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Research Article

AN UPDATE: ON NEEDLE FREE INJECTIONS

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ABSTRACT

The aim of modern needle-free injection is to enhance the prescribing and adoption of important drugs that require self-injection, such as biologics. Invention of needle-free injection technologies is to achieve this by improving the patient experience and removing the barriers to self-injection, such as the fear of needles. According to Food and drug administration [FDA] A needle-less or needle free injection is a device used for the parenteral administration of a medicament is disclosed. They can take the form of power sprays, edible products, inhalers, and skin patches. Needle-free systems are designed to solve these problems making them safer, less expensive, and more convenient. It can be placed in the bore of a barrel with the barrel having the shape of a nosecone at one end. A plunger is inserted into the other end of the bore. The plunger forces the medicament through the skin and into the subcutaneous layer of the patient without the need for penetration of the skin by a needle. A needle-free syringe is placed into the filling adapter and the liquid is drawn into the needle-free syringe and is slightly over filled. The plunger is broken off and discarded. With the adapter, needle-free syringe, and vial still engaged the needle-free syringe is placed into the injector with a ¼ turn to the right, this returns excess medicine or vaccine back into the vial and positions the plunger to deliver a 0.5ml dose. Today, this is the most promising tool for delivering the medicament for suitable requirement.

Keywords: Needle Free injection, Mhi-500, Recojet, Biojectorr 2000, Vitajet 3, Cool click.

INTRODUCTION

Needle-free injection devices (**NFID**) have been available for humans since the 1930s. Their implementation in farm production systems has been slow because of the low expense and ease of use of needle-syringe injection. 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. The Iject™ needle-free injection system, being developed by Bioject Inc, makes injected medications convenient, comfortable and non-threatening. The system is low-cost, pre-filled, easy of handling and totally needle-free.

OBJECTIVE OF THIS WORK

1. It is less pain full and potentially safer.
2. The key nebifits of avoiding a needle and ease of use of a liquid jet injector and do not outweigh over all we can say that the cost of goods compared with other delivery technologies.
3. The main advantages of this system are the elimination of broken needles, a more constant delivery of vaccines and drugs, and decrease worker safety risk.

ADVANTAGES

- Elimination of broken needles
- Consistent vaccine delivery
- Reduced vaccine volume
- Higher antigen dispersion
- Elimination of worker needle sticks
- Elimination of needle disposal
- Lower pain and stress.
- Patient compliance.

NEEDLE-FREE TECHNOLOGY: ORIGIN AND METHODOLOGY

Needle-free technology, first called *jet injectors*, was first developed in the year 1930s[2-3] In new generation people, needle-free technology uses

disposable single-dose cartridges eliminating re-use of the nozzle face and fluid path. Most needle-free technology in production animals use non-disposable nozzle faces. Newer devices use a disposable nozzle face that allows for fast and easy nozzle changes, when necessary, and when transferring to a different farm.

Needle-free injection technology was uses force generated by a compressed gas (typically air, CO_2 or nitrogen). 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 objection to needle-free injections has been the wetness associated with residual vaccine on the skin surface[4] Needle-free injection technology has been designed to deliver antibiotics[6-7], iron dextran or vaccine comfortably, accurately, and quickly without the use of a needle[8]. Needle-free injection is precise, reliable, and virtually the same every time[9] There are 3 stages in needle-free delivery, and the total amount of time required to deliver the vaccine is less than 1/3 of a second which is shown in Figure no 1.

TYPES OF NEEDLE FREE INJECTION SYSTEMS[10]

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

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**.** Market product of liquid based NFI is shown in table no 1.

WORKING PRINCIPLE OF NEEDLE-FREE INJECTION TECHNOLOGY

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 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 is as follow.

DIGRAMETICALLY REPRESENTATION OF WORKING

It is having the four stages is shown in figure no 2.

1) Medication is driven at high speed through a tiny orifice
2) A fine stream of medication penetrates the tissue
3) Injection event requires less than 0.5 seconds.
4) Injections can be IM, SC or ID.

DESIGN [16]

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.

RAW Material

Polymer easier to mold, fillers are added[18] 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. Lidocaine hydrochloride, a local anesthetic is suitable to be delivered needle free. Other medicines suitable for needle free systems include Fentanyl, Heparin and a variety of vaccines.

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[19] 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.

Assembling and labeling

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.

Making 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 been on an injection molding machine. They are heated to make them flow able. 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.

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.

APPLICATIONS

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

MANUFACTURERS OF NEEDLE FREE INJECTION [4, 7, 8, 11]

Mhi-500

Mhi-500 is the novel needle frees 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. 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.

Recojet

Shreya Life Sciences has recently launched its recombinant human insulin under the brand name Recosulin and a needle-free insulin delivery device, Recojet. 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.

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..

Biojectorr 2000

The system can also deliver subcutaneous injections, and is being used for intradermal injections in clinical trials 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, it provides healthcare workers with an unparalleled level of protection against accidental needle stick 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.

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 inspecting the dosage prior to injection and visually confirming loading and full discharge of your insulin after each use.

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. 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. Coool clik fig is shown in figure no 3.

SeroJet

The SeroJet is a needle-free injection system for delivering Serostim recombinant human growth hormone for treatment of HIV-associated wasting in adults in fig. 4 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. 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 customised dosage features to accurately deliver variable doses of Serostim.

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." Figure 5.

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.

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.

Quality control[19,20]

It 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.

RESCENT ADVANCES

Intraject Systems[21]

Intraject system is the world's first disposable, needle free injection device for the delivary 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 practioner, patient or a carer can deliver areliable, virtually pain free injection is shown in figure no 6.

Bioject®Zetajet [22]

Bioject's latest advance in needle-free delivery systems, consists of two components, the portable injector and an autodisabling disposable syringe figure 7 it is professional use and home use for patients who self-inject.

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.

INJEX. NEEDLE-FREE INJECTIONS FOR INFILTRATION ANAESTHESIA [23]

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 of 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 teeth1: 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. The shorter onset time also reduces the treatment induced stress for children. Since only 0.3 ml of local anaesthetic is administered figure 8.

Adult patients

Many adults are afraid of the syringes with the needle as well as the pain induced by the dental treatment. This problem can be alleviated with the 'needle- free syringe' is is shown in the figure no 9.

Some patent citations used in the needle free injection technology is mention in the Table 2.

CONCLUSION

Needle-free technology has the best alternative to deliver the medicament in to the skin without having a pain. Other 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. These 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.

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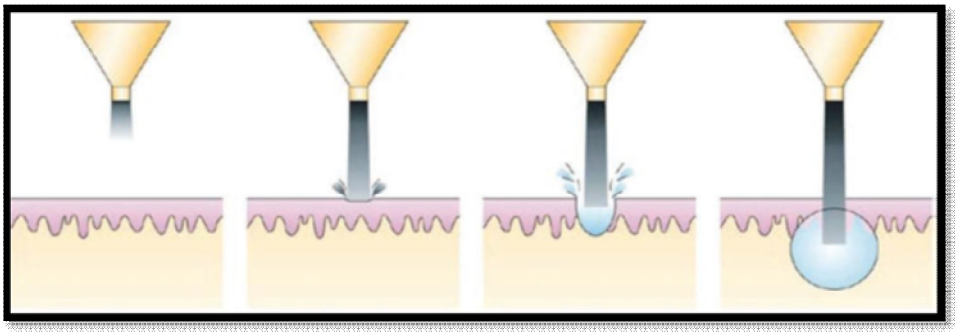

Fig. 1: Pressure profile in simulated injection of 0.5 mL fluid by needle-free injector device demonstrating Stage 1, peak pressure phase, optimal pressure used to penetrate the skin (< 0.025 second), Stage 2, delivery phase (approximately 0.2 second), Stage 3, drop-off phase (< 0.05 second).

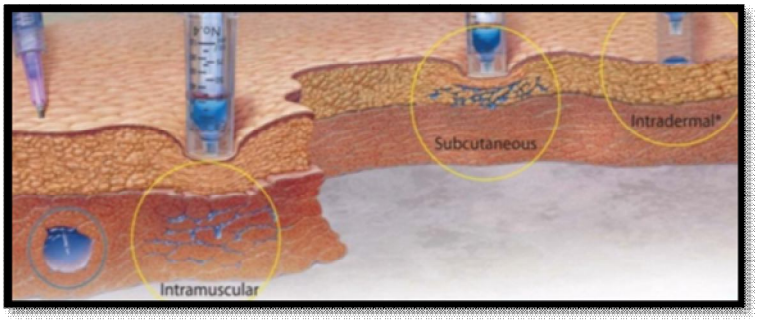

Fig. 2: Types of Parenteral Route

Fig. 3: cool.click needle-free injection system

Fig. 4: SeroJet

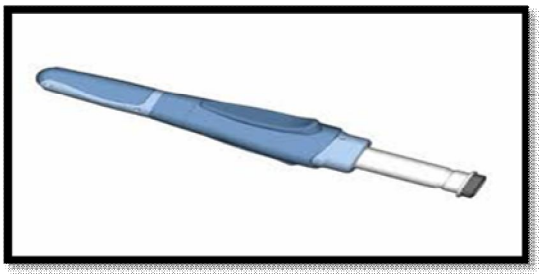

Fig. 5: Iject

Fig. 6: INTRAJECT

Fig. 7: Bioject system

Fig. 8: INJEX for pediatrics

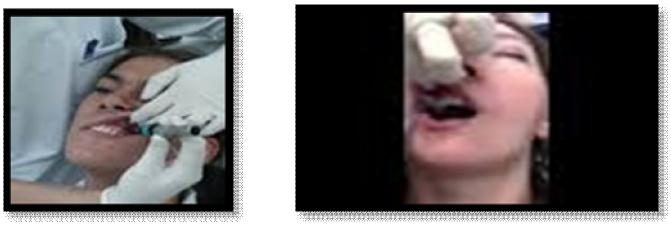

Fig. 9: INJEX for Adult patient

Table 1: Market Product of Liquid Based NFI [11-15]

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
Powderject system	Powderject pharmacueticals	Powder based needle free injection
Depixol Depot injection	Lundbeck Limited	Depot based needle free injection

Table 2: Patent citations used in the needle free injection technology

Cited Patent	Filing date	Publication date	Title
US2589388	12Mar 1951	18 Mar 1952	Suppository injector
US2630804	24 Feb 194	10 Mar 1953	Single dose cavity dispenser
US3072121	24 Jul 1956	8 Jan 1963	Pellet injector
US3572335	10 Jan 1969	23 Mar 1971	Cervical implant method and device
US4060083	1 Apr 1976	29 Nov 1977	Pill gun
US4808166	8 Oct 1987	28 Feb 1989	Anal medication applicator
US4871094	29Apr 1988	3 Oct 1989	Means and method for dispensing substances
US4994028	15Mar 1989	19 Feb 1991	Injector for inplanting multiple pellet medicaments
US5399162	23Feb 1994	21 Mar 1995	Automatic balling gun
US5405324	30 Mar 1993	11 Apr 1995	Implantation device
EP0292936A2	25 May 1988	30 Nov 1988	Device for administering solid preparations
US5823994	15Mar 1996	20 Oct 1998	Method and apparatus for soft tissue fixation
US6176857	22Sep 1998	23 Jan 2001	Method and apparatus for applying thermal energy to tissue asymmetrically
US6402716	12Feb 1999	11 Jun 2002	Syringe assembly
US7470250	18Mar 2003	30 Dec 2008	Apparatus for automatic insertion of a solid medicine
US7601137	5 Jun 2003	13 Oct 2009	Needle-less injector
US8465448	18Feb 2009	18 Jun 2013	Devices for the administration of drugs and vaccines in the form of injectable needles
DE102008005938A1	24Jan 2008	30 Jul 2009	Pre-filled syringe for use in ophthalmology field.
EP2065063A1	10Sep 2002	3 Jun 2009	Needleless injection device
WO2002060371A1	28Jan 2002	8 Aug 2002	Device for inserting a needle-shaped body into living tissue
WO2004014468A1	18Jul 2003	19 Feb 2004	Drug delivery system
WO2011042542A1	8 Oct 2010	14 Apr 2011	Formulation of drugs and vaccines in the form of percutaneous injectable needles

REFFERENCES

1. Willson P. Needle-free immunization as effective as needle and syringe method. Council Research News. Available at: April 19, 2007.
2. Reis EC, Jacobson RM, Tarbell S and Weniger BG. Taking the sting out of shots: control of vaccination-associated pain and adverse reactions. Pediatr Ann. 1998;27:375-386.
3. Hingson RA, Davis HS and Rosen M. The historical development of jet injection and envisioned uses in mass immunization and mass therapy based upon two decades experience. Mil Med. 1963;128:516-524.
4. Jones GF, Rapp-Gabrielson V, Wilke R, Thacker EL, Thacker BJ, Gergen L, Sweeney D and Wasmoen T. Intradermal vaccination for Mycoplasma hyopneumoniae. J Swine Health Prod. 2005;13:19-27.
5. Apley M and Thacker B. Determination of the pharmacokinetics of procaine penicillin in swine administered by intramuscular injection and with a needleless injection device. National Pork Board Research Abstract. Available at: http://www.pork.org/porkscience/research/documents/02-136-apley.abs.9-26-03.pdf. Accessed April 19, 2007.
6. Senn MK, Bradford JR, Cook DL and 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.
7. Almond GW and Roberts JD. Assessment of a needleless injection device for iron dextran administration to piglets. IPVS Proc. 2004;618.
8. Mitragotri S. Current status and future prospects of needle-free liquid jet injectors. Nat Rev Drug Discov. 2006;5:543–548.
9. Schloesser CA, Daniels CS, Cook DL. Accuracy and precision of Pulse Micro-dose injection device using Draxxin, Excede, Excenel and sterile water. AASV Proc. 2008.
10. United States Patent (needle free injection system) Patent No: US6,676,630 B2.
11. Weston Medical. Weston Medical.com FAQs. Available at: www.Weston medical.com/faqs.htm.
12. www.penjet.com
13. www.bioject.com
14. www.cdc.gov/nip/dev/N3draft0007 doc
15. www.cdc.gov/nip/dev/N2draft000603 doc.
16. http://www.pharmatutor.org/articles/needle-freeinjection-technology?page=0,1.
17. Mitragotri S. Current status and future prospects of needle-free liquid jet injectors. Nat Rev Drug Discov. 2006;5:543–548.
18. Needle-Free Injection Technology.www.cdc.gov/vaccinesafety/vaxtech/nfit
19. Epidermal delivery,Ideal platform to deliver vaccines and immunological compounds. http://www.pantec-biosolutions.com/en/products-and-services/epidermal-deliverys
20. Technology Overview, Needle-free injection What is it? http://www.bioject.com/about/technology.
21. http://www.ismp.org/Newsletters/acutecare/articl es/20061130.asp.
22. http://www.bioject.com/products/zeta jet.
23. Hunter Cora H. Suppository injector. US2589388. 1952.
24. Ortho Pharma Corp. Single dose cavity dispenser. US2630804. 1953.
25. Nat Tuberculosis Ass. Pellet injector. US3072121. 1963.
26. Robinson Ralph R. Cervical implant method and device. US3572335. 1971.
27. Hanson Raymond L. Pill gun. US4060083. 1977.
28. James Davidov. Anal medication applicator. US4808166. 1989.
29. Alcon Laboratories, inc. Means and method for dispensing substances. US4871094. 1989.
30. Endocon, Inc.. Automatic balling gun. US5399162. 1995.
31. US5405324. Cselle; Edward. Implantation device. 1995.
32. Sumitomo Pharmaceuticals Company, Limited. Device for administering solid preparations. EP0292936A2. 1988.
33. Oratec Interventions, Inc. Method and apparatus for soft tissue fixation. US5823994. 1998.
34. Oratec Interventions, Inc. Method and apparatus for applying thermal energy to tissue asymmetrically. US6176857. 2001.
35. Lg Chemical Ltd. Syringe assembly. US6402716. 2002.

36. Novo Nordisk A/S. Apparatus for automatic insertion of a solid medicine. US7470250. 2008.
37. Intervet International B.V. Needle-less injector. US7601137. 2009.
38. Azurebio SL. Devices for the administration of drugs and vaccines in the form of injectable needles. US8465448. 2013.
39. Arzneimittel Gmbh Apotheker Vetter & Co. Ravensburg. Pre-filled syringe for use in ophthalmology field. DE102008005938A1. 2009.
40. Glide Pharmaceutical Technologies Limited. Needleless injection device. EP2065063A1. 2009.
41. Hollert Astrid. Device for inserting a needle-shaped body into living tissue. WO2002060371A1. 2002.
42. Caretek Medical Ltd. Drug delivery system. WO2004014468A1. 2004.
43. Azurebio SL. Formulation of drugs and vaccines in the form of percutaneous injectable needles. WO2011042542A1. 2011.