company leverages its in-house capabilities in mechanics, electronics, software and connectivity for the development of new devices and digital product systems.

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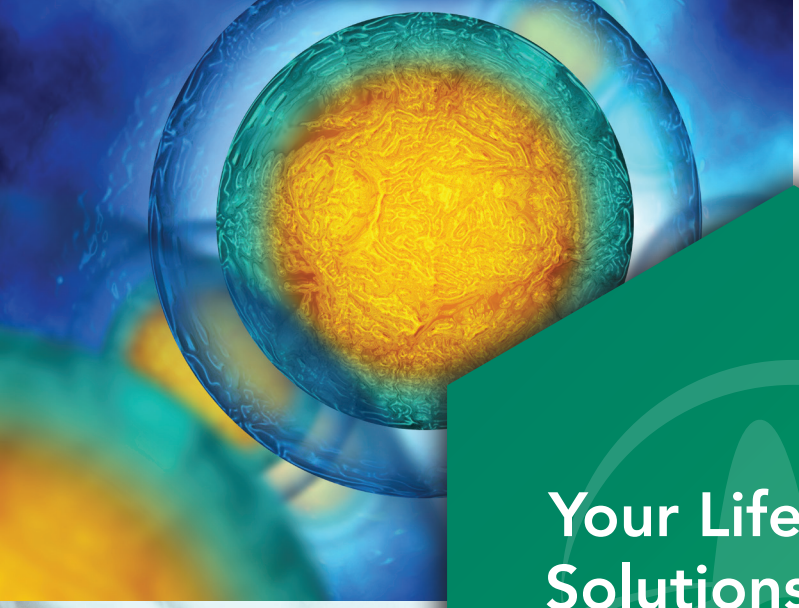

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