A "smart" move: The development of electronic devices for nasal aerosols

Electronic devices in nasal aerosols can improve patient compliance and meet user needs while driving down healthcare costs

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The evolution of nasal aerosol sprays over the past forty years has been akin to a long distance race: a challenging journey with many regulatory and manufacturing hurdles to overcome along the way. Although initially used for the treatment of decongestion and allergic rhinitis, nasal sprays are now showing great promise in the delivery of drugs for breakthrough pain relief and vaccines. Innovation is set to continue as electronic "smart" devices are being integrated into designs in order to increase patient compliance, a key market driver for nasal aerosols. However, an understanding of regulations concerning product safety, alongside human factor analysis and user needs testing, is critical if "e-devices" are to provide a winning formula for nasal drug delivery.

Ahead of the game: opportunities for nasal aerosols

For nasal sprays, success in innovation has mirrored market growth. In the next three years, in the United States alone, the market for nasal therapeutics is predicted to grow to $3 billion.[1] The key factors driving market growth are patient convenience and compliance, the scientific and medical advantages of nasal drug administration,[2] and the benefits to healthcare systems in terms of reduced financial burden and reliance on trained personnel to administer drugs. The highly vascularized, large mucosal surface of the nose makes it an ideal site for drug absorption into the body.[3] A rapid onset of action is observed for low molecular weight drugs delivered to this site, thus avoiding exposure to the gut and liver, and therefore ensuring the drugs are not metabolized before they reach their primary targets. Advantages over the oral route also include ease of administration for patients who have difficulty swallowing, including children and compromised elderly patients. Nasal delivery is also beneficial for drug formulations that are not designed to survive the gastrointestinal tract. Avoiding intravenous delivery of vaccines or drugs results in treatments that are less painful for patients while the use of bio-hazardous materials or needles is avoided.

Locally-acting therapies for nasal congestion and allergic rhinitis account for the lion's share of the intranasal drug delivery market. Growth is being driven, however, by the development of systemic applications; i.e., breakthrough pain management, osteoporosis, vitamin B_{12} deficiency, smoking cessation, migraine crisis, sexual dysfunction and nocturnal enuresis amongst others. Constraints on healthcare costs will also drive opportunities for nasal drug delivery. A possible move towards

self-administration of drugs to reduce the need to pay specialized personnel, plus home therapy of the growing elderly population, could be envisaged in the future.

Patient compliance: A force driving the market

One of the key factors driving the growth of nasal drug delivery products is the search for greater patient compliance.[1] Lack of compliance, i.e., not taking the correct dose at the correct time for the prescribed duration of treatment, can be harmful to patients and has significant cost implications.[4] Recently, there has been an increased focus on human factor analysis and testing,[5,6] which considers the user's environment, the user's influences (e.g., knowledge, ability and limitations) and device design elements (e.g., complexity, interface, specifications and failure modes). Use of such input during the device design phase can increase the usability of devices by reducing use error, injuries and product recalls. It can also control current risks and reduce future risks associated with device use. In order to incorporate the input of human factors early in the development of an aerosol device, it is advantageous to conduct patient acceptance studies with prototypes. In particular, feedback on topics such as ergonomics, handling and size/visibility of displayed information can be obtained. Other human-related factors to consider are the risks associated with the use of certain medicines, for example, potent molecules. Here, specific device design elements can be introduced to manage such risks. The incorporation of feedback from users during the development of the aerosol spray products should result in a more effective and safe device that fits user needs and meets current regulatory guidance.

E-devices: Stepping up a gear

One powerful innovation to improve patient compliance and meet user needs, while driving down healthcare costs, is the addition of electronic functions to nasal sprays. Electronics are becoming smarter (i.e., smaller components, less power consumption, higher integration levels and more functions), while decreasing in unit cost. In addition, these "smart" devices are becoming an increasing part of our everyday lives (phones, tablets, apps, etc.). E-devices can allow self-dosing of treatments such as breakthrough pain medication, without direct professional supervision, by providing protection to the patient with inbuilt lockout and counter systems, if adequate training is provided, especially to elderly populations who may be less familiar with electronic devices. An "e-lockout" mechanism can provide a range of functions to improve patient compliance, including a display to notify the patient of the time until next dose, and a locking mechanism to avoid accidental overdosing or diversion with potent or controlled substances. Diversion, the non-medical use of prescription drugs, is a major problem facing the drug industry. For example, in the United States during 2010, 2.4 million people used prescription drugs non-medically for the first time.[7]

Electronic counters can give useful information to the patient about the number of doses remaining in a nasal spray, making sure that a prescription can be refilled in sufficient time so the patient is not without medicine. For the physician, via data monitoring, these "e-counters" can provide information about how and when doses have been taken, which in the long term can lead to better health outcomes for patients. For example, healthcare professionals can use data stored in an e-device to adjust a dosage regimen to improve therapeutic efficacy on a patient-by-patient basis. The data also can help physicians understand how patients groups are using the devices and how that information can be used to improve compliance. It is envisaged that, in the future, information about patient dosage taken from electronic devices could be centrally gathered to provide population data for healthcare providers worldwide, which would feed into a telehealth approach. In this scenario, the delivery of health-related services is carried out at a distance using telecommunication and information technologies, with a move towards managing patients' healthcare outcomes away from a hospital setting and in their own homes.

Patients, physicians and healthcare systems are not the only stakeholders to benefit from the development of electronic devices. The addition of electronics can provide nasal spray manufacturers with new market potential, new product applications and opportunities to advance current technology, while ensuring user needs are fulfilled. Drug companies are also able to benefit from the new market potential and new product applications e-devices can bring. The devices can also make regulatory approvals easier for controlled substances and potent molecules, and reduce medical risks and liability that may result from drug diversion. Electronic devices can assure government regulators there will be no overdosing or abuse of drugs and that additional safe and efficacious medicines can be prescribed.

"Smart" devices: Transforming high-performance drug delivery devices

Aptar Pharma, a developer and manufacturer of nasal drug delivery devices, has developed a technology platform from which a series of "e-add-on" features could

be incorporated in aerosol or inhalation devices (Figure 1). The e-Dose Counter meets regulatory recommendations for spray devices in the European Union and United States and provides a robust and lightweight design. The large counting display is highly visible, making it suitable for patients of all conditions and ages and can provide acoustic feedback and flashing displays to inform and warn patients about dosage. The e-Lockout platform counts and displays the number of actuations. Its locking system status, which prevents overdosing, has been recommended by regulators for nasal and sub-lingual spray delivery of controlled substances, such as opiates used in breakthrough pain management. Fentanyl nasal sprays, used in both the EU and US for the delivery of acute breakthrough pain medication for adult cancer patients, are an example of products which would be good candidates for e-device add-on technology. Accurate dosing is critical for these potent molecules, therefore the features provided by e-add-ons in order to prevent abuse and overdosing, as well as ensuring a constant product supply, are highly beneficial to patients.

Figure 1

Examples of electronic features currently being developed for nasal inhalation products

Hurdles to jump: Challenges facing the integration of electronic devices

For electronic devices to become an integral part of nasal pump technology, it is important that they are carefully designed to cooperate with and enhance the functionality of devices. There should be no impact, for example, on critical quality attributes of the primary drug packaging, such as dose reliability, spray quality or droplet size distribution. Products such as those mentioned above present an important scenario because these electronic devices are add-on features, rather than an integral part of the packaging. This ensures there is no impact on the original design of the nasal pump technology and avoids problems of contact if new materials were to interfere with drug formulations. The benefits of a technology platform with a series of add-on features can also provide opportunities for product differentiation or options in the life cycle management of established drug products.

Other challenges to be met before e-add ons gain success include convincing regulatory authorities of the workability and safety of the designs. The US Food and Drug Administration's industry guidance document[8] recognizes that the design of the container system can affect the dosing performance of the drug product. The composition and quality of the materials used in the manufacture of electronic devices should follow the same rules as those for container closure systems. Materials should be chosen to minimize or eliminate leachables without compromising the integrity or the performance of the drug product. Data would need to be provided to prove the robustness (i.e., exposure to temperature/humidity cycles and drop tests) of the electronic components. Data should also prove that the shelf life requirements for pharmaceutical products can be met. Batteries or power sources should not need replacing and appropriate engineering strategies should be taken to prevent any possible leakage or corrosion of battery packs. Such devices also must adhere to current waste management requirements, such as the Waste Electronic and Electrical Equipment Directive, WEEE.[9] Introduction of electronic devices into the nasal market will therefore require careful collaboration between regulators, pharmaceutical companies and device manufacturers to ensure that the devices are carefully evaluated for their effect on the safety, clinical effectiveness and stability of the final drug product.

Consumer acceptance of add-ons will also determine the success of these electronic nasal devices. The needs and preferences of the patient must be kept in mind during their design. Ease of use, safety, reliability and portability are critical aspects to consider. Patient acceptance studies would be a prerequisite in order to determine the success of electronic additions to nasal pumps. Because the cost of the device should be kept as low as possible, the development of multi-use (re-useable) models would be a solution to reduce the cost per dose. Alternatively, low-cost, disposable devices could be more appropriate where field conditions or markets require these dosing formats.

Reaching the finish line

The success of any nasal drug product depends on the active molecule(s)-excipients combination and their related formulation. Nevertheless, drug delivery devices that can also increase patient compliance, improve patient safety and ease of use, and ultimately reduce healthcare costs, will be crucial in shaping the marketplace leaders of the future. The future of nasal inhaler design will be impacted by companies that are turning high-performance drug delivery devices into smart devices to create innova-

tions that meet the needs of the key market drivers. E-devices can be a powerful solution to preventing prescription drug misuse while ensuring patient adherence. Nevertheless, evolving regulatory standards and end-user needs are important considerations in the development of electronic components. Add-on features can ensure consistent product performance, satisfactory unit cost and user acceptance. It is also envisaged that data from e-devices could be fed into a telehealth approach, where modern information technology is used to centralize data for improved patient monitoring and treatment, thus offering a winning formula for healthcare services of the future.

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