ROUNDTABLE: CAPSULE-BASED DRY POWDER INHALERS

In this roundtable discussion, Frédérique Bordes-Picard, Business Development Manager for Innovative Products at Lonza's Capsules and Health Ingredients segment, Marco Franza, Sales and Business Development Director – Global Inhalation and Medical Devices at Berry, Mirjam Kobler, PhD, Head of R&D, BG Excipients and Technology at Meggle, and Marco Laackmann, Sales Director, Inhalation Technology at Harro Höfliger, discuss the accelerating development potential of capsule-based dry powder inhalers (DPIs) and the potential of these effective and efficient drug delivery devices in the modern drug delivery market.

FRÉDÉRIQUE BORDES-PICARD

Lonza
Capsules & Health Ingredients

Frédérique Bordes-Picard is Business Development Manager for Innovative Products at Lonza Capsules and Health Ingredients. A biochemical engineer by training (Bordeaux Polytechnic Institute, France), Ms Bordes-Picard holds a master's in business administration from KEDGE Business School (France). She has been working in the pharmaceutical industry for more than 20 years, first at AstraZeneca, working on analytical development of therapeutic proteins and antibodies, then within Bertin Pharma (now Eurofins), mainly on generic product development and licensing out. She then joined Capsugel in 2010 as Pharmaceutical Business Development Manager, providing technical and regulatory support for new capsule-based product developments. Ms Bordes-Picard has developed specific expertise around capsule-based DPI product development and filing, supporting multiple companies in the EMEA and US working on both innovative and generic DPI projects.

MARCO FRANZA

Berry | healthcare

Marco Franza is Sales and Business Development Director – Global Inhalation and Medical Devices at Berry and has worked in various different roles in the commercial area but has always remained part of sales, business development and marketing. As inhalation devices have constantly been identified as the key growth factor for Berry, Mr Franza has always had a particular focus on them, driven by both business reasons and personal interest.

MARCO LAACKMANN

Harro Höfliger

Marco Laackmaan is Sales Director, Inhalation Technology at Harro Höfliger. He has a degree in chemical engineering with applied biotechnology from the University of Applied Sciences Emden (Germany) and an MBA from the Bradford School of Management (UK), as well as 15 years' experience working in the DPI industry, including device development, manufacturing, device quality control, powder dosing technology and process development. Mr Laackmann joined Harro Höfliger in 2011 and in his current role he handles global business development, sales and product management for specialist production machinery for the DPI industry.

DR MIRJAM KOBLER

MEGGLE

Dr Mirjam Kobler, PhD, is Head Of R&D, Excipients and Technology at Meggle. She started working in the R&D Department of Meggle in 2013 as a Project Manager for Analytical Development, focusing on DPIs. In 2016 she became Senior Project Manager, with growing responsibilities in product development for lactose for inhalation, DPI technical support and characterisation techniques. Since February 2018, she has headed the R&D Department of Meggle's Excipients and Technology business group. Dr Kobler's background includes seven years of experience in various areas of lactose excipients, especially for DPIs.

Q Ms Bordes-Picard, can you give us an overview of the factors currently driving the increased therapeutic interest in pulmonary administration via DPIs?

FBP DPIs enable the delivery of an API for either local effect to treat respiratory diseases or for systemic indications, acting as a needle-free delivery system suitable for APIs ranging from small molecules to peptides and proteins. The lungs offer an enormous absorptive surface area, the highly permeable membrane in the alveolar region being of particular interest for systemic delivery. Slow clearance in the lung also results in the prolonged residency of APIs, and its low-enzyme environment is devoid of the problematic hepatic first-pass metabolism that reduces bioavailability for orally administered medications.

For local action, the pulmonary route allows for high concentrations of API to be delivered directly to the disease site, which can provide a rapid clinical response. Pulmonary delivery bypasses several barriers to therapeutic efficacy and can achieve a similar or superior therapeutic effect compared with oral delivery at a fraction of the systemic dose, thereby helping to minimise the risk of systemic side effects.

That being said, pulmonary pathologies remain a key target for the inhalation delivery route. Respiratory diseases account for five of the 30 most common causes of death – clearly there are still unmet needs. An estimated 65 million people suffer from moderate to severe chronic obstructive pulmonary disease (COPD), which makes it the third leading cause of death worldwide. Furthermore, asthma is similarly entrenched, especially when looking at children – more than 15% of children are affected, making it the most common chronic disease among this group.

According to Pharmacircle 2020, from preclinical through to Phase III development, 21% of DPI programmes are capsule based and 70% are developed by small or virtual companies. We now have studies being conducted for indications in infectious disease, the central nervous system and cardiology areas. About 44% of APIs are new molecular entities (NMEs), but there are even more promising compounds using 505(b)(2) development routes, with developers looking at either repositioning existing generic molecules or associating known molecules with DPIs to improve the treatment of existing pathologies. Asprihale (Otitopic, Los Angeles, CA, US) is one promising ongoing development, leveraging the faster bioavailability of compounds in the lungs to deliver a formulation of aspirin using a DPI to treat sudden myocardial infarction symptoms.

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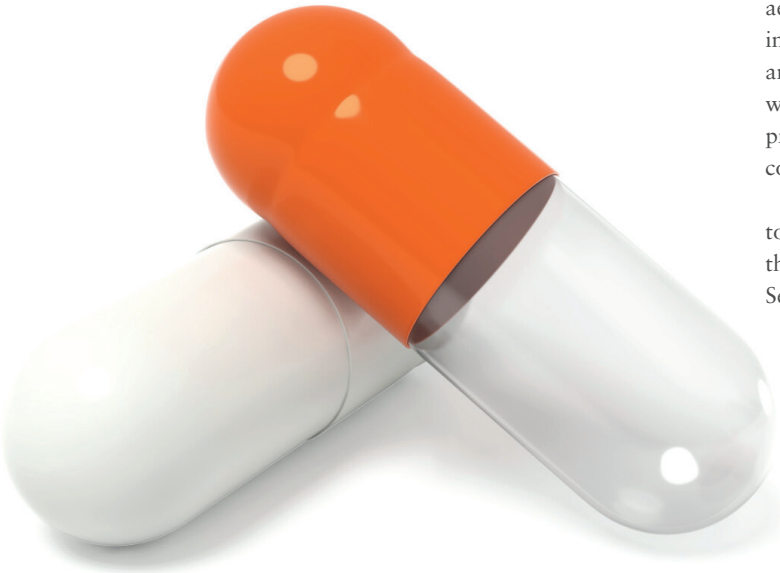

Figure 1: Capsule-based DPIs offer four key advantages: the capsule acts as both primary container and delivery device, integration of the capsule into the user experience, simplicity of design and cost efficiency.

Q Mr Franza, can you further expand on the advantages of DPIs compared with other drug delivery devices?

MF As Frédérique mentioned, there is an increasing interest in the inhalation route across pharma development – the industry has been consistently identifying new indications for DPI formulations and DPIs across the therapeutic spectrum.

Simple, patient-friendly DPI devices cost less and perform better than other device formats. DPIs are the preferred choice for high-tech biological inhalation formulations, have a low carbon footprint and are likely the most sustainable choice on the market today – they are re-usable, require less packaging and fewer components, and use no pressurised propellants to dispose of. A lightweight and well-designed DPI device can have less impact on the environment than other popular drug delivery solutions. These features support affordability and payer value – the keys to better patient access.

However, that's not to say that DPI formulation development is simple. There are a number of complex factors to consider, including aerodynamics, compatibility between specific chemistries and the interactions of varying particle morphologies relative to the container and device activation. There are a number of parameters to consider when it comes to DPI technology selection relative to the other primary device types, and it's important to make sure that patient compliance and user friendliness come first.

Regarding capsule-based designs, there are four key advantages to consider. Firstly, with current state-of-the-art DPI technology, the capsule acts as both primary package and delivery device. Secondly, capsules are thoroughly integrated into the user experience with designers leveraging both audio and visual cues to support confident dose delivery and better patient compliance. Thirdly, the simple design of DPIs requires fewer manufacturing resources. Lastly, from a cost-of-goods perspective, DPIs are less expensive to make overall, especially when combined with cost efficiencies associated with high-volume capsule manufacture (Figure 1).

Single-dose re-usable DPIs now account for a growing portion of the global DPI market. According to Berry's research, most of these are capsule based. Generally speaking, all these devices employ some sort of system to make the dose contained in the capsule accessible to the airflow generated by the device when the patient inspires.

This occurs one of three ways: opening the capsule by separating the body and cap, cutting the capsule with blades or piercing the capsule with needles.

Capsules deliver multifunctional characteristics to DPIs and have become integral to their performance. The mechanically actuated DPIs available to developers today can spin capsules at relatively high rates to deliver a high degree of controlled and repeatable turbulence. The aerodynamics of the spinning capsule help aerosolise the powder prior to it being propelled out of the device. As such, the capsule plays an essential role in a complex dynamic system, greatly influencing the pharmaceutical performance of the drug substance and offering a simple but highly functional synergy in combination that other drug delivery methods have a hard time matching (Figure 2).

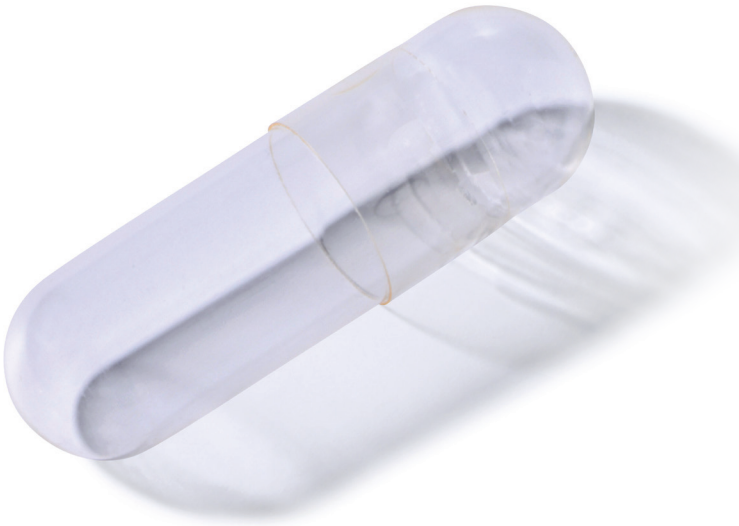

Figure 2: Modern DPI capsules form an integral part of their delivery device's functionality.

"Most successful DPI formulations depend on lactose as a carrier material for the API; lactose is proven and the *de facto* excipient for inhaled APIs."

DPIs are truly among the higher-performing devices available in terms of emitted dose and respirable delivery ratio on the market today. Access to a platform using capsules, proven to be compatible and functional with most DPI formulation chemistries, is key to further application and effective development.

Q **Dr Kobler, Mr Franz touched upon the complexities of formulating APIs for use in a DPI, can you shed some more light on common themes in DPI formulation?**

ML Most successful DPI formulations depend on lactose as a carrier material for the API; lactose is proven and the *de facto* excipient for inhaled APIs. Of course, developers need to carefully consider all aspects of the project as early as possible, including the formulation of the finished drug substance, the device, the dose's primary packaging – in this case the capsule, magazine or reservoir – and ultimately the filling and finishing of the product for commercial dispensing. When considering DPI formulations in combination with device and packaging, there are many synergistic aspects that developers need to be aware of. Ideally, all functional and formulation interactivity is evaluated at the beginning of development.

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Let's briefly talk about why a carrier material is such a pivotal excipient for a DPI formulation. Particles that are capable of being delivered to the lungs are typically in the range of 1–5 µL in size and often come with a common major disadvantage – they can be very, very cohesive. This leads to poor flow, processability and variation. Dispersing the API formulation in the lung requires a carrier material to support the function of airborne delivery and improve dispensing and metering. For most current formulations, that functionality is why lactose is the carrier of choice for many of today's top-selling DPI formulations.

Q **Ms Bordes-Picard could you elaborate on the key principles that need to be considered during the design of a DPI?**

FBP A DPI's success rests on four key pillars: formulation and flow, capsule compatibility, filling flexibility and device form and function. Additionally, for DPIs, the overall compatibility and functionality of the "triangle" of critical parameters – device, formulation and capsule – is of the utmost importance for developers to get right. For each of these components, there are a number of critical attributes to identify and key issues to mitigate.

Optimal DPI formulation composition and dose are generally primarily defined by particle mass, with particle size distribution (PSD) and the shape or morphology as significant characteristics. Formulation chemistries need to offer several other functional attributes to the mix as well, including chemical stability, hygroscopicity and the ability to deagglomerate. Generally speaking, optimal performance of an inhalable dry powder formulation depends on the aerodynamic PSD and the emitted dose's fine particle mass.

Q **Let's discuss commercial manufacturability. Mr Laackmann, could you shed some light on this topic?**

ML Of all the things to consider regarding DPI formulations in the context of effective downstream commercial scale manufacturing, compatibility with feeding and filling operations is absolutely critical. Within the DPI world, there are three semi-standard inhaler technologies to choose from: reservoir-based, blister-based and capsule-based. So far, we've been focusing on capsule-based DPIs, however, with reference to the filling and finishing of any of the three packaging types, it's important to understand the critical role of the powder-feeding process.

Powder feeding for DPI formulations can be challenging, especially with the micronised powders and engineered particles associated with some currently popular formulations. The top challenges DPI

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Powder segregation is often caused by incorrect mixing, poor powder storage, which creates an uneven distribution of the API, and errors in powder feeding, which leads to segregation within the powder blend. Segregation can also occur during the sieving process and during sliding, because of different friction coefficients, or can result from other kinetic forces.

Segregation is not optimal for flow. If not mitigated, it leads to poor content uniformity and an increased risk that fine particles of the powder will get lost. Segregation may also lead to an undesired drop in assay – the loss of active on machine surfaces. Fortunately, at this point in processing there are a few potential options for mitigation, including modifying the powder formulation, such as by adding magnesium stearate, and modifying the powder-feeding system.

Another formulation-induced issue between machine and chemistry is agglomeration. Generally caused by cohesion among particles, it occurs relative to the ambient conditions of the environment, including temperature, humidity and the moisture content of the formulation. These can all lead to unpredictable changes in the flowability of the powder and may require several additional powder preparation steps, such as sieving, conditioning or ionisation, for mitigation at commercial volumes.

Dealing with cohesion and adhesion, as well as other similar undesired properties limiting flow, can be challenging. If not addressed, these issues can compound causing increased variation and other quality and process control issues. Fortunately, powder-feeding technology suppliers have introduced innovations to mitigate formulation and environmental issues and support the optimal feeding of powdered formulations. These systems include features such as beam feeding, auger feeding, pneumatic assist feeding, vibration feeding, fluidisation and bag systems.

Manufacturing a highly feed- and flow-oriented formulation is a good place to start for any DPI developer to ensure the therapeutic and commercial success of their product. Although it may be the last component to think of in this scenario, in some ways the filling and finishing of the capsules should be considered first. It's very important to understand how the formulation can affect manufacturing as early as possible in development.

Q **Ms Bordes-Picard, can you offer some closing thoughts?**

FBP DPI combination products are providing the flexibility developers need to optimise the delivery of their increasingly complex DPI formulations. Because capsule-based DPIs offer an affordable delivery route for treating chronic conditions like COPD and asthma, they will always have a place in drug development. Furthermore, because capsule-based delivery can offer a more economical and sustainable DPI development path to developers, it will continue to feature prominently in advanced pulmonary drug development and delivery innovation. Compatible, affordable and patient-centric capsule-based DPIs are here to stay.

ABOUT THE COMPANY

Lonza's Capsules and Health Ingredients segment is a global capsule and equipment developer and manufacturer, which designs and produces products for a range of oral dosage forms. The company provides customised solutions that optimise formulations to more than 4,000 customers in 100 countries.

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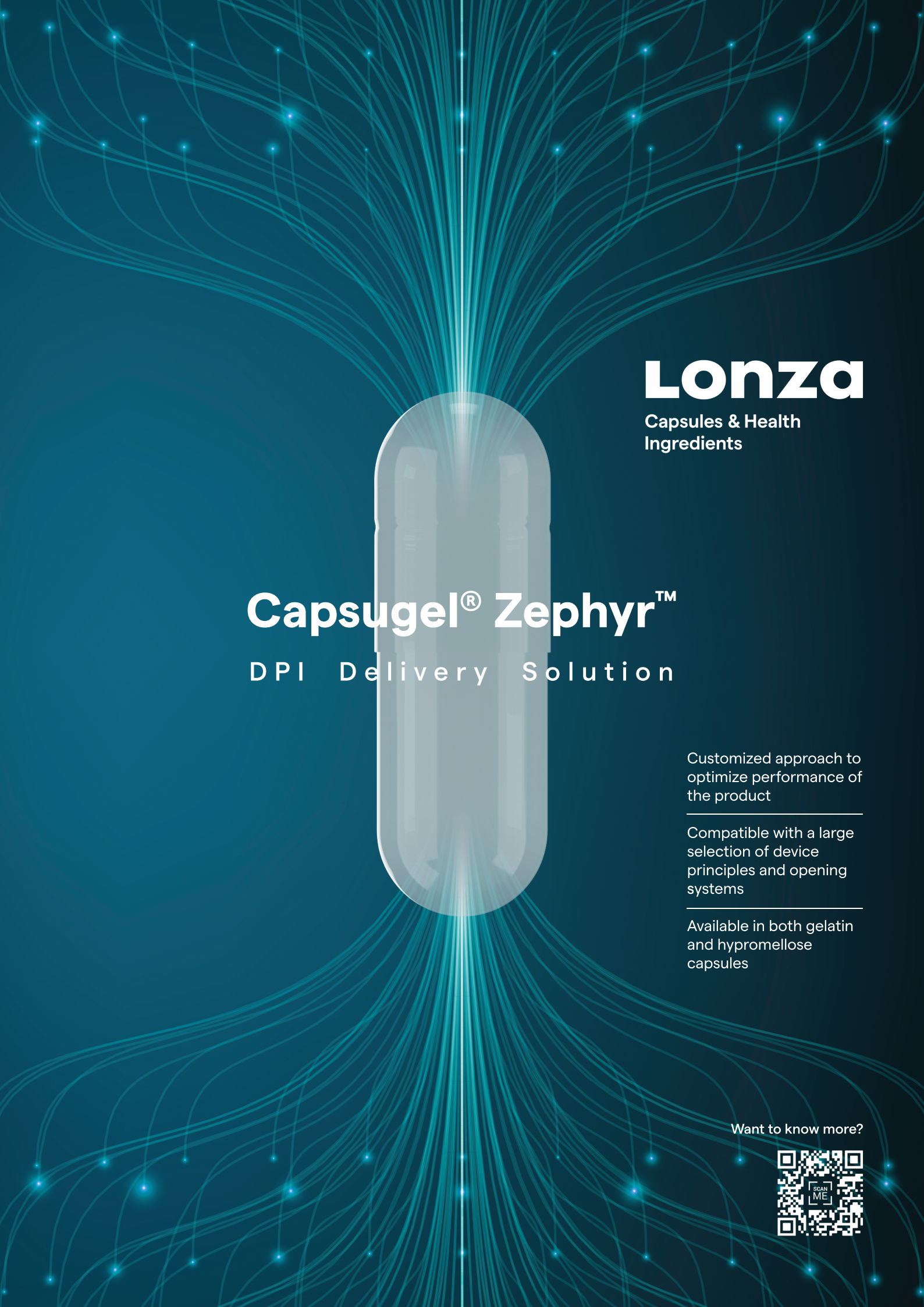

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Capsules & Health Ingredients

Capsugel® Zephyr™

DPI Delivery Solution

Customized approach to optimize performance of the product

Compatible with a large selection of device principles and opening systems

Available in both gelatin and hypromellose capsules

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