

THE PHARMA INNOVATION

Needle Free Injection Systems

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Needle-free injection systems are novel ways to introduce various medicines into patients without piercing the skin with a conventional needle. Needle-free technology offers the very obvious benefit of reducing patient concern about the use of needle. Needle free injection gives very effective injections for a wide range of drugs and bioequivalent to syringe and needle, results in less pain, and is strongly preferred by patients. 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. Today, they are a steadily developing technology that promises to make the administration of medicine more efficient and less painful.

Keyword: Needle Free Injections, Needle Free Devices, Drug Administration And Drug Delivery.

INTRODUCTION: Needle-free injection techniques can be used to administer vaccines and medications in the pork industry. Needle-free injection offers a fast, effective route of administration. There are hazards that must be addressed to safeguard employees who utilize needle-free injection systems; therefore, an enforced education program is crucial to the success of using needle-free injection in any pork operation.

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The first hypodermic syringes were first developed by French surgeon, Charles Gabriel Pravaz, in 1853, although there is a minor development in syringes since then, the technology has been remained unchanged for last 150 years. Needle-free systems was first described by Marshall Lockhart in 1936 in his patent jet injection. Then in the early 1940's Higson and others developed high pressure "guns" using a fine jet of liquid to pierce the skin and deposit the drug in underlying tissue. These devices were used extensively to inoculate against infectious diseases and were later applied more generally in large scale vaccination program. Today, they are a steadily developing technology that promises to make the administration of medicine more efficient and less painful².

BACKGROUND³

People are given injections to protect them from influenza, tetanus, cholera, typhoid, and other diseases. When a needle is inserted through the skin, the vaccine (or drug) it carries provides systemic immunity. This is because the vaccine gets into the bloodstream and provokes the body to create antibodies that are carried throughout the entire body.

In the United States, children may get over 13 vaccine injections by the age of 16. Unfortunately, there are a variety of problems associated with the hypodermic needles used for these injections. One of the most significant drawbacks is the relatively high cost of the needles. The cost results in a lower vaccination rate, especially for children in developing countries. Another problem with traditional needles is the lack of reusability. If a needle syringe is not sterilized, reusing it can lead to the spread of disease. Additionally, many people have a fear of needles which causes them to avoid treatment. These drawbacks have led to the development of alternative delivery systems to needle injections.

Needle-free systems are designed to solve these problems making them safer, less expensive, and more convenient. It is anticipated that these systems will increase the incidence of vaccination and reduce the amount of prescribed antibiotics. Moreover, they should reduce the number of needle stick accidents that have resulted in some health care workers contracting diseases.

More than a dozen companies have developed alternatives to needle injections. Some of the different designs include nasal sprays, nose drops, flavored liquids, skin patches, air forced and edible vaccine-packed vegetables.

The needle-free systems that are most like traditional injections involve the direct transfer of the medicine through the skin. One company offers an injection system where the drug is dispersed through the skin as a fine mist or powder. In this system, a tube-shaped device is

held against the skin and a burst of air forces the molecules of medicine into the body. The device is designed to force the medicine far enough through the skin so it enters the bloodstream. An application for which this system is particularly useful is for patients who need daily doses of growth hormone.

Patches have been introduced as needle-free delivery systems. These devices, which look like bandages, slowly transfer medicine through the skin. In one type of patch, thousands of tiny blades are imbedded on its surface. The patch is covered with medicine and then placed on the skin. The blades make microscopic cuts in the skin that opens a path for drugs to enter through. When an electric current is applied, the medicine is forced into the body. This process, called iontophoresis, does not hurt.

Nasal sprays, suppositories, and eye and nose drops are forms of needle free systems that deliver medications through the mucous membrane, where 90% of all infections occur. The mucous membrane is found throughout the body and includes the lining of the respiratory tract, digestive tract, and urinary and genital passages. These needle free systems prompt the body to produce both antibodies at the mucosa surfaces and system-wide.

The nasal shot may be the first needle-free flu shot. It is a syringe-like device that has an aerosol sprayer substituted for the needle. It delivers a weak flu virus directly to the nasal passages and creates immunity to the flu with minimal side effects.

Inhalers are another type of needle-free delivery system. In these systems, liquids or powders are inhaled and delivered into the lungs. These devices are good for delivering protein drugs because the lungs provide a rapid absorption into the bloodstream. In one system there is a pump unit that atomizes a powdered medication. This allows the patient to inhale the proper amount of medicine without it getting trapped in the back of the throat. For diabetics who require daily

injections of insulin, an aerosol inhaler has also been introduced.

Oral vaccines are needle-free systems that may replace vaccine injections. This technology has been difficult to perfect for many reasons. The primary problem with this type of delivery system is that the environment of the digestive system is harsh and typically destroys vaccines and other drugs. Also, vaccines do not work as well in provoking antibody production in the digestive lining. One of the latest oral vaccines involves freeze drying the medicine and mixing it with a salt buffer to protect it when it is in the stomach. Other edible forms include a sugar solution of a vaccine against the bacterium that causes ulcers. For travelers, a typhoid-vaccine capsule has been developed as an alternative to the two painful shots typically required.

Genetic engineering has enabled the production of oral vaccines in food. In 1998, potatoes were produced that contained genes from the virus that causes cholera. These potatoes showed efficacy in protecting people from this disease. This is particularly useful for developing countries where potatoes are a dietary staple and the refrigeration that is typically required for transporting vaccines is not readily available.

OBJECTIVE ⁴

To review needle vs. needle-free injection systems and describe the different types of needle-free injection systems.

a) Needle vs. Needle-free Injection

Cost Efficiency Needle-free injection systems can potentially reduce medical costs for the pork producer because the chance of injury to an employee from inadvertent needle sticks is eliminated. Needle-free systems also eliminate the purchase of needles. Needle breaks, which can damage tissue and cause a decrease in overall yield and profitability, are also therefore eliminated. However, the start-up costs associated with needle-free injection systems can be large. Pork producers should weigh the costs and

benefits to these systems before adapting new technology.

b) Worker Safety:

Safety is a key ingredient to any pork operation. Employees must be properly trained on the use and maintenance of all equipment. Needle injection can be dangerous due to inadvertent needle sticks or cuts. However, needle-free injection is not 100% safe. Needle-free systems are designed for a high force dose to be administered very quickly and should only be used with proper training. These systems do offer a limited amount of risk to the operator, if properly trained, and exclude the possibility of needle sticks and cuts.

c) Sterility

Sterility is a key factor to proper vaccination and drug delivery. Sterility can be affected by human error. For example, the same needle may be used on multiple animals. Workers may forget to change needles when drawing vaccine from a bottle. Needle-free injection takes the needle out of the equation, and due to the high powered dosing mechanism, there is a little to no chance of cross contamination.

d) Pork Safety

The use of needles, along with human error, may also cause pork carcass defects. If needles are disposed of correctly or dropped after use there is always of a possibility of an animal ingesting the needle or being stuck in an unassuming place. Needle-free injection systems eliminate residual needles and needle fragments from pork carcasses¹. The Pork Quality Assurance (PQA) Plus program recommends that all producers have a broken needle policy in place².

e) Proper Dosage

Injection site is a crucial element in making sure that a proper dosage is received by the animal. A needle injection provides many unknown variables that can prevent proper dosing and in turn create havoc in your vaccination program. Proper dosing is highly dependent on many factors. Among these factors are the size and age

of the pig and the recommended route of administration. Different methods of administration such as subcutaneous (SQ) or intramuscular (IM) are very important in guaranteeing quality vaccination. If a vaccine or drug is not administered accordingly the effectiveness of the drug and the withdrawal time are altered. Incorrect injection sites in both needle and needle-free injection can impair pork safety⁵.

f) Injection Methods

Subcutaneous injections in small pigs should be given by pulling loose skin in the elbow or flank area. This technique is called tenting. In sows, the area just behind the ear is an acceptable sight for SQ injection. Intramuscular injection is conventionally administered in the neck just behind the ear. IM injection anywhere else is not acceptable because it will compromise pork safety and it should never be injected in the loin or ham muscles.

STRUCTURE OF HUMAN SKIN⁵:

Knowledge of the structure of skin is essential for successful administration of drugs through needle free injection systems as these drugs are administered underneath the skin.

Human skin is generally made of two layers i.e., epidermis and dermis.

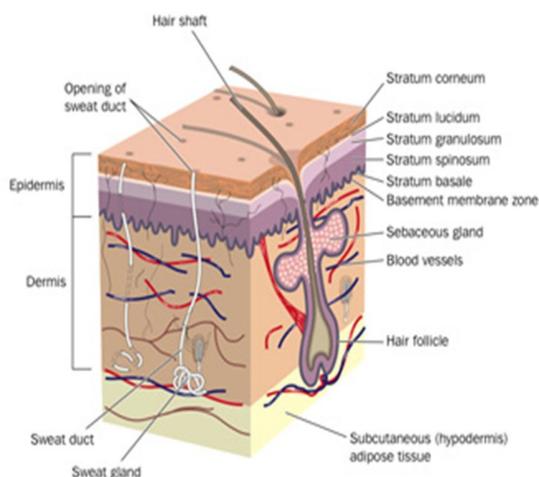


Figure 1: Layers of skin

Epidermis:

It is the outermost layer of the skin. It forms the waterproof, protective wrap over the body's surface and is made up of stratified squamous epithelium with an underlying basal lamina. The epidermis contains no blood vessels, and cells in the deepest layers are nourished by diffusion from blood capillaries extending to the upper layers of the dermis. The main type of cells which make up the epidermis are Merkel cells, keratinocytes, with melanocytes and Langerhans cells also present. The epidermis can be further subdivided into the following strata (beginning with the outermost layer): corneum, lucidum (only in palms of hands and bottoms of feet), granulosum, spinosum, basale.

Dermis:

The dermis is the layer of skin beneath the epidermis that consists of connective tissue and cushions the body from stress and strain. The dermis is tightly connected to the epidermis by a basement membrane. It also harbors many Mechanoreceptors (nerve endings) that provide the sense of touch and heat. It contains the hair follicles, sweat glands, sebaceous glands, apocrine glands, lymphatic vessels and blood vessels. The blood vessels in the dermis provide nourishment and waste removal from its own cells as well as from the Stratum basale of the epidermis.

Hypodermis:

The hypodermis is not part of the skin, and lies below the dermis. Its purpose is to attach the skin to underlying bone and muscle as well as supplying it with blood vessels and nerves. It consists of loose connective tissue and elastin. The main cell types are fibroblasts, macrophages and adipocytes (the hypodermis contains 50% of body fat). Fat serves as padding and insulation for the body. Another name for the hypodermis is the subcutaneous tissue.

TYPES OF NEEDLE FREE INJECTION SYSTEMS⁸

Needle free technologies are of three types:

- a) Powder injections
- b) Liquid injections
- c) Depot or projectile injection.

All these technologies have the same basic principle of delivering medication by pressurized contact of fluids with the skin. In powder injection systems, a pre measured powdered medication is put in a drug cassette which is opened by the compressed gas and thus the medication is delivered to tissue.

The powders used in these systems require specific properties and specific size to ensure their stability and proper dispersion into the tissue. These types have certain advantages over the others like the therapeutic agent will be more stable and may not require cold storage. In addition, for vaccines, a solid formulation presents the opportunity to combine fast acting and delayed-release forms of the vaccine so that the prime and boost shots can be given together in a single administration

Depot injections are given in the muscle where they create a store of a drug which is released continuously over a specified period of time.

Table 1: Market Product of Liquid Based NFI^{9, 10, 11, 12, 13, 14, 15, 16}

Product Name	Company	Type of systems
Intraject	Weston medical	Liquid based needle free injection
Medi jector vision	Antares Pharma Inc.	Liquid based needle free injection
Penjet	Penjet corporation	Liquid based needle free injection
Med-E-Jet	Evans enterprise	Liquid based needle free injection
Advantaget	Advantaget health services	Liquid based needle free injection
Gentlejet	Health for personal care	Liquid based needle free injection
J-tip	National medical products, inc	Liquid based needle free injection
Injex	Equidyne Systems, Inc	Liquid based needle free injection
Powderject system	Powderject pharmaceuticals	Powder based needle free injection
Depixol Depo injection	Lundbeck Limited	Depot based needle free injection

DESIGN¹⁷

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.

RAW MATERIALS

Since these devices directly contact the body, they must be made from materials that are pharmacologically inert. The materials also must be able to withstand high temperatures because they are heat-sterilized. Air forced injection systems are available in different shapes as sizes. 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. To 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.

THE MANUFACTURING PROCESS ¹⁷

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.

1. Making the pieces

- a) 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.
- b) 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.

- c) 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.

2. 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.

3. 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.

4. 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.

MECHANISM OF WORKING ¹⁷

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.

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. The design must ensure that a sufficiently high pressure is generated to puncture the skin, while the subsequent pressure is reduced to ensure that the molecule is deposited comfortably at a level that does not reach the muscle tissue.

High-pressure delivery could potentially damage fragile molecules, such as monoclonal antibodies. Successful delivery of such molecules, therefore, requires a device with carefully controlled power nuances. Several companies are involved in development of this technology, which includes, Antares Pharma Inc, Aradigm Corporation, Bioject Medical Technologies Inc and Biovalve Technologies Inc.

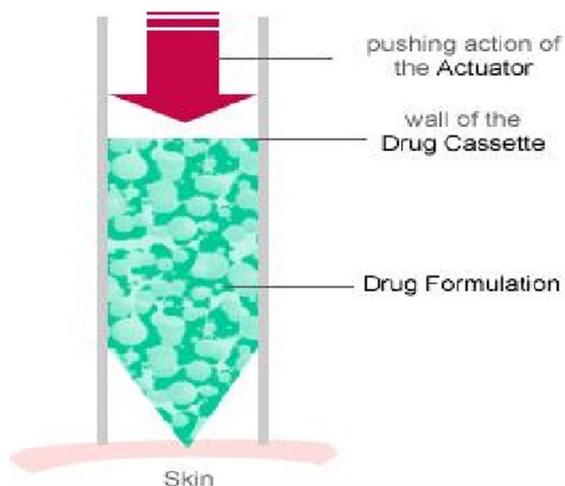


Figure 2: Mechanism of Working

HOW DOES IT WORK?

- a) Medication is driven at high speed through a tiny orifice
- b) A fine stream of medication penetrates the tissue

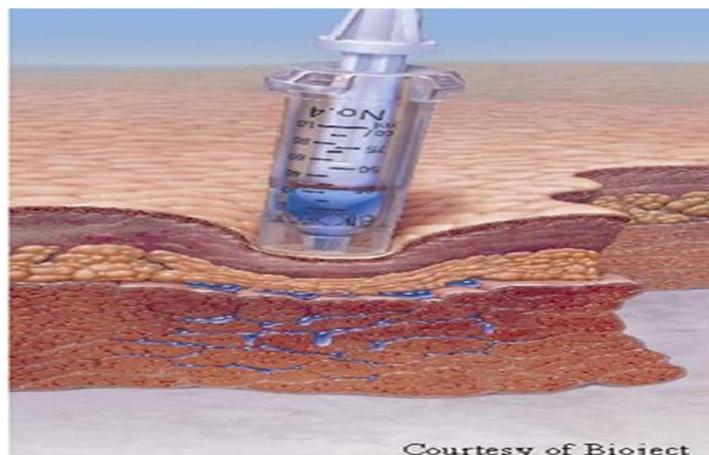


Figure 3: Injecting Medicament through Skin by Needle Free Injection

- c) Injection event requires less than 0.5 seconds
- d) Injections can be IM, SC or ID

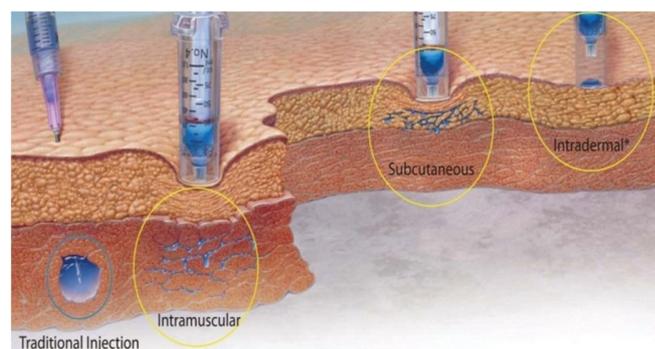


Figure 4: Types of Parenteral Route

Drug administration through conventional needle system and needle free injection technology. A spherical bolus is formed in case of conventional needle system where the surface area/volume ratio is very less when compared to needle free injected devices. Drug is dispersed as a spider web in case of needle free injected systems.

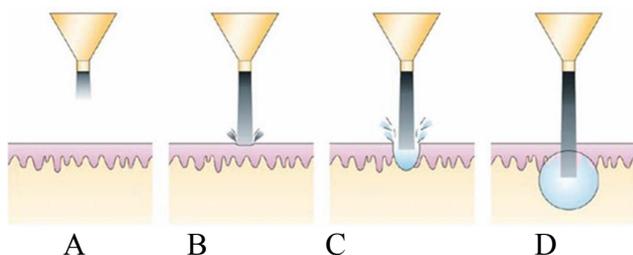


Figure 5: Visualizing the process of transdermal injection.

a) Impact of a piston on a liquid reservoir in the nozzle increases the pressure, which shoots the jet out of the nozzle at high velocity (> 100 m per second).

b) Impact of the jet on the skin surface initiates formation of a hole in the skin through erosion, fracture, or other skin-failure modes.

c) Continued impingement of the jet increases the depth of the hole in the skin. If the volumetric rate of hole formation is less than the volumetric rate of jet impinging the skin, then some of the liquid splashes back towards the injector.

d) As the hole in the skin becomes deeper, the liquid that has accumulated in the hole slows down the incoming jet, and the progression of the hole in the skin is stopped. The dimensions of the hole are established very early in the process (a few tens of microseconds) from the time of impact. The final distribution of the liquid varies by the type of device, injection site, thickness of the skin, viscosity of the liquid, and pressure¹⁸.



Figure 6: Distribution of methylene blue in the skin and underlying tissue following injection with a needle-free injection device. Distribution will vary by type of device, injection site, thickness of the skin, viscosity of the liquid, and pressure¹⁹.

PROBLEMS IT SOLVES:

1. Avoids needle stick hazard.
2. No sharps disposal problems.
3. Eliminates the concern for the re-use of needles.
4. Injection pain is reduced in most cases.
5. Speeds the injection cycle.
6. Improved bio-availability of vaccines.
7. Reduces the system cost of injection.
8. Key Needle Free Manufacturers Of The World

KEY NEEDLE FREE INJECTION SYSTEM MANUFACTURERS^{20, 21, 22, 23}

1. Mhi-500:

Mhi-500 is the novel needles free insulin delivery system which offers benefits for all those involved in diabetes care and also for those involved in the management of clinical waste. It is a real alternative to needle-based delivery systems.

Compared with a needle injection system, the mhi-500's needle-free insulin delivery technology improves the dispersion of the insulin throughout the tissue. This technology achieved the Food and Drug Administration (FDA) approval in 1996 for the subcutaneous delivery of insulin and is CE marked for sale throughout the Europe. This system has been used to give thousands of successful injections without the use of a needle.

The mhi-500 injects insulin by using a fine, high pressure jet of insulin. This jet then penetrates the tissue, depositing the insulin in the subcutaneous layer. The jet is created by forcing the insulin through a precisely designed nozzle that is held in contact with the tissue during the injection.

2. Recojet:

Shreya Life Sciences has recently launched its recombinant human insulin under the brand name Recosulin and a needle-free insulin delivery device, Recojet. According to the company sources, Recojet is India's first needle-free insulin delivery device and poised to revolutionise the insulin therapy.

The new device is expected to give a boost to the therapy, as needle phobia was one of the reasons preventing insulin use on a wider scale. 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.

3. 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's technology is unique because it delivers injections to a number of injection depths and supports a wide range of injection volumes. For instance, the Biojector 2000 can deliver intramuscular or subcutaneous injections up to one ml in volume.

In addition, Bioject is developing a syringe for the Biojector 2000 that delivers intradermal injections that is currently in clinical trials. Bioject has a portfolio of needle-free injection products to meet the varied needs of today's healthcare environment. Each product is unique in its power source.

4. Biojector 2000:

The Biojector 2000 is a durable, professional-grade injection system designed for healthcare providers. The Biojector 2000 is the only needle-free system in the world cleared by the FDA to deliver intramuscular injections. The system can also deliver subcutaneous injections, and is being used for intradermal injections in clinical trials.



Figure 7: Biojector 2000

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.

More than 10 million injections have been administered successfully using the Biojector 2000, with no reports of major complications. 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.

5. Vitajet 3:

The Vitajet 3 is an easy-to-use, economical needle-free injection system for delivering insulin. The system requires no maintenance or re-assembly. 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 exclusive, easy-to-read Crystal Check disposable transparent nozzle allows to inspect the dosage prior to injection and visually confirm loading and full discharge of your insulin after each use.

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.

6. Cool.click:

Bioject developed the cool.click needle-free injection system for delivering Saizen recombinant human growth hormone. In some children, naturally occurring growth hormone is absent or is produced in inadequate amounts. In these cases, Saizen or growth hormone replacement must be injected to maintain normal growth.



Figure 8: Coolclick

Cool.click is a customised version of Bioject's Vitajet 3 needle-free injection system. 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. The cool.click received FDA market clearance for delivering subcutaneous injections of Saizen in June, 2000.

7. **SeroJet:**

The SeroJet is a needle-free injection system for delivering Serostim recombinant human growth hormone for treatment of HIV-associated wasting in adults. HIV-associated wasting is a metabolic condition in which people infected with HIV lose body weight. If not treated, this could result in increased morbidity and mortality.



Figure 9: Serojet

Serono developed Serostim to treat this condition by utilizing the natural properties of growth hormone in increasing lean body mass. SeroJet is a customised version of Bioject's Vitajet needle-free injection system. The system includes customized dosage features to accurately deliver variable doses of Serostim. The SeroJet received FDA market clearance for delivering subcutaneous injections of Serostim in March 2001.

8. **Iject:**

Bioject has developed a second-generation gas-powered injector known as the Iject, which is based on the design and performance of the B2000 and is intended to serve as a single-use pre-filled device. The pressure profile of the Iject has been documented by in vitro testing to be virtually the same as that of the B2000, and injection performance of the two devices is therefore predicted to be equivalent.

The Iject is a pre-filled single-use disposable injection device configured to administer 0.5 to 1.00 ml subcutaneous or intramuscular injections. The device is distributed "ready to use." Thus, 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 (Figure 3) The Iject needle-free injection system is an investigational device, subject to the US Food and Drug Administration clearance for commercial distribution.

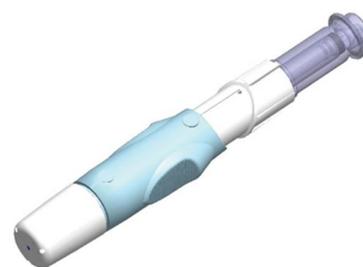


Figure 10: Iject

9. **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.

10. Biovalve's Mini-Ject technology:

The Mini-Ject represents the next generation in needle-free injection systems by combining the features of accuracy reliability, a variety of pre-filled options, comfortable administration, and full disposability, all within a patient friendly easy-to-use design. 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.

11. 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.

Advantages:

1. It is trouble free, simple, self-administered
2. Low sensation and safety
3. Solid dosage forms can be administered
4. Elimination of needle phobia
5. Minimal skin response and no bleeding or bruising

6. Easy and safe disposal
7. Easy to transport and store without refrigeration
8. Excellent dose response is observed with increased drug doses
9. Rapid delivery of the drug to the systematic circulation
10. Bio-equivalence has been demonstrated enabling the development of 'generic' drug proteins

Disadvantages:

1. High start-up cost
2. No one size-fits all system
3. Greater complexity
4. Cannot be used for Intravenous route

Applications:

1. Intramuscular, subcutaneous and intradermal administration of Vaccines e.g., smallpox, polio, measles
2. Intradermal administration of hormones e.g.; growth hormone
3. Intradermal administration of anesthetics e.g., lidocaine
4. Subcutaneous administration of insulin
5. Used in the treatment of migraine e.g., sumatriptan

ADVANCES IN NEEDLE FREE INJECTION TECHNOLOGY

1. Needle free, Auto and pen injectors

An autoinjector (or auto-injector) is a medical device designed to deliver a single dose of a particular (typically life-saving) drug.

Most autoinjectors are spring-loaded syringes. By design, autoinjectors are easy to use and are intended for self-administration by patients, or administration by untrained personnel. The site of injection depends on the drug loaded, but it typically is administered into the thigh or the buttocks. The injectors were initially designed to overcome the hesitation associated with self-administration of the needle-based drug delivery devices²⁷.

Advances in auto injector design and in needle-free injectors are helping pharmaceutical companies to market their drugs and to compete

more effectively by providing gains in market share, allowing greater penetration of markets, helping patients to comply with dosage regimes and providing safer injections. Indeed, injection devices were once considered as an afterthought but now in some product categories they are becoming an entry ticket; an essential part of the drug's presentation to the market, without which they would fail to attract patients. Pharmaceutical companies are developing injectors in parallel with their new drugs, in the knowledge that a device will be needed at product launch.

Auto injectors are advancing both commercially and technically with the recent launch of a second pre-filled single-use device, containing a standard pre-filled syringe, which automates needle insertion, drug delivery and automatically covers the needle after use. Drugs to treat RA, Anaemia and Neutropenia are now available in such pre-filled convenient patient-friendly presentations. In parallel to auto injector development there have been significant advances in needle-free and powder delivery which are increasingly showing that they offer an alternative to the needle ²⁸.

Design

The autoinjector keeps the needle tip shielded prior to injection and also has a passive safety mechanism to prevent accidental firing (injection). Injection depth can be adjustable or fixed and a function for needle shield removal may be incorporated. Just by pressing a button, the syringe needle is automatically inserted and the drug is delivered. Once the injection is completed some auto injectors have visual indication to confirm that the full dose has been delivered. Autoinjectors contain glass syringes, this can make them fragile and contamination can occur. More recently, companies have been looking into making autoinjectors syringes out of plastic to prevent this issue.

Examples

- a) Anapen, Epipens, or the recently introduced Twinjects, which is often prescribed to people who are at risk for anaphylaxis.
- b) Rebiject and Rebiject II autoinjectors for Rebif, the drug for interferon beta-la used to treat

Multiple sclerosis. An autoinjector for the Avonex version of this same medication is also on the market.

- c) Sureclick autoinjector is a combination product for drugs Enbrel or Aranesp to treat Rheumatoid arthritis and anaemia, respectively.

Military use

a) Autoinjectors are often used in the military to protect personnel from Chemical warfare agents. In the U.S.military, atrophine and 2-PAM-Cl (pralidoxime chloride) are used for first aid ("buddy aid" or "self-aid") against nerve agents. An issue item, the Mark I NAAK, provides these drugs in the form of two separate autoinjectors. A newer model, the ATNAA (Antidote Treatment Nerve Agent Auto-Injector), has both drugs in one syringe, allowing for the simplification of administration procedures. In the Gulf War, accidental and unnecessary use of atropine autoinjectors supplied to Israeli civilians proved to be a major medical problem.

- b) In concert with the Mark I NAAK, diazepam (Valium) autoinjectors, known as CANA, are carried by US service members.

Variants

a) A newer variant of the autoinjector is the gas jet autoinjector, which contains a cylinder of pressurised gas and propels a fine jet of liquid through the skin without the use of a needle. This has the advantage that the autoinjector can be reloaded, and a variety of different doses or different drugs can be used, although the only widespread application to date has been for the administration of insulin in the treatment of diabetes.

Using pens like vials ²⁹

a) In response to the rising costs of medications, some healthcare providers have replaced insulin vials on nursing units with insulin pen injectors (or just the pen cartridges) from which they routinely withdraw a patient's prescribed dose using an insulin syringe and needle. In some cases, the pens or cartridges are used as multiple-dose vials for a single patient,

and each dose is removed with a sterile needle and syringe; in other cases, the pens or cartridges are used as floor stock “vials” from which to obtain insulin doses for multiple patients using a new sterile needle and insulin syringe for each puncture into the cartridge membrane. The manufacturers do not recommend the withdrawal of medication from the pen, except in an emergency with a malfunctioning pen. In these instances, the pen should then be discarded, even if insulin remains in the pen. Similar to withdrawing medication from a vial, these practices may also result in unlabeled syringes of insulin.

b) Large pockets of “air” have been observed in cartridges of insulin pen injectors after aspirating some of the drug with a needle. If the pen injector or cartridge is not discarded, and the air is not eliminated before delivering a subsequent dose, the patient could receive less than the desired dose of insulin as well as a subcutaneous injection of air.

2. INTRAJECT SYSTEMS²⁹

Intraject system is the world’s first disposable, needle free injection device for the delivery of liquid medicaments. Invented by Terry Wetson. Intraject is specially designed to meet the patient needs; being pre-filled and disposable the system is designed for unobtrusive, contamination free self-injection. With minimal training a practitioner, patient or a carer can deliver a reliable, virtually pain free injection. It is replacing pre-filled syringes and autoinjectors in many commercial product areas. Intraject offers pharmaceutical companies opportunity to extend the product life-style and manage patent expiry. The system is designed for simple manufacture and, as a pre-filled device, provides pharmaceutical licensees with exclusivity which is critical for successful product differentiation at low cost.

3. BIOJECT®ZETAJET³¹

The Bioject® ZetaJet™, Bioject’s latest advance in needle-free delivery systems, consists of two components, the portable injector and an auto-disabling 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.



Figure 12: Bioject system

Advantages

1. Ability to deliver to all three injection depths: Intramuscular, subcutaneous or intradermal
2. Injection volumes range from 0.05mL to 0.5mL.
3. ZetaJet’s molded exterior can be customized by providing a multitude of ergonomic options to achieve specific attributes for different clinical or branding applications.
4. Eliminate needle-phobia thereby enhancing patient experience.
5. Leverages Bioject’s unique, patented pressure profile.
6. Indicated for both professional and patient self-injection.

7. Polycarbonate syringe provides exceptional strength, clarity and heat resistance.
8. Reliable stainless steel inner core enhances durability in rough environments.
9. Investigational use only

Convenience

1. Easier to train and use needle-free systems.
2. Delivers injection in a fraction of a second.
3. Reduces sharps waste.
4. The plunger is pre-assembled into the syringe and can be used for reconstitution and other pre-injection tasks

Safety

- a) No risk of needle-stick injury.
- b) Elimination of cross-contamination.
- c) Auto-disabling syringe

Unique Auto-disable Syringe

The single-use polycarbonate syringe has a unique “auto-disable” feature that dramatically reduces the risks of both the spread of disease from accidental needle-stick injuries and the re-use of a syringe or needle and prevents possible contamination of syringes and vials. Once an injection is given, the plunger disables and can not be re-used.

The plunger is pre-assembled into the syringe and can be used for reconstitution and other pre-injection tasks.

Energy Source

The ZetaJet™ is self powered by a spring and is ideal for use in mass immunization programs world-wide.

Easy to Use

The ZetaJet™ is designed to deliver injections fast and easy. Just follow these simple steps (for full instructions, see ZetaJet™ Instruction Manual):

- a) Draw medication into the syringe (if you are unsure of which syringe to choose, check the

Guide to Selection and Use of ZetaJet™ Syringes, or call 800.683.7221)

b) Insert the syringe into the ZetaJet™

c) Using firm pressure at the injection site, hold the injector at a 90° angle

Product Specifications:

Size	: 6.5 inches (16.5 cm)
Weight	: 16 ounces (450 grams)
Operation Temperature Range	: 60°-100°F (14°-38° C)
Power Source	: Spring
Syringe/Actuator Interlock	: Yes
Warranty	: One Year
Injection Depths	: Intramuscular and subcutaneous

4. INJEX. NEEDLE-FREE INJECTIONS FOR INFILTRATION ANAESTHESIA ³²

INJEX Pharma now offers a solution for previous local anaesthesia problems, a needle-free injection system. The INJEX System uses an injection ampoule with a micro orifice of only ø 0.18 mm through which the anaesthetic is administered under dosed pressure to the submucosa – virtually painless and exactly where it is needed.

Areas of application:

The ampoule has to be placed on the attached gingiva at an angle of 90° directly above the tooth to be anaesthetised. This defines a determined area of application (anaesthesia is possible with the following teeth: 15-25, 33-43, all teeth of the primary dentition 55-85).

Pediatric patients:

Children are especially difficult dental patients because they are so very much afraid and cannot understand the purpose of the treatment. Experienced dentists are able to use INJEX to administer anaesthetic to all deciduous teeth (KÖRPERICH, 2002). The shorter onset time (SALEH et al., 2002) also reduces the treatment-

induced stress for children. Since only 0.3 ml of local anaesthetic is administered, the maximum dose is hardly ever used. Even very young children can be treated with INJEX (KÖRPERICH, 2002) who are especially pleased with the needle-free injection. The stress for accompanying parents is also reduced significantly due to the shorter treatment time. Small children are frequently less willing to cooperate with the dentist. This is where INJEX reduces the stress of administering a local anaesthetic due to the lower risk of injury. Patients usually continue to request anaesthesia with this system the next time they visit their dentist (MUNSHI et al., 2001; GRAU et al., 1997; SARA VIA et al., 1991).

Adult patients:

Many adults are afraid of the syringe with needle (SCHNEIDER, 2001) as well as the pain induced by the dental treatment. This problem can be alleviated with the "needle-free syringe" but the application area for the permanent set of teeth is limited (15-25, 33- 43) (KÖRPERICH, 2002). Adults, even those who are highly anxious, report less painful injections with INJEX and usually request the same delivery system when visiting the dentist's office again (SCHNEIDER, 2001; FRIELING, 2000).

Areas of application:

Fillings, extractions, cleaning, and smaller periodontal procedures are possible with the teeth listed above after anaesthetising the individual tooth (KÖRPERICH, 2002; SCHNEIDER, 2001; FRIELING, 2000; SARA VIA et al., 1991). INJEX thus offers the option of needle-free anaesthesia for numerous routine dental procedures and interventions performed at the dentist's office. Patients are less afraid of dental procedures and trust their dentist more.



Figure 13: Injex

5. MADAJET XL PODIATRY NEEDLE-FREE INJECTOR³³

Easy to use and virtually painless compared to needles. Provides instant local anesthesia or regional blocking for most podiatric procedures. Minimizes tissue trauma and facilitates suturing as there is no tissue distention around the injection site. Provides adequate anesthesia for deep needle insertion. May be used with anesthetics, steroids and other medicaments. Has interchangeable Extenda Tips for easy sterilization between patients. Can be used on all age groups. Consistent depth of penetration of 4-5.5mm below the epithelium and makes a wheal at the base of the injection of 5-6mm in diameter. Consistent volume of 0.1cc per injection intradermally. Permits approximately 38 injections with single loading (to 4.0cc). May be sterilized by autoclaving or your usual sterilization process - do not use dry heat.



Figure 14: Madajet XL

THE FUTURE

Many of these needle-free alternative technologies are in the development stage. Companies are still working on producing devices that are safer and easier to use. They are also working on alternatives which can deliver even more types of medicines. Inhalers are being improved as are nasal sprays, forced air injectors and patches. In the future, other foods may be genetically enhanced to deliver vaccines and other drugs. These include foods like bananas and tomatoes. In fact, bananas are being looked at as carriers for a vaccine to protect against the Norwalk virus. Tomatoes that protect against hepatitis B are also being developed. In addition to new delivery systems, scientists are also

investigating methods for producing longer lasting drugs that will reduce the number of needle injections.

SUMMARY

Needle-free injection systems have potential to improve efficiencies. Major advantages of needle-free systems are the elimination of broken needles, a more constant delivery of vaccines and drugs, and decreased worker safety risk. Needle free injection systems are customizable to each operation and can be modified to optimize productivity. However, implementing a needle-free system can be challenging. Workers require training and education regarding any new technique. Start-up and training costs may also affect the interest in this technology for some pork producers.

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