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Nemera: The Holistic Partner for Your Combination Product Development

Q1: Nemera is a world leader in the design, development, and manufacturing of drug-delivery devices for the pharmaceutical, biotechnology and generic industries. Can you give our readers a brief history of Nemera, and where do you see Nemera positioned in the next five years?

As a world-leading drug delivery device solutions provider, our purpose of putting patients first enables us to design and manufacture devices that maximize treatment efficacy.

We are a holistic partner and help our customers succeed in the sprint to market of their combination products. From early device strategy to state-of-the-art manufacturing, we're committed to the highest quality standards.

Agile and open-minded, we work with our customers as colleagues. Together, we go the extra mile to fulfill our mission.

Q2: What therapeutic applications are the primary main focuses at Nemera today and why?

By focusing on solutions that make patients' lives easier and safer, we have built a strong portfolio of innovative products and technologies for five routes of administration: parenteral, ophthalmic, ENT (ear, nose, and throat), dermal and inhalation.

We partner with our customers to provide a wide range of device platforms, services, and commercial manufacturing capability to support their needs across their pipelines and associated delivery modalities. We strive to drive innovation across all routes of administration to serve the future needs of our customers.

Our parenteral offering includes reusable and disposable pen injectors, customisable platforms of passive safety device for pre-filled syringes (Safe'n'Sound®), as well as customised solutions based on parenteral technologies such as auto-injectors, implanters, and wearables.

In ophthalmics, we strive to improve patient experience by developing Novelia®, a safe and effective multi-dose eye-dropper platform to deliver preservative-free formulations. Novelia® is used all over the world, both for Rx and OTC treatments.

The number of drugs delivered through the ear, nose and throat is expanding. We develop and manufacture a comprehensive range of pumps and valves, compatible with a wide choice of actuators for each ear, nose and throat delivery, suitable for regulated and low regulated markets.

The dermal application is a convenient non-invasive way to administer lotions, gels or creams to the skin. Our devices deliver precise and consistent dosing with our metered-dose atmospheric or airless delivery systems for Rx and OTC formulations.

With long-standing know-how in inhalation delivery, we are today the leader in the dry powder inhalers (DPIs) manufacturing business. Our expertise covers dry powder inhalers (reservoir, blister pre-metered multi-dose, capsule) but also dose indicators and actuators for pressurised metered-dose inhalers (pMDIs).

Q3: With proven know-how of the combination products ecosystem, Nemera provides an end-to-end offering, to support its customers' device strategy. Could you please tell us more about that?

Successful combination product development revolves around critical patient insights, robust device strategy and targeted selection plan. We urge our customers to look at the larger ecosystem that must be considered to ensure optimal success. On the one hand, healthcare professionals, health systems, payers for value-based care and on the other hand, regulators for market access and the intended filing approach. The latter can significantly impact device selection and development strategies. These factors then need to be considered within the available or emerging technology landscape. This broader understanding is critical in meeting the needs of patients and can impact how technology may be selected, as well as early considerations around the impact of the other aspects of the ecosystem in development initiatives. We believe that success will come from addressing these factors both strategically and tactically. Once we have gained visibility into what the patient and stakeholder needs are, developers should consider how to best satisfy those needs as holistically as possible while continuing to work with patients and clinical stakeholders prior to new product development processes. This requires synthesising the patient and stakeholder information with other ecosystem inputs into a device strategy roadmap, which can be utilised in several ways to make device selection decisions. We believe a partner like Nemera with strong IP platforms, development services, and manufacturing capability allows customers to achieve the outcome of a successful regulatory submission and commercial launch of safe, effective, and differentiated combination products with a single partner who can manage all the aspects critical for success.

Q4: An effective drug-delivery device can be life-changing for patients needing continuous medication, but it is important to verify devices' usability and effectiveness. What experience have you had in the design and verification and what can you highlight for our readers about the challenges and learnings along the way?

At Nemera, whilst supporting our customers' combination product journey, we ensure that requirements are established properly, and device function is verified at the appropriate levels throughout each step of the development, clinical supply, industrialisation and commercial manufacturing processes.

Patients with chronic conditions have to become independent with their treatment

administration. This is why, at Nemera, we must ensure that every device we develop is user-friendly and highly performant. Combining design research and human factors, our goal is to deliver highly patient-centric solutions that encourage adherence and provide better clinical outcomes, improving devices' practicality, functionality, and efficiency. This focus during development makes a real difference in supporting users along every stage of the patient journey.

Q5: Could you explain the importance of the human factors in the development process of an effective device?

Human factors are critical, and we think that it is also closely linked to user experience differentiation. It is critical that human factors and patient experience activities are integrated for a successful drug-device combination product development process. It's incumbent on us to ensure that the selected device, in combination with drug, is appropriate, safe and effective for the target population. This also extends to optimising the patient experience to create competitive differentiation and to ensure adherence and engagement with patients and clinical stakeholders.

A good example of this approach might consider our pen injectors or large volume wearable concept under development. These devices are going to be of interest to customers in the biologic, biosimilar or generic markets, where in many cases competitors are targeting the same reference drug or devices, and differentiation wherever possible is critical.

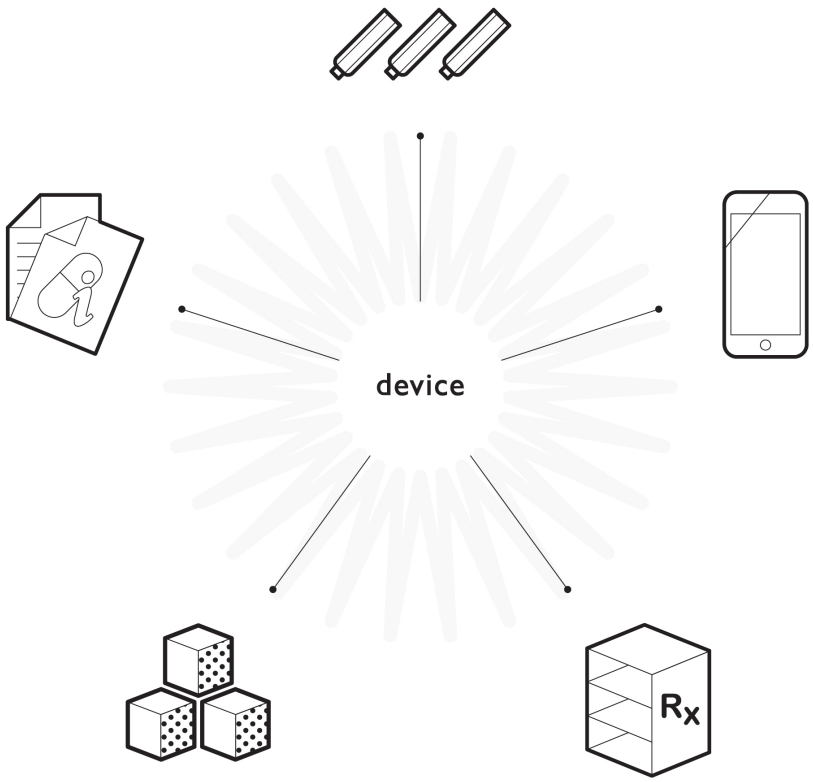
We need to be sure that we are addressing the defined user groups/populations and early use-related risk analysis activities to define the human factors and usability programme necessary for the intended regulatory/filing strategy. We also need to identify clinical risks through conducting formative and summative usability testing globally for all aspects of the device, and supporting assets in alignment with the human factors programme definition through human factors engineering report documentation for use in regulatory submissions. Human factors processes not only satisfy regulatory requirements but lead to the development of safe, effective, and differentiated combination products.

Q6: The drive to enhance biologic therapies through more convenient delivery methods is creating deal-making opportunities for companies with innovative delivery technologies. How does Nemera support organisations in this quest? Further to that point, self-administration is also a growing trend. What do you think are the key challenges in successful drug delivery and patient self-administration, considering that poor patient adherence is one of the main reasons for the ineffectiveness of a treatment? What contributions have you made to drug-delivery technologies which will help to reduce patient burden?

We believe at the earliest stages of establishing the functional requirements and user needs for a new device application, it is critical to fully understand the patient journey as well any related clinical

Key Milestones Along the Patient Journey

and Implications to Delivery Device Design



processes to ensure every decision we make is considering their needs first. This is very focused on adherence and to integrate new technologies into therapeutic areas. This foundation gained through understanding both this journey and interactions with the healthcare system and healthcare provider experience enables us to capture the complete process patients go through in managing their disease – both from a self-administration standpoint and from a longitudinal perspective – as they progress with their condition and treatment through the healthcare system and life stages.

Our team of design research experts does this by primarily utilising a technique called applied ethnography. This method relies on a combination of interviews and in-context observations of practices, processes and experiences within the patient's home or actual use environment. At this stage, potential use cases are looked at broadly, that is beyond the administration event or solely complying with instructions for use as you might see in a human factors study. This can potentially start from when a patient is first diagnosed, to receiving their device, through the entire process of preparing, administering, and disposal and the times in between treatment so we can understand how that process changes over time, and how frequency of administration may impact the patient experience. This gives the most natural view of the patient experience as related to their environment, social/emotional contexts and all the other factors that influence use. It is equally important to gain an understanding of the experience of healthcare professionals as well as to consider this in relevant settings in clinical environments. This is of particular importance in applications where care is being provided in both in-home and clinical environments as well as a migration of care, such as an oncology ward, which has built in support systems to an environment of self-administration, where clinical personnel are not present and the burden of support falls to a family member or caregiver. These cases are oftentimes driven by a migration in drug-delivery modality such as from IV to self-administered SC injection, and driven by the proliferation of biologics.

The outputs from this work include patient journey maps, clinical process maps, a robust understanding of prioritised user needs and values, and identification of pain points that can be leveraged into possibilities for improving the patient and provider experience across all aspects of the journey to make a significant impact on their lives beyond medication delivery.

This allows us to consider how to best satisfy those needs as holistically as possible while making decisions around assessing the technology landscape to identify existing IP or platforms that may be fit for the intended purposes related to function and drug product attributes. This includes decisions around modality such as auto-injector versus wearable injector, as well as variations within, if considering existing IP platforms. This includes 'surrounding the device' with custom support materials such as training programmes, instructions for use, and other means of engagement. At Nemera, we can offer customers both a variety of patient-centric IP platforms as well as custom development services to meet these needs.

Q7: Nasal delivery is the logical choice for topical treatment of local diseases in the nose and paranasal sinuses such as allergic and non-allergic rhinitis and sinusitis. New and emerging delivery technologies and devices with emphasis on bi-directional delivery, a novel concept for nasal delivery that can be adapted to a variety of dispersion technologies, are being developed. How does Nemera support these technologies?

As explained by Pascale Farjas, Nemera's Global Category Manager for Ear, Nose, Throat delivery, nasal drug delivery is a non-invasive method that allows for a rapid, high and local therapeutic effect. It offers significant opportunities for new drug development looking to deliver systemic drugs, vaccines and treatments for the central nervous system. The number of applications using the nasal route for local and systemic treatments is on the rise.

The clinical efficacy of a nasal treatment depends on how it is deposited in the nose. Since the pharmaceutical target (local, systemic, brain) is directly related to a specific nasal anatomical site, it is becoming increasingly important for device manufacturing experts to support new drug development in this area, while fostering patient adherence (i.e. easy-to-use and intuitive devices). We understand how vital it is to continue exploring customised solutions for nasal delivery treatments to address unmet medical needs. This is why we worked on a new concept, called RetroNose, to target nasal disorders through the oral cavity.

Four years ago, we initiated a collaboration with the Research Center for

Respiratory Diseases (CEPR) of Inserm and the University of Tours (France) to develop a different and portable delivery technology called RetroNose. CEPR's know-how in respiratory preclinical and clinical research joined forces with Nemera's expertise in the development of drug-delivery devices for a powerful partnership. The resulting technology, RetroNose, enables better drug deposition in the distal region of the nose without lung deposition.

RetroNose is a completely new drug-delivery device concept to dispense drug formulation to the nasal cavity. The principle of this concept is to deliver a spray through the oral cavity to deposit the drug in the nasal cavity from rear to front. The RetroNose pMDI concept involves device operation steps similar to breath-actuated pMDIs. It triggers positive pressure in the mouth from nasal expiration, possibly through mechanics or electronics. The first outcomes of our collaboration with CEPR were presented in 2018, demonstrating the advantages of RetroNose. The results show improved particle deposition in an upper airways model, which could be suitable for local, vaccine and systemic drugs delivery.

Spray triggering upon positive pressure in the mouth appears to be a promising path to ensure drug delivery in the nasal expiratory phase. In the future, a potential next step would be to test the clinical efficacy of RetroNose and its acceptance by patients through the human factors perspective.

Q8: You have a product called Novelia, your multi-dose closing tip system. Could you explain this innovative product, and the popularity behind it?

As explained by Zoe Davidson, Nemera's Global Category Manager for Ophthalmic delivery, eye drops are primarily used for glaucoma, dry eye disease (DED), conjunctivitis and allergy. For chronic diseases, when daily treatments are needed, preservative-free formulations are key to protecting the patient's ocular surface, as preservatives can cause allergic reactions and irritations, and can even damage patients' eyes. Thus, preservative-free formulations are needed for glaucoma and DED.

At present, two options are available for dispensing preservative-free ophthalmic formulations: unit-dose systems or preservative-free, multi-dose systems. Unit-doses are generally considered to be not patient-friendly, and are often costly and bulky, making them unsuitable for home use for chronic conditions.

Therefore, in order to improve patient compliance and limit waste, the preferable solution is to use preservative-free formulations with the convenience of a multi-dose bottle.

This is why we developed Novelia®, a multi-dose eye-dropper delivering consistent drops for better patient adherence, designed and developed with patients in mind.

To prevent the entry of bacteria into the bottle and/or to filter air, more than half of bottles designed for multi-dose preservative-free eye drops on the market rely on a filtering system. As significant research has been carried out that challenges their effectiveness, we developed an alternative to filters: a non-return valve system used in conjunction with a silicone membrane to filter the returning air. The non-return valve ensures that no contaminated liquid can be re-introduced to the container after the drop has been dispensed – completely removing the need to filter the liquid. The intake of air into the Novelia dispenser takes place via a separate venting system with a silicone membrane called PureFlow® Technology.

Novelia's PureFlow® has a double function: venting system for air diffusion into the bottle and flow control. Nemera has adapted the flow-control technology within Novelia that avoids multiple drop delivery into the eye and ensures that only one calibrated drop is dispensed at a time. Nemera offers three different PureFlow® versions, each tailored to formulations of differing viscosities, from highly liquid to highly viscous.

Four user studies have been conducted between 2009 and 2018 with a total of 230 people interviewed (120 in Europe / 110 in the US) including senior users with chronic eye disease. These tests concluded that 76% of patients interviewed preferred Novelia over other similar devices on the market. Contributing factors to Novelia preference included the intuitiveness of the screw-on cap and the associated reassurance, and the squeeze force required towards the end of the product's life. Novelia required only 6% more pressure to squeeze the bottle from the beginning to the end of the treatment, compared with 35% for the other device.

Also, 43% of patients think that Novelia® would enhance compliance over their current treatment.

One example of the importance of our user tests during the development phase is the choice of the blue tip of Novelia®. Originally intended to be transparent, Novelia's patented blue tip was the result of a previous user study, during the development phase. One test revealed that some patients had difficulties seeing where the drop was coming from as it emerged from the dropper. This was because the dropper valve was transparent and thus hindered patients when targeting the eye. Consequently, the valve was changed from transparent to blue, providing an obvious contrast between the dropper tip and the rest of the top. Novelia's patented blue tip continues to be a key driver of patient preference for the dropper, allowing for enhanced eye targeting and patient control. Today, the Novelia® platform includes a broad range of configurations to handle different ophthalmic formulations and is used by patients all over the world for packaging of medical devices, and both over-the-counter and prescription products. For instance, Novelia® was the first multi-dose eye-dropper approved for Rx preservative-free formulations in Europe.

Mark Tunkel

Mark Tunkel is Global Category Director, Services at Nemera. He was previously a partner at Insight Product Development, which was acquired by Nemera in 2019 and became the Insight Innovation Center. With more than 20 years of global business development experience and a deep understanding of the marketplace challenges and trends impacting the pharma industry, Mr. Tunkel has advised many of the world's leading companies on their product development and innovation strategies, with an emphasis on driving realization and the most favorable business outcomes.

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