

Inhalation

Volume 4 Number 5

October 2010



Software for respiratory device testing
High pressure homogenization
Intranasal vaccines: Protecting public safety

Intranasal vaccines: Protecting public safety

In a pandemic or bio-terror event, faster production, deployment and delivery for less cost are the mission

Timothy Sullivan
Mystic Pharmaceuticals

Novel advances in intranasal delivery technologies are broadening the nasal route as a viable solution for systemic delivery of a wide range of drugs, biologics and vaccines.¹ Nasal delivery offers compelling advantages including bypass of hepatic first-pass metabolism, reduced nausea, reduced toxicity and rapid onset. In addition, non-invasive nasal delivery systems eliminate the risk of inadvertent needle sticks and the disposal of biohazardous “sharps,” a safety concern of vaccines administered with a syringe. Precision, metered dose, intranasal delivery systems, introduced by device manufacturers such as Mystic Pharmaceuticals, Aptar Group and Optinose, provide the capability for individuals to safely self-administer. This capability to self-administer reduces dependency on trained healthcare personnel, a critical consideration for rapid deployment of therapeutics or vaccines to large populations in crisis situations such as a pandemic or bio-terror event.

Protecting the Public

The H1N1 flu of 2009 was the fourth influenza pandemic event in the past 100 years. The 1918 Spanish Flu is believed to have originated in the US. It reached all corners of the globe and killed between 25-50 million people worldwide in two years. The 1957 to 1958 Asian Flu killed one to four million people. The 1967 to 1968 Hong-Kong Flu pandemic killed an estimated two million worldwide.

Responding to the expanding combined threats of virulent infectious diseases and bio-terror agents, the

The White House
December 30, 2009



Executive Order – Medical Countermeasures Following a Biological Attack²

“The Secretaries of Health and Human Services and Homeland Security, in coordination with the US Postal Service, within 180 days of the date of this order, shall establish a national US Postal Service medical countermeasures dispensing model for US cities to respond to a large-scale biological attack, with anthrax as the primary threat consideration.”

—Barak Obama

United States government created the Biomedical Advanced Research and Development Authority (BARDA) within the Department of Health and Human Services (HHS) in 2006. BARDA was specifically chartered and funded to plan, develop and procure qualified countermeasures to protect the US population against such threats.

A key initiative of BARDA and similar government organizations around the world is the acquisition and stockpile of medical countermeasures to proactively protect civilian and military populations. In the US, the Center For Disease Control (CDC) and Department of Homeland Security (DHS) are jointly responsible for managing the Strategic National Stockpile (SNS). The SNS is a strategic repository for hundreds of millions of doses of vaccines and drugs, pre-packaged in pills, syringes and other dosage forms, for rapid deployment in the event of a pandemic or bio-terror crisis. The current paradigm for vaccine production, packaging and deployment requires long lead times. This current reality makes stockpiling a necessity to ensure a sufficient supply and rapid response to a crisis. This stockpiling strategy comes at significant cost. Recent directives announced by HHS Secretary Katherine Sebelius point

to shifts in US strategy to build rapid manufacturing capacity for the production of vaccines and biomedical countermeasures.³

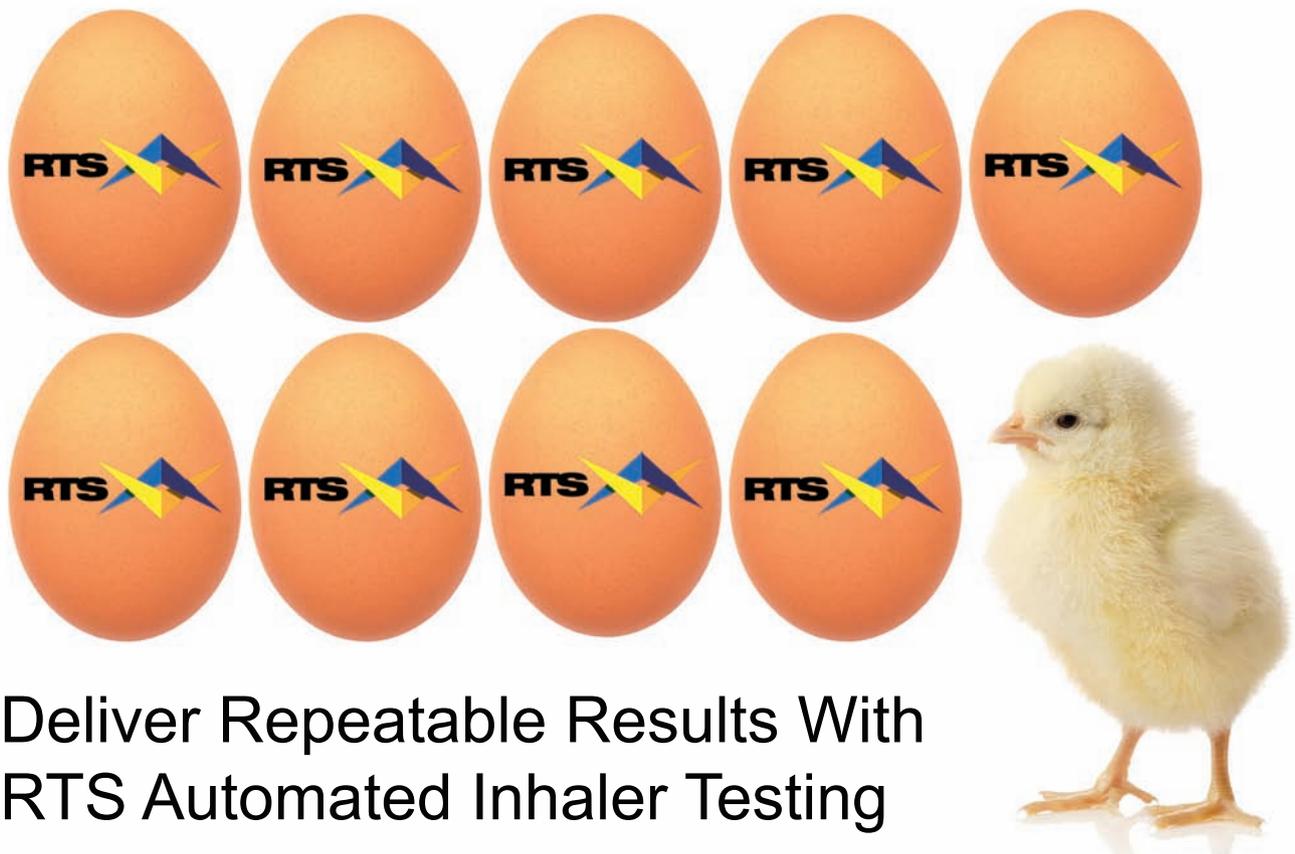
Vaccine Stockpile Challenges

Most of the current generation of vaccines designed to combat infectious diseases or bio-terror pathogens such as H5N1, H1N1, anthrax, smallpox, Ebola or plague must be stored, transported and deployed under strict cold chain conditions. Typically, this requires storing and transporting vaccines at -4 °C to -25 °C to the point of dispensing (POD) for tens of millions of doses potentially dispersed across the globe. Cold chain management must be rigorously maintained up to the point of administration to the patient or the potency of the vaccine is at risk. These logistics are a daunting and expensive challenge for developed nations, while the availability of extensive cold chain management and transport infrastructure in developing nations is virtually non-existent. The requirement for cold chain is driving major development efforts to find new methods to thermostabilize vaccines to reduce the logistical complexities and cost of storing and deploying vaccines to global populations.

Freeze drying techniques such as lyophilization have been in use for more than a decade to thermostabilize temperature sensitive vaccines. Techniques such as

spray drying,⁴ nano-particles⁵ and sugar glass crystallization⁶ are emerging as potentially viable alternative methods. Most of these methods reduce the vaccine to a powder that must either be reconstituted to liquid form just prior to administration or delivered as a powder. The reconstitution procedure for a powdered vaccine is complex, typically designed for injection-based administration and requires a highly trained healthcare provider to ensure sterile reconstitution and accurate dose administration to the patient. This one-to-many approach reduces the requirements for cold chain storage but can increase the deployment cost and complexity while eliminating the option for self-administration by the general population.

Stockpiled medications have limited shelf life and must be destroyed and replaced upon expiration. Influenza viruses employ a genetic structure that enables them to mutate.⁷ This capability can render a stockpiled vaccine ineffective. In addition, safe disposal of millions of doses of vaccine and replacement cost become a significant ongoing cost element of the stockpile paradigm. During 2010, forty million doses of H1N1 vaccine produced in the fall of 2009 were discarded at a cost of \$260M with an expected 31 million additional doses to be destroyed in the US alone.⁸ A 2008 US Government Accountability Office (GAO) report estimated that \$100 million of stockpiled



The advertisement features a row of ten orange eggs, each with the RTS logo (a stylized blue and yellow mountain range) and the letters 'RTS' in black. To the right of the eggs is a small, fluffy yellow chick. Below the eggs and chick, the text reads: 'Deliver Repeatable Results With RTS Automated Inhaler Testing'.

anthrax vaccine would expire each year.⁹ The ongoing costs of storing and replacing expired medical countermeasures in the Strategic National Stockpile are an element of the true economics of the cost per delivered dose calculation. However, these costs can be easily overlooked when evaluating new vaccine production and alternative delivery systems that can improve the overall economics of protecting large populations against pandemic or bio-terror threats.

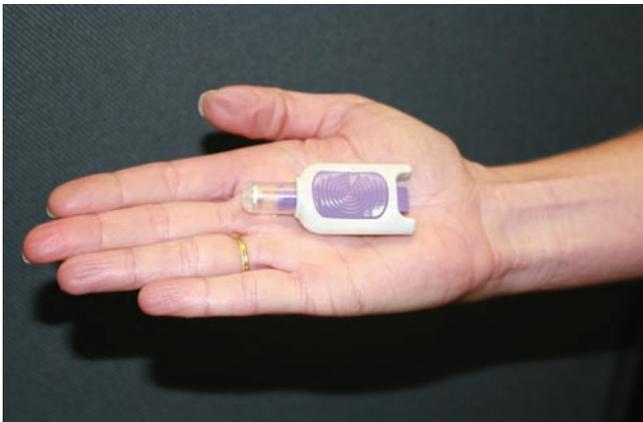
Traditionally, most vaccines have been developed for intramuscular or sub-cutaneous administration via syringe injection. This approach requires administration by trained healthcare personnel and, when applied to mass vaccination campaigns, requires a well orchestrated healthcare infrastructure and coordinated logistics that can be sustained under crisis conditions across large geographies.

Post-event analysis of the recent H1N1 pandemic and the January 2010 report released by the Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism¹⁰ point to serious shortfalls in US preparedness to respond to a pandemic or widespread bio-terror event.

Stockpiling requires ongoing investments of billions of taxpayer dollars to maintain and replenish. Combined, these realities are driving demand for a new paradigm of technologies and infrastructure that can economically accelerate the production, packaging, deployment and delivery of medical countermeasures to large populations while reducing the costs associated with stockpiling.

Advanced Vaccine Delivery

Innovations in non-invasive vaccine delivery encompass a variety of techniques including transcutaneous patches, micro-needles, pulmonary inhalation, ballistic delivery through the skin and intranasal adminis-



Nasal delivery systems can be self-administered, enabling them to be deployed and used with nominal training or instructions.

tration. Non-invasive intranasal delivery may offer compelling advantages over traditional parenteral delivery using needles for administration of vaccines and medical countermeasures. Medimmune was an early pioneer in intranasal vaccines with FluMist, commercially introduced in 2003. The FluMist vaccine utilized the Accuspray intranasal delivery system developed by Becton Dickinson (BD). Optinose, Becton Dickinson (BD) and Mystic Pharmaceuticals have developed intranasal delivery systems capable of administering both liquid form and dry powder vaccines. BD's T107 inhalation device dispenses the vaccine as a dry powder, while Mystic's VRx2 auto-reconstitutes the powdered vaccine to a liquid form at the time of administration and dispenses it as a liquid. These technologies offer the advantage of non-invasive delivery of thermostabilized powder vaccines. Mystic's VersiDoser and VRx2 intranasal delivery systems are designed to be deployed into the population and self-administered.

The option for self-administration reduces the demand for a trained healthcare infrastructure and enables alternative point of distribution (POD) strategies to be employed in a crisis. Non-invasive intranasal delivery reduces the risks of inadvertent needle sticks and biohazardous sharps disposal and can improve compliance within selected populations. Systemic absorption via the nasal mucosa yields a rapid onset time for both therapeutics and vaccines.^{11,12} Clinical data demonstrates that vaccines will rapidly generate a local immune response within the respiratory track, a primary route of infection for airborne pathogens.^{13,14,15}

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 reduce mucociliary clearance. In 2000, safety concerns over a nasally-administered inactivated influenza vaccine were raised when patients were diagnosed with Bell's Palsy.¹⁶ However, a subsequent review of the research by the Center 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 of the Bell's Palsy risk.¹⁷

Protecting large populations from the combined threats of pandemics and bio-terror agents in a manner that is responsive, effective and sustainable requires major innovations in vaccine formulation, rapid manufacturing, logistical deployment and deliv-

The Self-Administration Controversy

Self-administration of vaccines and medical countermeasures continues to be a controversial subject. Concerns raised point to the general population's ability to properly administer an intranasal vaccine and technical performance issues of the delivery system. Variability in a user's hand strength and in actuation speed can adversely influence spray characteristics of mechanically operated, intranasal delivery systems. This can result in inconsistent delivered dose volume or plume characteristics, critical to optimum nasal deposition. These concerns are countered by the inherent weaknesses of the current point of dispensing (POD) model, requiring people to gather at centralized locations to receive a vaccine by trained healthcare personnel and the need for rapid deployment across large populations in a crisis situation. Federal agencies and world health organizations responsible for protecting public safety are investing in the development of the self-administered option for selected bio-threats.¹⁸ The new generation of nasal vaccines and delivery systems under development by companies such as Medimmune, Vaxin, Novavax, BD, Optinose, Aptar and Mystic Pharmaceuticals are designed to overcome the personal use and technical concerns.¹⁹

ery. The ideal non-invasive vaccine delivery solution would be:

- safe and effective for a wide range of vaccines and medical countermeasures
- intuitively simple to use while providing precise dose administration under a variety of field operating conditions
- cost effective rapid manufacture (fill, fit, finish) at production volumes of one million doses or more per day
- deployable through existing, well established distribution channels
- adaptable to both liquid and powder vaccine formulations
- safely disposable after use
- capable of administering liquid and reconstituted vaccines

Rapid Manufacturing

Another critical element of the US preparedness strategy is the capability to rapidly manufacture and package vaccines in final form within the US. Domestically based rapid manufacturing capacity has recently emerged as a major consideration for US bio-defense preparedness policy. Lessons learned from the H1N1 pandemic demonstrated the need for improving both vaccine and fill, fit, finish production capacities.¹⁸ In August 2010, Health and Human Services Secretary Kathleen Sebelius announced plans for major investments in Centers of Innovation for Advanced Development and Manufacturing 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.³

Advances in vaccine development technologies, such as Novavax's Virus Like Particle platform combined with rapid vaccine production platforms like

Xcellerex's FlexFactories, are establishing the new generation of rapid manufacturing for vaccines. 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 funding to advance the development of intranasal vaccines and delivery systems has recently emerged as a priority. However, there are a handful of companies that are early innovators in nasal vaccine development. Some of these include Medimmune, Novavax, Vaxin, Inc. and AVIR Green Hills Biotechnology.

A successful transition to needle-free intranasal delivery systems for pandemic or bio-terror countermeasures requires economically scalable fill, fit, finish production technology. To address this need, Mystic Pharmaceuticals has developed the MVP blister production system. The MVP system incorporates an aseptic form, fill, seal production process to manufacture and fill intranasal vaccine at volumes of up to 300,000 doses per production day/line. Consequently, four MVP production systems would have the capability to fill more than a million doses per day, which could reduce the need for advanced stockpiling.

Conclusion

The true economic costs and logistic requirements of the current stockpile paradigm for medical countermeasures are unsustainable over the long term, given the challenges of protecting large populations against the broad array of threats. Manufacturing and stockpiling tens to hundreds of millions of doses of vaccines packaged in syringes for long durations is expensive. The requirement for inventory rotation and cold chain storage add significantly to cost and complexity. Point of dispensing (POD) deployment models, caregiver based administration under potential crisis conditions and safe disposal of millions of biohazardous sharps must evolve to a more cost

effective, reliable and responsive strategy to effectively protect the US population.

The emerging vision for protecting the public against pandemic and bio-terror threats is expected to embrace rapid manufacturing for medical countermeasures and fill, fit, finish packaging. Thermo-stabilized vaccines, deployment through conventional, established, distribution channels as well as non-invasive, self-administered, intranasal delivery technologies will play a key role in shaping the new paradigm for protecting the US population and military personnel. Shifting to this new paradigm requires embracing a systems perspective, overcoming inertia and the inevitable struggles that arise as business economics shift to a new structure. At potential risk are millions of human lives and national economies.

References

1. Global Industry Analyst, Inc., Intranasal Drug Delivery, June 2007.
2. Office of the President, Executive Order – Medical Countermeasures Following a Biological Attack, December 30, 2009.
3. Secretary Kathleen Sebelius, US Department of Health and Human Services, Review for New Federal Approach to Medical Countermeasures Press Release, August 19, 2010.
4. Hickey, Anthony J. AAPS PharmSciTech, Formulation of a Dry Power Influenza Vaccine for Nasal Delivery, Article 19, 2006.
5. Shahiwala, Aliasgar. Nanocarriers for Systemic and Mucosal Vaccine Delivery, Department of Pharmaceutical Sciences, School of Pharmacy, Northeastern University, Bentham Science Publishers Ltd., December 4, 2006.
6. Alcock, Robert. Sci Transl Med, Long Term Thermostabilization of Live Poxviral and Adenoviral Vaccine Vectors at Supraphysiological Temperatures in Carbohydrate Glass, The Jenner Institute, University of Oxford, Vol. 2, Issue 19, February 17, 2010.
7. Lindstrom, Stephen E. Journal of Virology, Comparative Analysis of Evolutionary Mechanisms of the Hemagglutinin and Three Internal Protein Genes of Influenza B Virus: Multiple Cocirculating Lineages and Frequent Reassortment of the NP, M, and NS Genes, 1999 May;73(5):4413-4426.
8. Drug Discovery & Development, Quarter Billion Dollars of Swine Flu Vaccine to be Destroyed, July 01, 2010.
9. US Government Accountability Office, Project Bio-shield: Actions Needed to Avoid Repeating Past Problems with Procuring New Anthrax Vaccine and Managing the Stockpile of Licensed Vaccine, October 2007.
10. Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism, Prevention of WMD Proliferation and Terrorism Report Card, January 26, 2010.
11. Asanuma H, Hirokawa K, Uchlyama M, Suzuki Y, Aizawa C, Kurata T, Sata T, Tamura S. Immune Responses and Protection in Different Strains of Aged Mice Immunized Intranasally with an Adjuvant-Combined Influenza Vaccine, Vaccine, July 2001;19(28-29):3981-3989.
12. Pires A, Fortuna A, Gilberto A, Falcao A. Intranasal Drug Delivery: How, Why and What for? J Pharm Pharmaceut Sci, Oct 2009;12(3)288-311.
13. Illum L. Nasal Drug Delivery: New Developments and Strategies, Drug Discov Today, 2002;7:1184-1189, PubMed DOI: 10.1016/S1359-6446(02)02529-1.
14. Groneberg DA, Witt C, Wagner U, Chung KF, Fischer A. Fundamentals of Pulmonary Drug Delivery, Respir Med, 2003;97:382-387, PubMed DOI: 10.1053/rmed.2002.1457.
15. Roth Y, Chapnik JS, Cole P. Feasibility of Aerosol Vaccination in Humans, Ann Otol Rhinol Laryngol, 2003 Mar;112(3):264-270, U.S National Library of Medicine, PubMed.gov.
16. Mutsch M, Zhou W, Rhondes P, Bopp M, Chen R, Linder T, Spyr C, Steffen R. Use of the Inactivated Intranasal Influenza Vaccine and the Risk of Bell's Palsy in Switzerland, NEJM, 2004;350:986-903.
17. Zhou W, Pool V, DeStefano F, Iskander JK, Haber P, Chen RT. A Potential Signal of Bell's Palsy After Parenteral Inactivated Influenza Vaccines: VAERS Working Group. Epidemiology Program Office, Centers for Disease Control and Prevention, commented in Pharmacoepidemiol Drug Saf, 2004 Aug;13(8):505-10.
18. Gottlieb S. Responding to the H1N1 Pandemic with Vaccines: Vulnerabilities and Lessons Learned, American Enterprise Institute For Public Policy Research, AEI Outlook Series, November 2009.
19. PATH, Landscape Analysis: Trends in Vaccine Availability and Novel Vaccine Delivery Technologies: 2008-2025, June 2008.

Timothy Sullivan is the President, Chief Executive Officer and founder of Mystic Pharmaceuticals, Inc., 2006 Windy Terrace, Austin, Texas, 78613, US. Tel: +1 512 918-2900, tsullivan@mysticpharmaceuticals.com. Website: www.mysticpharmaceuticals.com.