

AN EVOLUTIONARY APPROACHS IN DEVELOPMENT OF NEEDLE FREE INJECTION TECHNOLOGIES

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ABSTRACT

The demand for novel drug delivery technologies is ever increasing though majority of the drugs are administered via oral, inhalation, transdermal and parenteral route. However, there are large numbers of therapies, particularly protein-based, gene-based and vaccine-based that cannot be delivered by this route for example insulin, growth hormones and other similar biologics. This emerging technique is a major sector in drug delivering system. It offers numbers of benefits for instances, reduced needle phobia, better patient compliance and reduce risk of needlestick injury. Moreover, this work by forcing liquid medication at high speed through a tiny orifice that is held against the skin. This creates an ultrafine stream of high pressure fluid that penetrates the skin without the use of a needle thus faster administration of drug compared to conventional needles. Its low cost provides benefits to patients and health professionals. Several technologies are available on the market including Ferring's Zomajet 2 Vision, Merck Serono's Saizen Cool.Click and Teva's Tev-Tropin Tjet etc. There appear to be tremendous opportunity for needle-free technology to have major impact in the industry. It is likely that dramatic change may occur only when a large pharmaceutical or biotechnology company adopts needle free technology and demonstrates it needle free injections are well being supported by organizations like WHO and CDC (Centre for Disease Control). It become more feasible technology for injecting the protein based drug's versatility, acceptance and value in major therapeutic area.

INTRODUCTION

The demand for novel drug delivery technologies is ever increasing. These drug delivery technologies can be broadly classified into four principle routes like oral, inhalation, transdermal and parenteral. The main goal for the delivery of any drug therapy is oral administration with once or twice daily dosing. However, there are large numbers of therapies (protein-based, gene-based and vaccine-based) that cannot be delivered by this route for example insulin, growth hormones and other similar biologics. Pulmonary delivery is suitable for small molecules and proteins. However, for drugs with very large molecular weights (monoclonal antibodies), penetration through the lung for systemic delivery may require some type of transport enhancement mechanism. The pitfalls of needle-based injections are psychological resistances to self-injection or needle-phobia, awareness of serious problems has caused physicians and their patients to either delay therapy initiation or seek out less-invasive alternatives and even at some cost to clinical effectiveness. To overcome the problems related to needle based injections, there is one technology that has received considerable attention during the past few years and that offers all of the sought after benefits is— Needle Free Injection Technology (NFIT) [1]. These technologies have been developed for injecting liquid formulations, as well as injecting drugs and vaccines in a solid dosage form. Several liquid jet injection technologies are available on the market including Ferring's Zomajet 2 Vision, Merck Serono's Saizen Cool.Click and Teva's Tev-Tropin Tjet, which are all human growth hormone products [2]. This technology was first described in the 19th century in France, when the French company-H Galante-manufactured an 'apparatus for aquapuncture'. It was first commercialised in the US in 1960s. Bioject had summed up the reasons for it in their brochure stating "Patients hate needles, healthcare professionals fear accidental needle stick injuries, drug companies are looking for new and innovative ways of delivering their products. PowderJet Pharmaceuticals one of the first companies to develop a needle-free technology for injecting powdered drugs into the skin. Avoiding the use of needles, the technology also enabled a drug to be used in solid dosage form, which enhances the stability of the product while also offering the opportunity for controlled release. In general, needle-free injection technology works by forcing liquid medication at high speed through a tiny orifice that is held against the skin. This creates an ultra-fine stream of high-pressure fluid that penetrates the skin without the use of a needle. The design of the device has a major influence on the accuracy of subcutaneous delivery and the stresses imposed on the product to be delivered. Several companies are

involved in development of this technology, which includes, Antares Pharma Inc, Aradigm Corporation, Bioject Medical Technologies Inc and Biovalve Technologies Inc. The human growth hormone market, (Pfizer, Merck Serono, Genentech and Novo Nordisk) that offer multiple delivery technologies for human growth hormone. It is a high velocity dry powder injection, a new development in drug delivery, provides needle free and pain free delivery of traditional and biotechnology drugs and vaccines. For delivery via skin, the particles must only breach the outermost barrier, the stratum corneum. So, drugs delivered with powderjet's technology or Needle Free Injection (NFI) reach the circulatory system faster than those administered by subcutaneous injection, because it's an intradermal delivery and the capillary blood supply is immediately adjacent to where you're placing the drug. Appropriately formulated fine particles of 1 - 70 μm diameters are accelerated to sufficiently high velocities in a hand held device [3,4]. The technology can be applied to traditional small molecules, peptides, proteins, or DNA, i.e., any pharmaceutical agent or vaccine that can be formulated into solid particles of the appropriate size distribution, mass and strength, and it also successfully deliver testosterone, lidocaine hydrochloride, and macromolecule such as calcitonin and insulin [5,6]. Improvements in vaccines and their delivery systems that increase vaccine efficacy, safety, or compliance and minimize animal stress would be valuable for the dairy industry. Needle-syringe devices have been the predominant method for vaccine and drug delivery for dairy cattle. Although needle-syringe devices are inexpensive and easily adaptable to different settings, needle-free technology offers significant advantages compared to conventional vaccine delivery methods including enhanced safety, enhanced immunogenicity, and fewer injection site lesions [7]. Needle-free injection devices can be divided into 2 types based on the source of power: spring-powered or compressed gas-powered. Spring-powered devices are compact and lower cost, but suffer from limited range of force and reduced versatility. Spring-powered devices have been primarily used for subcutaneous administration of drugs. Gas-powered devices (jet injectors) have sustained force generation, greater flexibility, and the ability to deliver larger volumes [8,9].

NEEDLE-FREE TECHNOLOGY: ORIGIN AND METHODOLOGY

Needle-free technology (Jet injectors), were developed in the 1930s and used extensively over 50 yr in mass vaccination programs in people for smallpox, polio, and measles [10]. Using mechanical compression to force (generated by a compressed gas typically air, CO₂ or nitrogen) fluid through a small orifice, these devices produced

a high-pressure stream that could penetrate skin and subcutaneous tissue to deliver the vaccine. When administered through the skin, an ultra-fine stream of fluid penetrates the skin, delivering the vaccine in a fraction of a second to the skin, subcutaneous tissue, and underlying shallow muscle. One major problem to needle-free injections has been the wetness associated with residual vaccine on the skin surface [11], may cause the vaccine administrator to think that the vaccine was improperly administered. Needle-free injection technology has been designed to deliver antibiotics [12], iron dextran [13] or vaccine comfortably, accurately, and quickly - without the use of a needle. Needle-free injection is precise, reliable, and virtually the same every time [14]. There are 3 stages in needle-free delivery: Stage 1, the peak pressure phase, optimal pressure used to penetrate the skin (< 0.025 sec); Stage 2, the delivery or dispersion phase (~ 0.2 sec); and Stage 3, the drop-off phase (< 0.05 sec). This pressure profile is consistent with each administration of vaccine ensuring each animal is vaccinated at the proper tissue depth. The needle-free injection technology improves the dispersion of medication throughout the tissue. As the fluid stream forces its way through the tissue, it follows the path of least resistance, resulting in a widely dispersed, spider-web-like distribution of the medication [15].

ADVANTAGES OF NFI TECHNOLOGY

The technology allows patients to self-administer, reduces tissue damage and distributes medicine more effectively and widely in the subcutaneous tissue without penetration in to deeper layers [16]. Delivery by this means could consequently induce mucosal as well as humoral immunity. Important therapeutic and / or prophylactic advantages over the other drug delivery techniques are following:

- Avoid real as well as needle phobia based pain and obviate needle stick hazard and sharps disposal.
- Enhance stability by ambient storage and delivery as a dry powder and eliminate complexity of reconstitution and any effects of shear.
- Provide rapid delivery and reproducibility comparable with needle and syringe and improve bioavailability over other non- or less invasive drug delivery systems.
- Improve immune response to DNA and conventional vaccines
- Provide the capability to alter the pharmacokinetics of certain drugs
- Jet injectors are used to deliver mass immunization of influenza, tetanus, typhoid, diphtheria, pertussis, and hepatitis A vaccines.

- Injection sites from needle free jet injectors may also tend to bleed more than those at a needle injection site [17].

ADVANTAGES OVER CURRENT NEEDLE-SYRINGE ADMINISTRATION

In addition to delivering vaccines that result in a protective immune response, needle-free vaccine delivery offers significant advantages for dairy producers over conventional needle-and-syringe vaccine administration including:

- Targeted immune response and improved carcass quality by eliminating broken needles and reducing carcass bruising and abscesses.
- Smaller volume of vaccine.
- Reduced mechanical spread of infectious disease and improved safety for workers by eliminating accidental needle sticks when using traditional needle-and-syringe administration.
- Safety, use of needle-free injections avoids risks of accidental needle stick injuries for friends, family and healthcare workers. Contaminated needles can transmit HIV, hepatitis, and other blood-borne pathogens, and pose a major risk to health.
- Reliable, repeatable delivery of insulin into subcutaneous tissue and remove the danger of needle-stick injuries.
- Ideal for those who dislike injecting with needles and remove the need for disposal of contaminated sharps.
- May help avoid skin problems associated with using needles
- The only maintenance needed for the SQ-PEN is to change the nozzle assembly once every two weeks.

COMPLEMENTARY APPROACHES TO NFI

There are two approaches to NFI: liquid and powder drug delivery.

(1) Liquid based NFI

The principle of NFI was first demonstrated in 1936 but the second generation of NFI technologies came during the 1970s and 1980s and focused primarily on the insulin market for diabetes therapy [18,19]. These technologies are used by the same basic principle to deliver the drug, if a high enough pressure can be generated by a fluid in intimate contact with the skin, and then the liquid will punch a hole in to the skin and be delivered in to the tissues in and under the skin. Although the same principle is applied as in powder but there is difference in the actual design and operation of the devices. Device has major influenced by the accuracy of delivery and stress subjected to the product delivered. The device has sufficient pressure to puncture the skin.

Table 1: Market product of liquid based NFI [20-27]

S. No.	Technology with Company	Applications
1.	Intraject (Weston medical)	Applicable to drugs including proteins, peptides, monoclonal antibodies, small molecules and vaccines.
2.	Medi-Jector vision (Antares Pharma, Inc.)	It uses pressure to create a micro thin stream of insulin that penetrates the skin.
3.	Penjet (Penjet Corporation)	A pre filled and disposable needle free injector.
4.	Med-E- jet (Evans enterprise)	Needle free injection
5.	Advantaget (Advantage health services Inc.)	Needle free injection
6.	Gentlejet (Health for personal care corporation)	Needle free injection
7.	J-Tip (National medical products, Inc. (NMP))	Pain free injection of insulin for diabetes.
8.	Injex (Equidyne Systems, Inc.)	Reusable spring powered device
9.	Medajet- XL (M.E.C. in U.S.A.)	Delivering local anaesthetics

(2) Powder based NFI

The Powderject system for particle delivery is the combination of a device with a specially formulated powdered drug. The principle of all the devices is the same; i.e. the harnessing of the energy of a transient gas jet to accelerate a pre measured dose of particulate drug formulation. The most common orifice size is 0.127mm, compared to a 25-gauge needle, which is about 1mm. So, process is completely painless. The Powderject systems are powered by a manufactured helium gas aluminum microcylinder of ampoule design and use a drug cassette or package to introduce the powder into the

gas flow. In operation, the microcylinder tip can be broken when the device is pressed against the tissue site to be treated. This releases the compressed helium suddenly to open the drug cassette for delivery of its payload to the tissue.

The gas does not actually penetrate the skin, instead, it is reflected back in to the device through a silencer [28,29]. The Powderject injection systems for intermittent use are fully disposable and contain all the required components within a fully assembled, sealed system. Drug or vaccine penetration will occur through the stratum corneum in to the epidermis.

Table 2: Market product of powder based NFI [30]

S.No.	Technology with Company	Applications
1.	Powderject (Powderject pharmaceuticals)	Delivered inulin to hairless guinea pigs, delivery of large macromolecules across the skin, used for intradermal DNA immunization against influenza a virus in mice.
2.	Jet injectors	Proteins such as B- interferon as well as small organic conventional therapeutic agents such as lidocaine (lignocaine) for local anaesthesia.

HOW IS A NEEDLE-FREE INJECTION SYSTEM MADE?

Needle-free injection systems are novel ways to introduce various medicines into patients without piercing the skin with a conventional needle. They can take the form of power sprays, edible products, inhalers, and skin patches. While hypodermic needles were first introduced during the 1800s, needle-free systems are relatively recent inventions. Today, they are a steadily developing technology that promises to make the administration of medicine more efficient and less painful.

Raw Materials

Since these devices directly contact the body, they must be made from materials that are pharmacologically inert, withstand high temperatures because they are heat-sterilized. The outer shell of the device is made from a high strength, lightweight thermoplastic such as polycarbonate. Polycarbonates are polymers produced synthetically through various chemical reactions and make the polymer easier to mold, fillers are added. These fillers make plastics more durable, lightweight, and rigid. Colorants are also incorporated into the plastic to modify the appearance. Prior to manufacture, the plastics are typically supplied in pellet form with the colorants and fillers already incorporated. Air-forced systems typically use carbon dioxide or helium gas to propel the medicine into the body. Certain types of medicines work better with needle-free injection systems than other. Insulin, which must be administered daily to diabetics, can be incorporated into an inhaler system. Lidocaine hydrochloride, a local anesthetic is suitable to be delivered needle free. Other medicines suitable for needle free systems include Fentanyl (an opioid analgesic), Heparin (an anticoagulant) and a variety of vaccines. Various adjunct ingredients included in these medicines include cyclodextrins, lactose, liposomes, amino acids and water.

Design

The air-forced needle-free injection systems are typically made up of three components including an injection device, a disposable needle free syringe and an air cartridge. The injection device is made of a durable plastic. It is designed to be easy to hold for self-administration of medicine. The needle-free syringe is also plastic. It is sterilized and is the only piece of the device that must touch the skin. The syringe is made to be disposed after every use. For portable units, pressurized metal air cartridges are included. Less mobile devices have air hook-ups that attach to larger containers of compressed air. Some air-forced systems use a re-usable spring to generate the pushing force instead of pressurized air cartridges.

The Manufacturing Process

There are numerous methods of producing each needle-free injection system. The following process focuses on the production of an air-forced system. These systems are made through a step by step procedure which involves molding the pieces, assembling them, and decorating and labeling the final product. The individual pieces are typically produced off-site and assembled by the needle free injection system manufacturer. All of the manufacturing is done under sterile conditions to prevent the spread of disease.

Making the pieces

The first step requires the production of the component plastic pieces from plastic pellets. This is done by a process called injection molding. Pellets of plastic are put into a large holding bin on an

injection molding machine. They are heated to make them flowable. The material is then passed through a hydraulically controlled screw. As the screw rotates, the plastic is directed through a nozzle which then injects it into a mold. The mold is made up of two metal halves that form the shape of the part when brought together. When the plastic is in the mold, it is held under pressure for a specified amount of time and then allowed to cool. As it cools, the plastic inside hardens. The mold pieces are separated and the plastic part falls out onto a conveyor. The mold then closes again and the process is repeated. After the plastic parts are ejected from the mold, they are manually inspected to ensure that no significantly damaged parts are used.

Assembling and labeling

The parts are next transported to an assembly line. In this production phase various events occur. Machines apply markings that show dose levels and force measurements. These machines are specially calibrated so each printing is made precisely. Depending on the complexity of the device, human workers or machines may assemble the devices. This involves inserting the various pieces into the main housing and attaching any buttons.

Packaging

After the assembly step, the injection devices are put into packaging. They are first wrapped in sterile films and then put into cardboard or plastic boxes. Each part is packaged so movement is minimal to prevent damage. For consumer products, an instruction manual is included along with safety information. These boxes are then stacked on pallets and shipped via truck to distributors.

Quality Control

Quality control checks are done throughout the manufacturing process. Line inspectors check the plastic components to assure they conform to predetermined specifications. Visual inspections are the first test method, but measuring equipment is also used to check the dimensions including size and thickness. Instruments that can be used include laser micrometers, calipers and microscopes. Inspectors also check to make sure the printing and labeling is correct and that all the parts are included in the final packages. Since these devices can have various safety issues, their production is strictly controlled by the Food and Drug Administration (FDA). Each manufacturer must conform to various production standards and specifications. Announced and unannounced inspections may occur to ensure that these companies are following good manufacturing practices. For this reason detailed records must be kept related to production and design [2].

DIFFERENT TECHNOLOGY

[1] Bioject's needle free injection technology

Bioject's needle-free injection technology works by forcing liquid medication at high speed through a tiny orifice that is held against the skin. The diameter of the orifice is smaller than the diameter of a human hair. This creates an ultra-fine stream of high-pressure fluid that penetrates the skin without using a needle. Bioject has developed a broad technology platform for delivering many different types of medications and vaccines to the subcutaneous and intramuscular depths. Bioject was founded in 1985. To develop needle-free injection technology to improve the comfort and safety of routine injections.



Intramuscular injections are the deepest injection type, delivering the medication into the muscle tissue. Most vaccines are currently delivered to the intramuscular depth.



Subcutaneous injections are delivered to the adipose (fat) layer just below the skin. Many therapeutic proteins are delivered to the subcutaneous depth, such as human growth hormone.



Intradermal injections are very shallow injections that deposit the medication between the layers of the skin. Many new DNA-based vaccines are delivered to the intradermal layer.

Dispersion Patterns

Bioject's needle-free injection technology improves the dispersion of medication throughout the tissue, it follows the path of least resistance, resulting in a widely dispersed, spider web-like distribution of the medication [31].



[A] Bioject's new Intradermal (ID) Pen spring-powered needle-free injector

Intradermal (ID) Pen Injector

Bioject's ID Pen spring-powered needle-free injector is intended to be used for intradermal injections for vaccinations and drug therapy. The system consists of a hand-held, user-filled device that incorporates single-use, auto-disable disposable syringes. The ID Pen is designed to deliver .05 mL or .10 mL for each injection. The injector is entirely mechanical and is intended for administration by trained clinicians and properly trained users in home settings.

Iject® and Iject® R

Iject is a small, lightweight, gas-powered injection system designed for home or professional use. This system has two versions, one is a pre-filled, single-use disposable injector, and the other is a reusable injector that accepts pre-filled medication cartridges.

Intradermal Syringe

Intradermal injections are shallow in comparison to other injection types. They are very difficult to administer with a traditional needle because of the skill and accuracy required to deliver them properly.

Jupiter Jet

The Jupiter Jet, a unique hand-held device that is capable of administering small volumes (0.03 to 0.2 mL) of drugs at SC, IM or ID depths. The Jupiter Jet is simple and very easy to use – essential traits for a product targeting the self-injection market or procedures with repeat injections.

Multi-Port Orifices

Bioject is also developing multi-port orifices for improved intradermal injections. This new injector nozzle allows for a greater dispersion of injectable materials, improving the delivery and therapeutic effect of the drug. For many vaccines that require an intradermal injection, this new development could offer significant benefits.

[B] The ZetaJet™,

Bioject®ZetaJet™

The Bioject®ZetaJet™, Bioject's latest advance in needle-free delivery systems, consists of two components, the portable injector and an auto-disable disposable syringe. It is intended to deliver vaccines and injectable medications either subcutaneously or intramuscularly and is indicated for both professional use and home use for patients who self-inject. The syringe assembly has a unique "auto-disable" feature that prevents re-use of the syringe. The Bioject®ZetaJet™ has FDA clearance for delivering subcutaneous or intramuscular injections of liquid medication, including vaccines and other injected medications.

Advantages

Ability to deliver to all three injection depths: Intramuscular, subcutaneous or intradermal. Injection volumes range from 0.05mL to 0.5mL. ZetaJet's molded exterior can be customized by providing a multitude of ergonomic options to achieve specific attributes for different clinical or branding applications. Eliminate needle-phobia thereby enhancing patient experience. Leverages Bioject's unique, patented pressure profile. Indicated for both professional and patient self-injection. Polycarbonate syringe provides exceptional strength, clarity and heat resistance. Reliable stainless steel inner core enhances durability in rough environments [32].

[2] Biojectorr 2000

The Biojector 2000 is a durable, professional-grade injection system designed for healthcare providers. The Biojector 2000 uses sterile, single-use syringes for individual injections, which prevent the cross-contamination that has been reported with fixed-nozzle jet injection systems. Because there is no needle, the Biojector provides healthcare workers with an unparalleled level of protection against accidental needlestick injuries. In high-risk situations, such as delivering injections to patients known to be infected with HIV or hepatitis, the Biojector is an ideal injection system [33].

[3] Vitajet 3

The Vitajet 3 is an easy-to-use, economical needle-free injection system for delivering insulin. With disposable nozzles that are replaced once-a-week, the Vitajet 3 offers the quality of a reusable medical product, with the convenience and safety of a sterile disposable. The Vitajet 3 received the FDA marketing clearance for delivering subcutaneous injections of insulin in 1996. Since then, the system has been used to deliver hundreds of thousands of injections, safely, economically, and without the use of a needle [34].

[4] Cool.click

Bioject developed the cool.click needle-free injection system for delivering Saizen recombinant human growth hormone. The system includes customized dosage features to accurately deliver variable doses of Saizen and was designed with bright colors to make the injector attractive and non-threatening to children [35].

[5] SeroJet

The SeroJet is a needle-free injection system for delivering Serostim recombinant human growth hormone for treatment of HIV-associated wasting in adults. SeroJet is a customised version of Bioject's Vitajet needle-free injection system. The system includes customised dosage features to accurately deliver variable doses of Serostim. The SeroJet received FDA market clearance for delivering subcutaneous injections of Serostim in March 2001 [36].

[6] Iject

The Iject is a pre-filled single-use disposable injection device configured to administer 0.5 to 1.00 ml subcutaneous or intramuscular injections. It requires no additional parts or modifications for function. The device is primed by rotating the trigger sleeve 180 degrees, and an injection is administered by advancing the trigger sleeve while the nozzle is held against the injection site. The Iject needle-free injection system is an investigational device, subject to the US Food and Drug Administration clearance for commercial distribution [37].

[7] Non-invasive DDS: Untapped potential

Aradigm Corporation has recently acquired the Intraject technology, initially developed in the UK by Weston Medical. It is the only pre-filled and disposable needle-free device in late-stage development, with commercial scale-up in process. Aradigm's Intraject collaborators include Roche for the delivery of pegylated interferon alpha (Pegasys) and GlaxoSmithKline for Imitrex. The Intraject device is about the size of a fountain pen. The drug capsule is glass, a material that has demonstrated excellent stability profiles for liquid protein formulations. The energy to drive the actuator forward to deliver the 0.5-ml formulation is provided by compressed nitrogen. The delivery process is completed in less than 60 milliseconds with less bruising and discomfort than may be encountered with syringes, pens or other devices.

[8] Biovalve's Mini-Ject technology

The Mini-Ject can deliver a wide range of drugs, ranging from small molecules to large proteins, fragile antibodies, and vaccines. Delivery can be targeted to intradermal, subcutaneous or intramuscular depending on the clinical need. No other single-use needle-free delivery technology provides the same level of performance as the Mini-Ject technology with the ability to target specific tissue layers over such a broad range of drug volumes (0.1 mL to 1.3 mL) and viscosities [38].

[9] Antares' Medi-Jector Vision technology

Antares Pharma, one of the pioneers in the field of needle-free injection technology has developed Medi-Jector Vision technology which is used to deliver insulin to diabetes sufferers. It is a newest marketed version of the reusable, variable dose, spring-powered device for insulin delivery. This technology is also being used to deliver human growth hormone. Its plastic, disposable needle-free syringe allows the patient to see the dose prior to injection. It is marketed in US and Europe for insulin administration since 1999 [39].

[10] Implaject

Simple, hand-held needle free injection device. Can be configured to be reusable with disposable cartridges.

[11] Crossject

Prefilled, single use disposable NFI. Uses chemical reaction to generate propellant at the time of administration.

[12] PowderJect

It painlessly delivers DNA vaccines to the skin in a dry formulation.

[13] Zoma-jet 2 Vision

Customized version of Medi-jector vision licensed to Ferring for administration of their human growth hormone, Zomacton for distribution in Europe. Launched in Europe in 2003.

[14] Valeo (MJ8)

Next generation pen-style, spring-powered device. Designed for use with drugs in cartridge containers, rather than vials. Clinical Trials completed, available for licensing.

[15] Injex 30

Spring-powered hand-held device with disposable ampoules that delivers 0.05-0.3 ml. Focused on insulin delivery. Marketed in US.

[16] mhi-500

Spring-powered hand-held delivers volume in the range of 0.02-0.5 ml. Marketed in Europe as an insulin delivery device for insulin delivery [40].

[17] Solid dose injector technology

Our Glide SDI (Solid Dose Injector) enables the injection of APIs in a solid dosage form without the need for a needle. The drug is mixed with selected excipients and individual dosages are produced as tiny rods with a point at one end. A dosage is then pre-filled into a single-use drug cassette. In use, the drug cassette is placed into a spring powered, handheld actuator. Pushing the end of the cassette against the skin target charges the spring in the actuator. At a preset spring force, the actuator automatically triggers, pushing the dosage from the drug cassette into the skin. The small, low cost drug cassette, which contains no sharps, can be safely thrown away and the actuator can be reused hundreds of times, resulting in low cost per administration. Because the drug is administered in a solid dosage form, the Glide SDI offers enhanced stability and potentially avoids the need for refrigeration, as well as providing the opportunity for controlled release formulations by using slower dissolving excipients rather than fast dissolving sugars. In the clinic in volunteer studies, the Glide SDI has been overwhelmingly preferred to an injection with a standard needle and syringe. A wide range of proteins, peptides and small molecules can be delivered using the technology. Preclinical studies with a range of antigens have also shown improved efficacy for vaccines in the Glide SDI when compared to a standard needle and syringe injection (data held on file at Glide Pharmaceutical Technologies Ltd) [41].

[18] SQ-PEN technology

The SQ-PEN was developed by Medical House Products Ltd and has been owned by Diabetes Management International since October 2007. The SQ-PEN uses pressure from a spring-loaded piston to create a fine stream of insulin through a small-bore nozzle. The pressure and speed of exit of the insulin stream causes it to penetrate the skin, delivering insulin to the subcutaneous layer. SQ-PEN uses a plunger which is activated when there is sufficient depression of the nozzle tip into the skin. A recent randomised cross-over study compared a needle free insulin delivery device to the Novopen 3. The Vitajet needle free insulin delivery system was fully evaluated in a randomised, controlled study reported by Katoulis et al. (1989). The authors concluded that Vitajet constitutes an efficient, safe and less painful needle-less route than the conventional syringe for delivering insulin." The authors demonstrated that falls in blood glucose occurred earlier with

Vitajet following injection with Actrapid insulin, with statistically lower levels of blood glucose for up to 2 hours post-injection. On the other hand however, short and long-term glycaemic control is reportedly improved by needle free insulin delivery. It should be noted that there are a wide range of factors that influence the absorption kinetics of insulin and the usage of the SQ-PEN needle free insulin injection device should be viewed within this context. As a direct consequence of changing to a needle free delivery device, the risks of hypoglycaemia are small. Indeed, less insulin overlap is seen with needle free insulin delivery as a result of the shortened duration of insulin. Therefore, on a twice-daily insulin regimen, less hypoglycaemia is more likely with a needle free delivery system, than with a needle-based system [42].

APPLICATIONS OF NEEDLE FREE INJECTION TECHNOLOGY

1. Intraject (Weston medical) technology used to deliver drugs including proteins, peptides, monoclonal antibodies, small molecules and vaccines.
2. Medi-Jector vision (Antares Pharma, Inc.) technology used to create a micro thin stream of insulin that penetrates the skin.
3. Powderject¹⁷ (Powderject pharmaceuticals) technology delivered insulin to hairless guinea pigs, delivery of large macromolecules across the skin, used for intradermal DNA immunization against influenza virus in mice.
4. Jet injectors' technologies deliver proteins such as B- interferon as well as small organic conventional therapeutic agents such as lidocaine (lignocaine) for local anaesthesia.
5. The Disposable Syringe Jet Injector (DSJI) Project is supporting clinical research on the delivery of vaccines with jet injectors. Our current research includes the work described below.

• Inactivated polio vaccine

Inactivated polio vaccine has a long history of safety and effectiveness; furthermore, it will be critical following the eradication of polio worldwide once oral polio vaccine is no longer used. Intradermal delivery at reduced doses could stretch vaccine supplies and reduce costs to programs, improving access to this important vaccine within developing countries. Jet injectors, which offer a simple approach to intradermal injection, could facilitate uptake of this vaccination strategy.

• Influenza vaccine

Seasonal influenza vaccine is often omitted from national immunization programs. This study examined the safety and effectiveness of flu vaccine when given to toddlers in the Dominican Republic. This study tested whether a fractional dose given intradermally by jet injector works as well as a full dose given with a standard delivery method.

• Intradermal delivery landscape

In conjunction with Project Optimize, the DSJI project supported a literature review to evaluate the landscape of intradermal vaccine research. The resulting report provides an overview of clinical research on intradermal vaccination and intradermal delivery devices and reviews the vaccines which are most appropriate for future research on intradermal delivery for use in developing-country immunization programs.

• More recently, PATH and Working in Tandem collaborated on a bulletin about the potential benefits and current challenges of intradermal delivery of vaccines. The bulletin, posted by the World Health Organization, examined intradermal delivery of vaccines in terms of novel delivery devices, the suitability of vaccines type, costs—both cost savings associated with reduced doses and cost modeling associated with changes to routine vaccinations of some vaccines to intradermal delivery—as well as manufacturing challenges and regulatory issues

• Measles-mumps-rubella vaccine

PATH is conducting a study to examine the safety and effectiveness of this childhood vaccine when delivered by jet injector.

• Yellow fever vaccine

Given in endemic areas of South America and Africa, as well as to travelers from other countries, there are periodic shortages of this vaccine. Reduced-dose intradermal delivery by jet injector could mitigate shortages and expand access to yellow fever vaccine.

• DTP-Hib-hepB vaccine

This combination vaccine protects against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib) and hepatitis B. Vaccines for these diseases are used in most immunization programs around the world. PATH's planned research will compare delivery of this vaccine to delivery with a needle and syringe.

• BCG vaccine

This vaccine is used to protect children against tuberculosis. It is delivered intradermally, but there are challenges with the standard intradermal injection method. DSJIs may provide a safer and more reliable means of administering this vaccine.

• Rabies vaccine

Rabies can be prevented by vaccination after a bite by a potentially rabid animal, but in some countries, many people who need it do not receive the vaccine. Intradermal delivery of reduced doses of rabies vaccine has been approved by the WHO. Use of intradermal delivery devices could increase the availability of this life-saving vaccine.

IS THE FUTURE NEEDLE-LESS?

Patients' want safer and better methods of taking their medicine. Additionally, with increased competition, pharmaceutical companies need new ways of differentiating their products and extending the patent life on proprietary drugs. Many drugs and vaccines need to be administered parenterally, but there is limited scope for further new developments in the area of autoinjectors and peninjectors. As such, there will always be demand for new technologies, such as needle-free injection devices. Although they are currently viewed as being costly — which is one of the reasons the technology is not more widely used — the price of liquid jet injectors will fall as use increases. They may also be able to offer other liquid formulation benefits such as improved stability or controlled release. Although these benefits can also be offered by needlebased technologies, needlefree devices will also offer the benefit of ease of use and no needle. The biggest advances in needlefree injection technologies will probably relate to their ability to inject solid dosage forms. The key challenge, however, will be the successful commercialisation of the first solid dose injection product to prove that the key perceived risks of manufacturing scaleup and regulatory approval for a novel drug delivery platform can be achieved.

CONCLUSION

Needle-free technology offers the very obvious benefit of reducing patient concern about the use of needle. Additional benefits include very fast injection compared with conventional needles and no needle disposal issues. Not only it can benefit the pharmaceutical industry in increasing product sales, it has the added potential to increase compliance with dosage regimens and improved outcomes. In the developing world, there are major challenges of disease transmission through re-use of needles. Organisations such as WHO and CDC (Centre for Disease Control) and groups like Gates Foundation have supported the development of needle-free alternatives for drug delivery. The biotech revolution is bringing in a range of protein-based therapeutics into the marketplace at rapid pace - more than 300 products in active development. This protein-based therapeutics especially monoclonal antibodies (MAbs), which are anticipated to represent 30 per cent of pharmaceutical sales by 2007 and which are otherwise challenging to deliver non-invasively, will continue to be formulated as injectables. There appears to be tremendous opportunity for needle-free technology to have major impact in the industry. It is likely that dramatic change may occur only when a large pharmaceutical or biotechnology company adopts needle-free technology and demonstrates its versatility, acceptance and value in major therapeutic area.

REFERENCES

1. www.expresshealthcaremgmt.com/20050715/pharma01.shtml
2. Potter C. Needle-Free Injection. *Pharmaceutical Technology Europe*. 23 (2).
3. Sarphie DFJ. *Controlled Release* 1997; 47:61-65.
4. Hickey PL. AAPS Conference, November, 1998; San Francisco.
5. Burkoth TL. *Critical Reviews in Therapeutic Drug Carrier Systems* 1999; 16(4): 331-384.
6. Kwon SY, Burkoth TL. *Pharm. Sci. Suppl.* 1998; 1(1): 103-106.
7. Willson P. Needle-free immunization as effective as needle and syringe method. *Council Research* 2004.
8. Mitragotri, S. 2006. Current status and future prospects of needle-free liquid jet injectors. *Nat. Rev. Drug Discov.* 5:543-548.
9. Baizer L, Hayes J, Lacey C, D'Antonio L, Mathews M. Needle-free injectors: advantages, current technologies, and future innovations. *Pharm. Manu. Pack. Resour.* Spring 2002:96-100.
10. Reis EC, Jacobson RM, Tarbell S, Weniger BG. Taking the sting out of shots: control of vaccination-associated pain and adverse reactions. *Pediatr. Ann.* 1998; 27:375-386.
11. Jones GF, Rapp-Gabrielson V, Wilke R, Thacker EL. Intradermal vaccination for *Mycoplasma hyopneumoniae*. *J. Swine Health Prod.* 2005; 13:19-27.
12. Apley M, Thacker B. Determination of the pharmacokinetics of procaine penicillin in swine administered by intramuscular injection and with a needleless injection device 2003.
13. Almond GW, Roberts JD. Assessment of a needleless injection device for iron dextran administration to piglets. *IPVS Proc.* 2004:618.
14. Senn MK, Bradford JR, Cook DL, Loskutov A. Comparison of pharmacokinetic parameters for Excenel RTU when injected by needle or Felton Pulse 250 needle-free injector. *AASV Proc.* 2004: 263-265.
15. Grosenbaugh DA, Leard T, Pardo MC. Comparison of the safety and efficacy of a recombinant feline leukemia virus (FeLV) vaccine delivered transdermally and an inactivated FeLV vaccine delivered subcutaneously. *Vet. Ther.* 2004;5:258-262.
16. Parent du Chatelet I, Lang J, Schlumberger M, Vidor E, Soula G, Genet A, Standaert SM, Saliou P. Clinical immunogenicity and tolerance studies of liquid vaccines delivered by jet injector and a new single use cartridge (Imule): comparison with standard syringe injection. *Imule Investigators Group. Vaccine* 1997; 15: 449-458.
17. Illum L, Davis SS. Nasal vaccination: a non invasive vaccine delivery method that holds great promise for the future, *Advanced Drug Delivery Reviews* 2001; 51: 1-3.
18. Baichal A, Neville DA. *Drug Delivery Technology* 2001; 1: 60-62.
19. Hingson RA, Hamilton SD, Rosen M. The historical development of jet injection and envisioned uses in mass immunization and therapy based upon two decades' experience. *Military Medicine* 1963: 516-524.
20. www.Weston-medical.com/faqs.htm.
21. www.penjet.com
22. www.bioject.com
23. www.advantaget.com
24. www.equidyne.com
25. www.medajetxl.com
26. www.cdc.gov/nip/dev/N3draft0007doc
27. www.cdc.gov/nip/dev/N2draft000603doc
28. Sarphie DF. Gas Propulsion of Microprojectiles for the Transformation of Biological Cells, D. Phill. Thesis, university of oxford 1992.
29. Haynes JRJ. *Biotechnology* 1995; 44:37-42.
30. www.powderject.com/company/company_overview.html#5.
31. www.bioject.com/about/technology
32. www.bioject.com/products/zetajet
33. www.bioject.com/biojector2000.html
34. medgadget.com/2005/03/vitajet_3.html
35. www.bioject.com/cool_click.html
36. www.bioject.com/serojet.html
37. www.bioject.com/iject.
38. www.drugdeliverytech.com/ME2/SiteMaps/Sites/Document.asp
39. www.wikinest.com/.../Antares.../Antares_Medijector_Series_Needle
40. www.diabetesforums.com/forum/type-1.../1831-mhi-500-a.html
41. pharmtech.findpharma.com/pharmtech/Drug...Injection/.../707036
42. www.sqpen.nl/index.php?mid=12&lang=en