



NOVEL ADVANCES IN RAPID MANUFACTURING, DEPLOYMENT, AND DELIVERY OF INTRANASALLY ADMINISTERED DRUGS AND BIOLOGICS

In this article, Timothy Sullivan, President, Chief Executive Officer and Founder of Mystic Pharmaceuticals, provides background information on the drivers for the development of stable, nasally administered vaccines, which can be manufactured and deployed rapidly, and describes the drug delivery devices and dosage forms under development by Mystic, as well as the company's rapid form-fill-seal manufacturing processes.

INTRODUCTION

Systemic delivery of drugs, biopharmaceuticals and vaccines via the nose offers many compelling advantages including bypass of hepatic first-pass metabolism, reduced nausea and toxicity and rapid onset. Compared with parenteral administration, nasal delivery devices improve patient compliance by providing improved ease of use via either caregiver-based or self administration, as well as obviating the need for biohazardous disposal of needle sharps. These advantages are especially apparent in the case of chemical, biologic, radiation and nuclear (CBRN) threats, where nasally administered vaccines and drugs and the properly designed devices to deliver them can greatly reduce the logistical burden entailed in storage, deployment and large-scale administration. Mystic Pharmaceuticals has developed a highly adaptable platform-based nasal delivery technology that includes rapid form, fill and seal manufacturing of stabilised unit doses and highly customisable devices for precise and controlled nasal administration.

RAPID MANUFACTURING

The need for rapid manufacturing capacity for vaccines has recently emerged as a major consideration for US bio-defense preparedness policy. Lessons learned from the 2009 H1N1 flu pandemic demonstrated the need for improving

both vaccine manufacturing and fill-fit-finish production capacities. US Health and Human Services Secretary Kathleen Sebelius announced plans for major investments in Centers of Innovation for Advanced Development and Manufacturing in August 2010 with an emphasis on the development of platform based manufacturing technologies that can produce a variety of medical countermeasures and build a realistic surge capacity in the US rather than relying on foreign manufacturing.¹

While formulating vaccines for intranasal delivery is in its infancy with many vaccine manufacturers, these recent initiatives from HHS and the defense constituencies will accelerate the development of these capabilities. Federal mandates and much needed funding to advance the development of intranasal vaccines has only recently become a priority. However, there are a handful of companies that have emerged as early innovators in nasal vaccine development, including Medimmune, LLC (Gaithersburg, MD, US), Vaxin, Inc (Birmingham, AL, US), and NanoBio Corporation (Ann Arbor, MI, US), among others.

A successful transition to needle-free intranasal delivery systems for pandemic or bioterror countermeasures requires economically scalable fill-fit-finish production technology. To address this need, Mystic Pharmaceuticals has developed the MVP™ unit-dose blister production system (Figure 1).



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Figure 1: Mystic Pharmaceuticals' Versidoser™ intranasal unit dose Form-Fill-Seal production system.

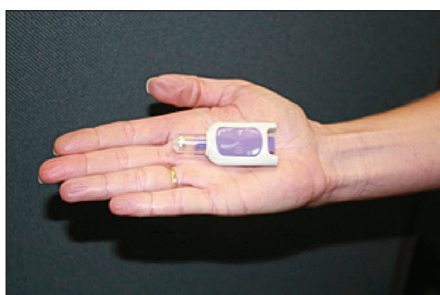


Figure 2: Mystic Pharmaceuticals' Intranasal Delivery System.

The MVP system incorporates an aseptic form-fill-seal (FFS) production process to manufacture unit-dose blisters at volumes of up to one million doses per day on a single production line. The MVP production systems employ a fully automated process for forming, filling and sealing the drug or biologic in the blister. These operations occur within a Class 100 barrier isolator to ensure sterility. Unit-dose blisters are formed using USP pharmaceutical-grade, aluminum-core, thin-film laminates. These engineered laminates provide exceptional barrier properties against oxygen, water vapour and light transmission for improved shelf stability. Additionally, MVP production systems can be configured to package live- and killed-virus vaccines, bacterial vaccines, recombinant protein- and DNA-vaccines, and small-molecule drug compounds for dose volumes ranging from 15-500 µL.

THE COMPLEXITIES OF COLD-CHAIN MANAGEMENT

Once manufactured, the proper management of immunological drugs and biologics becomes the next critical challenge. Nearly all of the current generation of vaccines designed to combat infectious diseases or bioterror pathogens – such as influenza H5N1 and H1N1, anthrax, smallpox, Ebola virus and plague – require strict adherence to cold-chain conditions throughout the product life-cycle from manufacturing, storage, transportation and through deployment and delivery.

Typically, this requires maintaining stockpiles of pre-packaged syringes in large storage facilities with transport capability at -4°C to -25°C for tens of millions of doses that are dispersed and staged across the globe in order to respond quickly in the event of a crisis.

Such daunting and expensive logistics challenges are especially burdensome for developing nations where the availability of cold-chain storage and transportation infrastructure may be virtually non-existent. Thus the cold-chain burden is the key impetus behind major development efforts to find new methods to thermostabilise drugs and biologics to reduce the logistical complexities and costs associated with storing and deploying vaccines across the globe.

Lyophilisation has been in use for decades to thermally stabilise vaccines through a freeze-drying process. Techniques such as spray drying², nano-particles³ and sugar-glass crystallisation⁴ are emerging as potentially viable alternative methods. Some compounds may be directly administered in powder form, but most first reduce the vaccine to a powder or glassy substrate that is then reconstituted back to liquid form just prior to administration. The reconstitution procedure for a lyophilised vaccine is itself a complex process, which is still typically designed for injection-based administration and requires a trained healthcare provider to ensure sterile reconstitution and accurate dose administration to the patient. Consequently, while most current thermostabilisation methods do reduce the requirements for cold-chain management, they can unfortunately complicate field deployment and remove the option for self-administration by the general population.

Intranasal delivery systems designed for safe and effective storage and self-administration facilitate rapid deployment to large populations in crisis situations while eliminating the need for biohazardous sharps disposal.

NEW PARADIGMS FOR PACKAGING AND DELIVERING THERMOSTABILISED AND OTHER MEDICINES

Novel advances in delivery technologies are upgrading the nasal route as a viable and advantageous route for systemic delivery of drugs and biologics.⁵ The possible indications range from treatments for and immunisation agents against CBRN threats such as pandemic influenza, anthrax and radiation poisoning, as well as a host of conventional drugs such as anti-emetics, anti-convulsants and hormones, and drugs for pain management, anaphylactic shock, diabetes, and migraine, to name but a few.

Non-invasive intranasal delivery can improve patient compliance within selected populations while eliminating needle sticks and biowaste. Systemic absorption via the nasal mucosa yields a rapid onset time both for therapeutics and vaccines.^{6,7} Clinical data demonstrates that vaccines can rapidly generate a local immune response within the respiratory track; a primary route of infection for airborne pathogens.^{8,9,10}

While nasal vaccine administration offers advantages, there are challenges that must be overcome. The nasal epithelium is rich in immune cells. However, protective immunity is not easily achieved because of mucociliary clearance and potentially poor absorption in individuals with nasal congestion. Vaccine developers have responded to this challenge by investigating the use of muco-adhesive agents such as chitosan and pectin to aid absorption.

In 2000, safety concerns over a nasally administered inactivated influenza vaccine were raised when patients were diagnosed with Bell's Palsy.¹¹ However, a subsequent review of the research by the US Centers for Disease Control concluded a possible Bell's Palsy risk was due to parenterally delivered inactivated influenza vaccines, reducing the probability that nasal delivery was the source.¹²

A low-cost, rapidly adaptable, and broadly applicable platform delivery technology is needed that can perform across the full spectrum of possible drug morphologies from liquid, powder, and solid to liquid and it must be capable of spanning a range of material properties. Mystic Pharmaceuticals' precision, metered, unit-dose delivery technology represents a new generation of advanced capabilities for packaging and systemic nasal administration of drugs and biologics.

Mystic Pharmaceuticals has developed two delivery platforms, the Versidoser™ and the VRx2™.

The Versidoser™ Delivery Platform (shown in Figure 2) is designed for aseptic unit-dose packaging of drugs and biologics to be directly administered as liquids (Figure 3) or powders (Figure 4). The Versidoser™ delivery device can be configured for dual-dose, bi-dose, or mono-dose regimens (see Figure 5). Further, each system can be configured for one-time use or multiple use, with replaceable tips containing the blister.

The VRx2 Delivery Platform (shown in Figure 6) is designed to package drugs or biologics that are initially in powder or solid substrate form but require reconstitution back to the liquid form just prior to administration. (Ophthalmic, otic and sublingual routes of delivery are also supported by both of these Mystic platforms.)

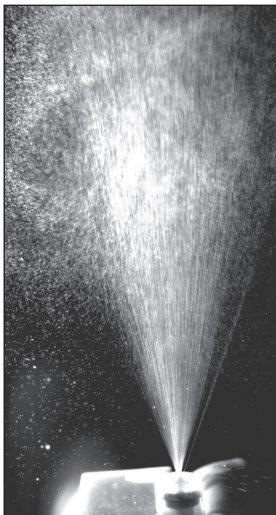


Figure 3: Liquid spray.

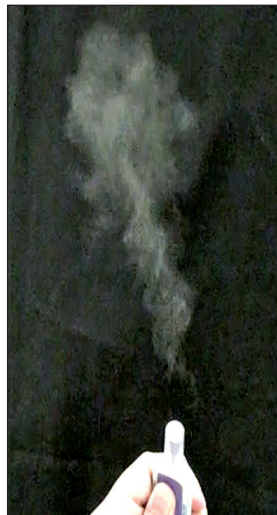


Figure 4: Powder delivery.



Figure 5: Dual-, bi- and mono-dose system configurations.

ADVANCED DELIVERY PLATFORMS

Each delivery platform comprises a customised hand-held delivery device either pre-loaded or user loadable with single or multiple aseptically packaged unit dose blisters. Each blister contains the drug or biologic material as well as a VJet™ internal piercing mechanism that also serves as the dispensing nozzle (Figure 7).

Each VJet™ is specifically optimised for the fluidic properties of the drug material such that the dispense sequence (Figure 8) results in the desired targeted spray characteristics (droplet size distribution, angle and velocity).

The VRx2™ reconstitution delivery system provides for automatic reconstitution of the drug or biologic via use of a diluent contained inside a sealed multi-chambered blister while maintaining sterility (see again Figure 6). The reconstitution procedure is virtually transparent to the user. Auto-reconstitution within the delivery device eliminates the need for trained personnel to execute the reconstitution procedure, ensures sterility up to the point of administration, and eliminates complex mixing and measuring to result in an accurate delivered dose volume.

Advanced design ergonomics of the delivery devices provide the capability to self administer, reducing the need and cost associated with a physician visit. All VersiDoser™ and VRx2™ intranasal delivery devices incorporate novel safety and ease-of-use features including the “Safety Interlock” which prevents inadvertent discharge of the device dur-

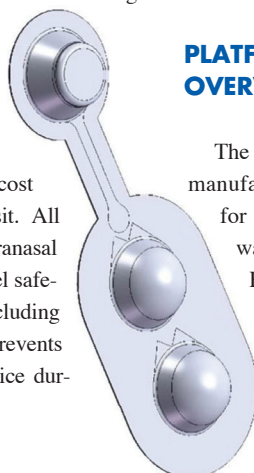


Figure 6: VRx2™ blister for reconstitution.

ing handling and secures the device from being repurposed or abused after it has been used. The user provides the force required to actuate mechanically operated mono- or bi-dose intranasal delivery systems.

Variability in the user hand strengths and actuation speeds can adversely influence spray characteristics of mechanically operated intranasal delivery systems, resulting in inconsistent delivered dose volume or spray-plume characteristics such as particle size or particle distribution, that are critical to optimum deposition and uptake within the nasal cavity. These dispensers employ a threshold-force actuation mechanism that requires a minimum force be exerted by the user before the delivery system will operate. The threshold force can be calibrated to ensure it can be used by a broad range of users. This feature reduces the influence of the user on the dispensing process and results in a consistent, reliable delivered dose volume, spray size and geometry.

The VRx2™ dry-powder delivery systems self pressurises at the time of administration and provides for direct delivery of the drug or biologic as a dry powder systemically or locally via the nasal route (see again Figure 4).

PLATFORM PERFORMANCE OVERVIEW

The MVP™ unit-dose rapid form-fill-seal manufacturing process demonstrated that for a 125 µL target fill, fill repeatability was tightly controlled within $\pm < 1.0$ µL. Figures 9 and 10 summarise the performance test results of delivered dose consistency and delivery efficiencies for a 100 µL liquid mono-dose nasal delivery system. Dose delivered volume exceeded 105µL with a high degree of consistency ($\sigma=4.8$ µL) for a

dose efficiency approaching 85% of fill volume actually delivered.

Droplet size distributions measured at two distances indicate an overall D50 median size of 65 µm (range 30-114 µm) at 35 mm and 92 µm (range 46-197 µm) at 65 mm. The span at both distances was approximately 2.3. The percentage of droplets < 10 µm was 4.3% (range 0-8.3%) and 1.9% (range 0-3.2%) at 35 and 65 mm, respectively.

The above data are representative; each performance characteristic – delivered volume and mean droplet size, for example – is readily customisable via appropriate modification of blister geometry and various piercing nozzle dimensions.

CONCLUSION

Exigencies related to the need for improved systemic administration have propelled the nasal cavity and capillaries to the forefront of preferred routes for delivery of drugs and biologics. Logistical issues of storage, ease of use and rapid deployment, especially in relation to vaccines and CBRN countermeasures, demand a quantum leap in our present ability to manufacture, store, and rapidly deploy unit doses of critical medicines that are readily accessible and simple to administer. Mystic Pharmaceuticals



Figure 7: Mystic VersiDoser™ unit-dose Blister with VJet™.

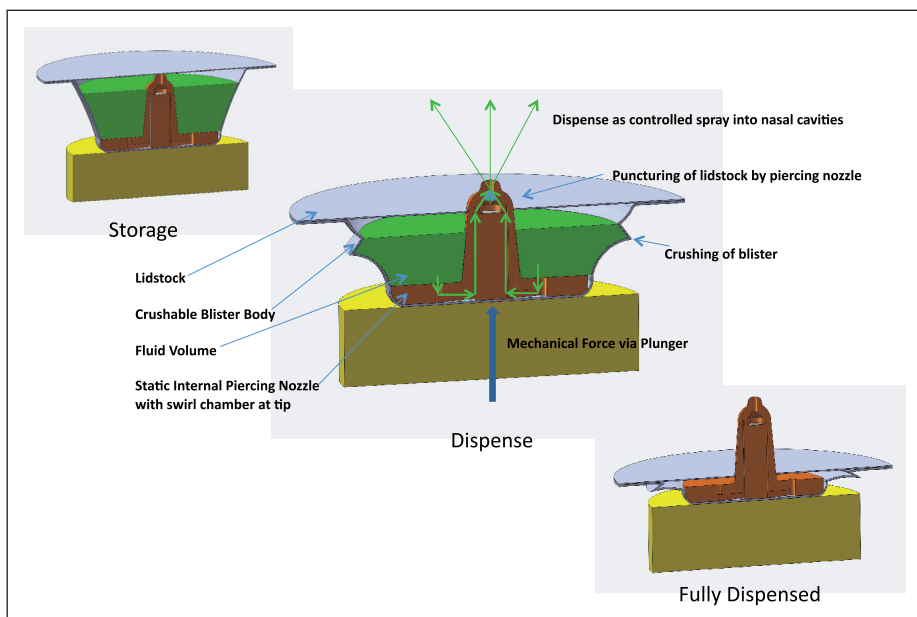


Figure 8: Versidoser™ unit-dose blister dispense sequence.

has developed a platform nasal delivery technology that addresses each of the present pitfalls in the current production to administration chain from packaging to final use and disposal.

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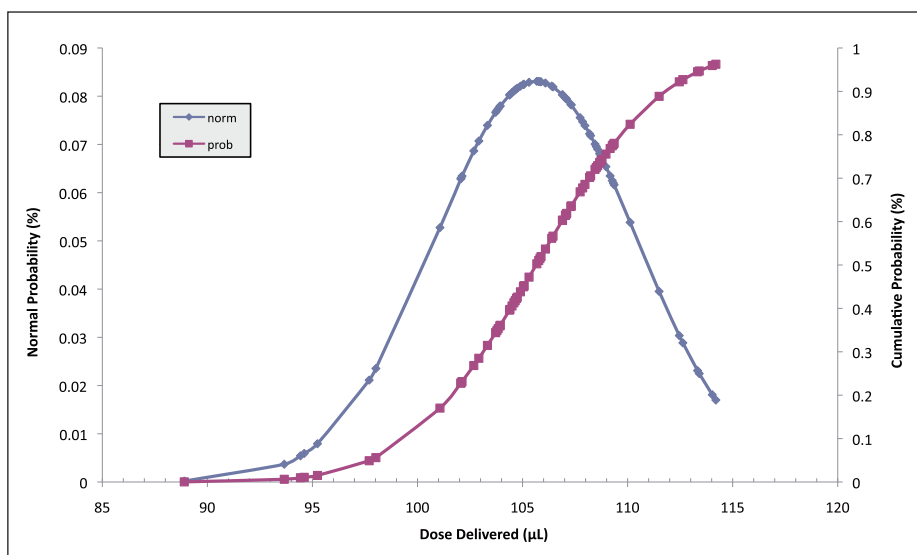


Figure 9: Versidoser™ nasal (as liquid) dispense efficiency.

n	70
Mean	105.65 µL
Median	105.99 µL
Eff(%)	84.52
stdev	4.80
min	88.90 µL
max	114.2 µL

Figure 10: Dose summary.

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