E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/10.01.11

Review Article

Delivering Biologics in Prefilled Syringes: An innovation in parenteral packaging

PURUSHOTTAM S. GANGANE[1], NILESH M. MAHAJAN[1], UJWALA N. AHAJAN[2], SANDHYA R. HIRANWAR*

[1]Department of Pharmaceutics, Dadasaheb Balpande College of Pharmacy, Besa, Nagpur-440037, India.
[2]Department of Quality Assurance, Dadasaheb Balpande College of Pharmacy, Besa, Nagpur-440037, India.
E-mail id: Hiranwarsandhya311@gmail.com, (m): +91 9130971218
Received: 12.09.19, Revised: 12.11.19, Accepted: 12.12.19

ABSTRACT
A prefilled syringe is a single-dose packet of vaccine in which a needle has been fixed by the manufacturer, used to deliver parenteral medication. In the past metal or glass syringes were popular, but increasingly there has been a movement towards plastic and disposable syringes so the needle is protected and cannot be re-used. This has stimulated the demand for convenient and safe prefilled syringes in the medical field over conventional glass vials for packing parenteral drugs. Parenteral packaging innovations and applications have made devices easier to use for both the healthcare professional and the patient. Prefilled syringes are used to package injectable drugs and diluents. Filling and stoppering of prefilled syringes are carried out by three process traditional filling and stoppering, online vacuum filling and stoppering and online vacuum filling followed by offline vacuum stoppering in a vacuum chamber. Pre-filled devices which are available in the market as dual chambered syringes, unijet prefilled syringe and BD ready fill TM. Sterilization of prefilled syringe was mainly done by ionizing radiation or by autoclaving. Prefilled technology developments are primarily to accommodate the increasing number of biologic drugs reaching the market. Additionally, the companies have developed multi chamber prefilled syringes for use with lyophilized drugs.

Keywords: Prefilled syringes, Auto injector, Leva auto jet, Flex pen, Vacuum stoppering

INTRODUCTION
Prefilled syringes are pharmaceutical product which is used to deliver parenteral medications. A prefilled syringe are single dose packet of parenteral drug in which a needle has been fixed by a manufacturer. Prefilled syringes are ready to use disposable syringes contains premeasured dosage, reduce dosing errors and increase patient compliance, dosing accuracy, convenience and safety, enhance patient quality of life and reduce patient time in the clinic. Pre-filled syringes are more convenient devices for the delivery of parenteral medications. They are small which makes them easy to carry and are dependable for delivering a precise dose of medication. There are many other reasons are leading to their growth in the pharmaceutical market. Pre-filled syringes have emerged as one of the fastest-growing choices for unit dose medication as the pharmaceutical industry seeks new and more convenient drug delivery methods. Pharmaceutical companies are able to minimize drug waste and increase product life span, while patients are able to self-administer injectable drugs at their home instead of the hospital. In the past, glass syringes mostly used in the market, but there has been a movement toward plastic and disposable syringes. Pre-filled syringes have also been utilized across a wide range of therapeutic sectors, such as vaccines, blood stimulants and therapeutic proteins.[1,2] Injectable drug delivery systems, conventional syringes with vials has been traversed to prefilled syringes, auto-injectors, pen injectors and needle free systems. Mostly preferred devices for parenteral administration of drugs in the forms of prefilled syringes. Specifically, the demand for prefilled syringes has been increasing strongly over the past several years. The prefilled syringes was not limited to healthcare settings & less popularity; self-injection by patients possible more easier and safer methods also prefer using prefilled syringes for drug administration in home settings. The rise in parenteral drugs, especially biologics are used in the treatment of diseases and chronic conditions, such as multiple sclerosis and rheumatoid arthritis, has forced drug and packaging manufacturers to seek more sophisticated container closure and drug delivery systems. Responding in which increasing preference, pharmaceutical companies are packaged a number of their injectable drugs and vaccines in prefilled syringe formulation. Over 100 injectable drug products are available in prefilled syringes and a rising number of pipeline drugs are targeted to be delivered by this method.[3,4]

History of prefilled syringes
First official injection morphine appeared in the British Pharmacopoeia in the (1867) and monographs of seven sterile glass sealed ampoules comes in the US National formulary in 1926. Since then, list of injectable products has grown. In 1980, the origins of prefilled syringes can be found when Sanofi and Rhone Poulenc-Rorer (Sanofi-Aventis) introduced them as drug delivery devices for heparins in Europe. They have been around for more than three decades now and are used for administration of all major classes of therapeutics,

including vaccines, anticoagulants, anti-arthritic drugs and anti-anemic drugs. Prefilled syringes have improved significantly over the years. Manufacturers have recently developed multi-chamber syringes for use with lyophilized drugs. Such syringes are also being developed with advanced injection devices, such as auto injectors and pen injectors. In addition, prefilled diluent syringes and flush syringes are already more popular. With more than 60% of candidate drugs/therapies in the clinical pipeline being biologics that usually require parenteral administration, the adoption of prefilled syringes was anticipated to further increase in the mid-long term.[5,6]

Advantages of prefilled syringes

For both patient and doctors, pre-filled syringes make injections easier and safer. With a prefilled syringe, the right dosage always received by patient. In addition, pharmaceutical companies can benefit from less overfill in a pre-filled syringes (compare to vials) – which is an important advantages, particularly with costly biopharmaceuticals. Last but not least, pre-filled syringes work well with increasingly popular safety devices and auto-injection systems making the injections easy, safe and convenient.[7]Many important drugs are available only in parenteral dosage forms. Notable among them are numerous biotechnology drugs, insulin, several cephalosporin antibiotic products, glucagone, heparin, and protamine. In addition, parenteral formulation are available for drugs such as lidocaine hydrochloride and many anticancer products.

Disadvantages of prefilled syringes

Pharmaceutical companies must be sure about patient safety, by demonstrating that material and component which has not any extractables and leachables (E&L) and the primary packaging have not any adverse interaction with the drugs. Some of the E&L comes in contact with drug molecule and interfere with the drug molecules and could diminish the effectiveness of a drug. In ampoules, the drug comes in contact with only glass and in vials drug is in contact with glass and rubber. Pre-filled syringes, on the other hand, are in contact with not only the drug, but more materials and components creating additional opportunities for interactions and E&L.[7,8]

Challenges and Opportunities

A prefilled syringe is a single-dose packet of vaccine in which a needle has been fixed by the manufacturer. In past, glass and metal syringes were popular, but increasingly replaced by plastic and disposable syringes so the needle is protected and cannot be re-used (prefilled disposable systems). This has stimulated the demand for convenient and safe prefilled syringes in the medical field over conventional glass vials for packing parental drugs. Parental packaging innovations and applications have made devices easier to use for both the healthcare professional and the patient. Prefilled syringes have actually been around for more than two decades. The European market for prefilled syringes is relatively more mature compared to the US market, which is still relatively smaller and younger. However, the market for prefilled syringes has seen healthy growth in recent years as the pharmaceutical industry has grown and become more sophisticated. The European market for prefilled syringes is worth $300 million and is growing at between 8-10 percent per annum. Prefilled syringe manufacturers have had to therefore respond to increasing demand, new requirements and more sophisticated forms of drug delivery. There has been great development in syringes. New products are being put in syringes now. Prefilled syringes are used to package injectable drugs and diluents. Some of the categories of drugs packaged in prefilled syringes are vaccines, blood stimulants, therapeutic proteins, erythroproteins, interferons, and rheumatoid arthritis.[9,10]

Types of prefilled syringes system

There are two types of prefilled syringes are as follows: Glass based system, Plastic based system.

Glass Based System

Traditionally barrel has been made from glass tubing. These glass tubes are transformed by heat in to barrel which is used to hold the medicament. But it has main disadvantages that glass is easily breakable in nature and requires added care while handling. Other drawbacks with glass are glass contains small amount of alkali which may cause a PH shift in some products.[11]

Plastic Based System

Plastic syringes are gaining high acceptance compare to glass system because they can easily handle. Syringes which are made up of COC (cyclic olefin copolymer) and COP (cyclic olefin polymer) have been developed. These cyclic olefin copolymers and polymers have excellent transparency, good moisture barrier properties, and are chemically clean with very low extractable. They have good dimensional tolerance and high flexibility in design and no tungsten or adhesive is involved in fixing a staked needle to plastic syringes.[10]

Pre-filled syringe components [12]

Pre-filled syringes includes following parts: A barrel having an opening at opposite ends and an inwardly projecting annular wall at a distal end. A plunger fluid-tightly inserted in the proximal end of the barrel so as to be slidable along the inner wall of the barrel; A needle-connecting member,

attached to the annular wall to fluid-tightly close the opening of the annular wall; A flexible plastic film tube within the barrel hermetically bonded to the needle-connecting member and the plunger at each end; Needle-connecting member having at its rear end a skirt portion of an outer diameter equal to an inner diameter of barrel, skirt portion being fitted in the distal end of the barrel, film tube being bonded to the outer wall of the rear side of the skirt portion.

Preparation of pre-filled syringes

The method for the preparation of a pre-filled plastic syringe, comprising the steps of:[12,13]

(a) **Preparation of components** Providing a barrel and plunger molded under conditions which are substantially free of pyrogens and viable and non-viable particulates, from non elastomeric material, such as polypropylene, polycarbonate or other medical grade plastic, within at least a class 100 environment. Optionally, providing a tip seal and/or a piston which is also molded under conditions which are substantially free of pyrogens and viable and non-viable particulates. The plunger cover and tip seal are moulded from an elastomeric material, such as rubber, by any suitable molding method such as compression molding. After moulding and contaminant removal, the plunger cover and tip seal are lubricated with silicone oil, hereinafter referred to as 'silicone', to facilitate the assembly of the plunger cover onto the plunger substrate to form the plunger, and the assembly of the tip sealed to the distal end of the barrel to form the barrel/tip seal combination. The plunger cover and tip seal may also require sterilization by any suitable method, such as use of ethylene oxide or autoclaving. Maintaining said barrel and, optionally, tip seal and/or piston, under clean conditions for use in step (b).

(B) Filling and assembling the syringe:[13]

The pre-filling and terminally sterilizing a syringe, having the following sequential steps: Providing an empty syringe barrel having first and second opposite ends, where first end having a port through with a connector member formed about an exterior of port and second end being open; Removing particulate matter from the interior of syringe barrel; Sterilizing the cap and stopper, stopper being at the first and second opposite longitudinal ends; Prior to filling empty syringe barrel, insert first end of stopper into the second open end of empty syringe barrel and stopper move toward first end of empty syringe barrel until first end of stopper was reached a position against the first end of empty syringe barrel; Prior to connecting the cap to the connector member to seal the port, fill syringe barrel with a desired fluid medicament through the port of first end of syringe barrel wherein substantially no air enters syringe barrel, then stopper moves from first end to second end of syringe barrel by fluid pressure of fluid medicament as the syringe barrel is filled; After filling the syringe barrel through the port, connect the cap to connector member of first end of filled syringe barrel to seal port; and Terminally sterilize pre-filled and assembled syringe barrel, stopper and cap in an autoclave having a spray over-pressure cycle which maintains pressure about the exterior of syringe barrel at least equal to the pressure within the interior of syringe barrel.

Pre-filled devices in the market

Dual-Chambered Syringe: To great extend and advantages of a prefilled syringe to manufacturers of lyophilized drugs, Vetter Pharma Fertigung developed the Vetter Lyo-Ject dual chambered syringe. Dual chambered syringe is a glass-barrele/d syringe with a stopper. Stopper in the middle to serve as a barrier between the two chambers. Better lyophilizes the drug in the syringe itself and seals that chamber while the syringe is still in the lyophilizer. Filling equipment then dispenses the diluent into the remaining volume of the syringe and adds another stopper. On the distal portion is a screw taper plunger rod that goes through the finger rest. As the user advances the plunger, it puts pressure on the diluent. The diluent moves the center stopper into a bypass in the side of the glass. Eligard delivered by atrigel drug delivery technology is an example of the same.[14,15]

Prefilled Diluent Syringe: While dual-chambered syringe or dual syringe delivery systems are elegant and not compatible with many lyophilized drugs. Freeze dried product will be put into a vial due to the volume of liquid filled and the corresponding lyophilized plug size but also to get the best freeze-drying characteristics, which in turn yields longer stability. West currently offers Clip'n Ject, a modernize system consisting of a prefilled diluent syringe which containing the lyophilized or dry powder drug will be packaged with the drug vial.[15]

UniJect Pre-filled Syringe (non-reusable injection device)

UniJect is a plastic disposable injection device and a single dose of medication. It is activated by pushing the needle cap toward the body of the device, opening the fluid path between the needle and the blister. The cap is then removed, the needle inserted into the subject, and the dose is delivered by squeezing the blister until it collapses.[16]

BD Hypak PhysiolisTM

Glass Prefillable Syringe: The BD Hypak Physiolis syringe features patented needle-point geometry and a new latex-free needle shield material. The needle has five bevels and, at 29 gauge, is thinner than previous offerings. Its unique design results in a needle point that, while being thinner, is actually stronger. In combination with a new needle shield material such as BD Hypak Physiolis syringe needle

which is sharper and easily penetrated through the skin, which enhances patient comfort.[17]

BD Ready fill™

The BD Ready fill™ syringe has more value and innovative formulation, differentiating it from those of vials or ampoules. Compared to alternative prefilled devices, the unique formulation in combination of integrated features of the BD Ready fill™ syringe offers increased product differentiation, like Quality staked needle: Using only the highest quality preattached needle helps ensure the smoothest, most comfortable injection possible. The needle never punctures or is embedded in rubber.[44,56]

Rigid Needle Shield: A hard plastic shield increases end-user safety and cap cannot be easily removed.

Needle Isolation: Separating the liquid from the needle confirm that drugs sensitive to needle contact and during storage are not affected.

Baked Silicone: Binding the silicone occurred with the glass barrel so that it was important that a proprietary technology reduced the level of free silicone, clear benefit for silicone sensitive drugs.

Integrated Backstop: Integrating the backstop and the syringe barrel prevents accidental removal of the plunger during aspiration.

Ergonomic Design: Oversized finger grip means maximum ease of use for the end user and promotes overall injection safety.[30,31]

BD Preventis TM prefilled syringe automatic needle shielding system

The main features of the BD Preventis are:[33]Compatible with 0.5 mL and 1 mL long BD Hypak™ syringes with attached needle Single hand activation Designed for either low or high speed assembly lines No change in sterile filling operation Secondary packaging for filled syringe Enables easy visualization of the syringe contents.

ChaSyr Pre-filled Syringes

The ChaSyr DDS is a prefilled, multi– chamber, sequential delivery syringe. In a nutshell, it means that the syringe has more than one medication chamber separated by a rubber stopper with a valve that keeps the medications disparate and prevents air/gas from passing through the valve. In the posterior chamber, syringe becomes prefilled with saline or heparinized saline. In the front chamber, the clinician aspirates medication. After infusion of the medication from the front chamber, the clinician simply continues to push the syringe plunger. When the rubber stopper (ChaSyr valve) comes in contact with the tip of the syringe a valve opens allowing the saline solution in the back chamber to flow through the valve thus flushing the Y-site and IV line of the original medicant and leaving a saline lock in the system. The ChaSyr DDS with its prefilled inline post flush simplifies nursing procedure, reduces line manipulations and line breaks by up to 50% thereby reducing contaminations rates and nosocomial infections.[72,73]it can be seen that rear chamber of the ChaSyr DDS has a prefilled saline flush. The front chamber of the ChaSyr DDS is filled by the pharmacist with the drug of choice and a saline lock is placed in an extension set with a clamp. From figure it can be seen that the clinician removes the cap from the extension set (only clinician exposure is to saline) and attaches the extension set to the catheter. After opening the clamp, the syringe plunger is pushed thus infusing the saline pre-flush then the drug through the IV.[33]

Accessories used with pre-filled syringes [64, 78]

LEVA® Auto ject

LEVA® is disposable and designed for subcutaneous injections of fixed doses. A skin sensor and automatic needle retraction persuade a maximum safety. With an intuitive design and small size & few user steps; LEVA® provides a fast, easy and safe pathway to injection.

Flex Pen® Device

Product benefits: Enhanced safety features, Enhanced simplicity, Discreetness Simple, single-step dose setting and delivery.

Filling process of prefilled syringes

There are four principal methods for filling and stoppering syringes, each with its own advantages and challenges. A high-speed equipment filling, online high-speed filling followed by offline vacuum stoppering & online vacuum filling followed by online vacuum stoppering. These three methods can create bubble in the syringe. During shipping this bubble may increase the risk of stopper movement, and cause loss of product during expulsion activities prior to administration. For some proteins and oxygen-sensitive compounds may causes stability issue. The new innovation in filling and stoppering syringes by using online vacuum filling and stoppering and combination with other proprietary patented technology of syringe produced that was bubble-free was the fourth method. It is called as 'Bubble free filling'. It is most advantageous for non-viscous products, since viscous products can be filled without bubbles using online vacuum filling and stoppering alone. The advantages of bubble-free filling include: Enhanced dosing accuracy, improved product sterility, decreased waste/greater safety and increased product stability. [30]Filling and stoppering of prefilled syringes are carried out by three process.

They include: Traditional filling and stoppering, online vacuum filling and stoppering and online

vaccum filling followed by offline vacuum stoppering in a vacuum chamber.

In traditional processes

Syringes are filled and stoppered using conventional filling equipment. In these processes, a needle is inserted into a presterilized syringe and product is forced out. Next, the syringe stopper is removed from a tube- the insertion tube, which is narrower than the syringe. The insertion tube is then placed in the syringe above the liquid level line and a rod pushes the stopper out the insertion tube into the syringe. The drawback, however, is that conventional methods leave a gas bubble inside the syringe which can pose significant challenges. Additionally, conventional methods which use insertion tubes are not suitable for coated stoppers since the force of the compression of the stopper and the action of the insertion rod will cause the coating to wrinkle or tear.

In online vacuum filling and vacuum stoppering syringes are first evacuated and filled under vacuum. They are advanced to the stoppering position where a vacuum is again applied in the filled syringes, and by differential pressure a stopper is pushed into position. In this process, there is no compression of the stoppers and insertion rods are not required. By these process, bubble free filling of syringes can be done. Pressures during shipment, Enhanced stability profile of oxygen sensitive compounds. Enhanced stability profile of certain protein products and rearrange them in gas-liquid interfaces, improved accuracy and precision of delivered dose, Creation of an unfavorable environment for the growth of aerobic micro-organisms. The major benefit of this method over the conventional method is that reduction of the bubble which present between the product and the stopper in traditionally filled syringes. It also works well with coated stoppers since using differential pressure the stopper is placed rather than force.

In online vacuum filling followed by offline vacuum stoppering: The syringes are filled under vacuum. Then filled syringes could alternatively place into an offline vacuum chamber for stoppering. However, offline vacuum stoppering requires increased operator intervention which increases the chances of contamination and can slow the process down.

Sterilization of prefilled syringe:[25, 64]

Medical device manufacturers do not have to face the same challenges as their pharmaceutical counterparts, as devices are normally manufactured using plastics, metals or other materials that are easily adapted to terminal sterilization. But prefilled syringes is considered as combination product therefore challenges posed in sterilization of prefilled syringes are different than challenges faced by medical device manufacturers [31] To ensure that the prefilled syringes can be sterilized using an appropriate technique following detailed considerations are very important: [32] Drug stability with chosen sterilization technique. Development trials to determine processing parameters and product limitations. Packaging configuration – orientation during sterilization. Temperature sensitivity and transportation requirements. Time lines between process of manufacturing, sterilization of formulated product and delivery to market. Regulatory compliance: UK MHRA, US FDA and other notified bodies. Sterilization of prefilled syringe was mainly done by ionizing radiation or by autoclaving. Moist heat sterilization typically involves heating the device in a steam autoclave. Such steam sterilization, however, is time and labour consuming, and compromises the aesthetics of the product due to packaging degradation from the steam treatment. [33] Over the last 20 years, the developments of 10 MeV sterilisation beams (which are commercially viable and used by a large proportion of the medical device industry) have created new options for pharmaceutical manufacturers Solution contained within the syringe may dictate the sterilization method. Goal is not only sterilization but to maintain a safe solution within the syringe which meets pharmacopoeia requirements.[34] Radiation exposure is also commonly employed for sterilizing medical devices, in which the product is subjected to ionizing radiation, such as gamma irradiation. Gamma irradiation of polyolefin syringes can result in weakened container integrity, leakage, increased gas permeability and an undesirable yellowing of the container, and that gamma radiation treatment inherently causes the generation of highly reactive species. The generation of such reactive species can alter the contents of the container being treated, thereby causing the contents of the container to fail the European and/or U.S. Pharmacopoeia requirements, such as pH standards (required to be between 4.5 and 7.0), UV absorbance levels (required to be below 0.2 at 220-340 nm), and presence of hydrogen peroxide and oxidizing substances (required to be below 3.4 ppm). Syringe made up of radiation stable polyolefin is probably solution to this problem.[31]

The label and labeling of a prefilled syringes

A device like prefilled syringes are coupled with a biologic products are "combination drugs". Prefilled syringes act as the primary container for drug products, and in regulatory terms constitute the immediate packaging in contact with the drug. [35] As the prefilled syringe is a fixed product, attention must be paid to the prefilled syringe package label to avoid improper use, (which leads to reduced efficacy), and to minimize adverse drug reactions. The label and labeling of a drug product are the primary basis means for which patients and

practitioners (depending on configuration), interact with the pharmaceutical product and formulation. The carton and container labels communicate critical information including the proprietary and established name, along with the strength, form, container quantity, expiration, and so on. The package insert labels (US PI or EU SmPC), communicates all information which are relevant to the approved uses of the drug, including the correct dosing and administration of drug product.[36]

Advances in prefilled syringes

The increasing demand of prefilled syringes so during the manufacturing, manufacturer had been introduced improvements in technology related with the material of prefilled syringes, and lubrication technology to reduce leachables and extractables. Prefilled technology developments are primarily to accommodate the increasing number of biologic drugs reaching the market. Additionally, the companies have developed multi chamber prefilled syringes for use with lyophilised drugs. Advances in the industry with respect to syringe design include new types of components, changes to the manufacturing process to reduce the quantity of silicone used to coat the syringe, required changes in the process to decrease tungsten and adhesive residuals, dual-chamber devices, and needle-free devices. Advances condition in which the types of components contain changes in the construction of material such as the polymeric syringes are changed with in tip cap and plunger formulations as well as plungers can be changed. [38,82]

Future

The numbers of innovative injectable products available in market are increasing day by day. If a greater number of new drugs are placed in prefilled syringes then uptake of these by end users will increase. Prefilled technology would need to adapt to these new innovations for this pharmaceutical companies will require more sophisticated forms of delivery. In order to maintain competitiveness in the market place, this means greater investment is required by the manufacturers. At present there is not enough supply of prefilled syringes. Manufacturers will need to keep up with demand. For the manufacturers of prefilled syringes, the major processing and quality control challenges include the stability issues due to interaction of packaging materials of prefilled syringes with the drug. Manufacturing costs of formulated product was raised because of adaptation of safety measures to diminish needle stick injuries. The safety systems are very costly. The percent of prefilled syringes with safety systems is very low and this trend is expected to change in the forthcoming years with more focus of the healthcare industry on needle stick safety aspects. [66, 86]

CONCLUSION

From this review article it can be concluded that there is more scope for development of prefilled syringes market. A Prefilled syringes are ready to use disposable syringes contains premeasured dosage, reduce dosing errors and increase patient compliance, dosing accuracy, convenience and safety, enhance patient quality of life and reduce patient time in the clinic. Pre-filled syringes are more convenient devices for the delivery of parenteral medications. They are small which makes them easy to carry and are dependable for delivering a precise dose of medication.

Acknowledgement

The authors are grateful to the authorities of Dadasaheb Balpande College of pharmacy, Besa, Nagpur for the facilities.

Conflict Of Interest

The authors declare no conflict of interest.

REFERENCES

1. Krayukhina. E, Tsumoto. K and Uchiyama. S. Effects of syringe material and silicone oil lubrication on the stability of pharmaceutical proteins. Journal of Pharmaceutical Sciences. 2014;1-9.
2. www.pda.org/prefilled2008.
3. www.ondrugdelivery.com.
4. Sacha.G, Rogers. A and Miller. L. Prefilled syringes: A review of the history, manufacturing and challenges. Pharm Dev Technol. 2015; 20(1): 1-11.
5. Kale. N, Kazi. A and Kale. S. Drug prefilled non-reusable syringes as drug-device, World J Pharm Sci. 2015; 3(10): 2095-2110.
6. Schmid. D, Biegun. A and Rauscher. M. Development and introduction of a ready to use pediatric pentavalent vaccine to meet and sustain the need of developing countries-Quinvaxem, vaccine. 2012: 6241-6248.
7. Melinda. E, Justin.J and Traina. A. Stability of U-500 regular insulin in prefilled syringes, J Am Pharm Assoc. 2013; 53: 304-306.
8. Nayef. L. Khan. M. and Brook. M. The stability of insulin solutions in syringes is improved by ensuring lower molecular weight silicone lubricants are absent. Heliyon. 2017:1-17.
9. Phillips. J, Goelz. S. and Jethwa. V. A multicentre, open-label, phase II study of the immunogenicity and safety of a new prefilled syringes (liquid) formulation of avonex in patients with multiple sclerosis. Clinical therapeutics. 2004;26(4):511-521.s
10. James c Boylan; Steven L Nail. Parenteral Products. In: Banker GS, Rhodes CT, eds. Modern Pharmaceutics. New York: Marcel Dekker, 2002: 360-410
11. Makwana S, Prefilled syringes: An innovation in parenteral packaging. Int J Pharm Investig. 2011; 1(4): 200–206.
12. Medical Devise & Diagnostic Industry (MDDI). Global Injectable Drug Delivery

Technology:http://www.mddionline.com/article/global-injectable-drug-market (Accessed on June, 20, 2015).
13. The Free Dictionary by Farlex. Syringes:http://www.thefreedictionary.com/syringe (Accessed on June, 22, 2015).
14. A medical equipment database. Syringes: http://www.thefreedictionary.com/syringe (Accessed on June 23,2015)
15. Odell R, Paterson P, Ren J, Zhao X, Terminal sterilization of prefilled containers, PCT Patent No: WO2005058377 A2 , Jun 30, 2005.
16. Persistence, Injectable Drug Delivery Market. Global Industry Analysis and Forecast to 2015 to 2021: http://www.persistencemarketresearch.com/market-research/injectable-drug-delivery-market.asp (Accessed on June 25, 2015).
17. Medical Devise & Diagnostic Industry (MDDI). Global Injectable Drug Delivery Technology:http://www.mddionline.com/article/global-injectable-drug-market (Accessed on June 25, 2015).
18. Medical Devise & Diagnostic Industry (MDDI).Combination Medical Products: Capitalizing on Convergence: http://www.mddionline.com/article/combination-medical-products-capitalizing-convergence (Accessed on June, 25, 2015).
19. Safe Medical Devices Act of 1990.
20. Michael Gross, The Combination Product Problem http://chimeraconsultingna.com/wp-content/uploads/2014/12/2009-June.pdf.
21. Medical Devise & Diagnostic Industry (MDDI).Combination Medical Products: Capitalizing on Convergence. http://www.mddionline.com/article/combination-medical-products-capitalizing-convergence (Accessed on June 25, 2015).
22. Vorgelegt V. Development of an adequate strategy for a global change in the primary container closure system of a parenteral herbal drug. PhD Thesis. The University of Bonn, Bonn, Germany December 2013.
23. Wikipedia, the free encyclopedia. Title 21 of the Code of Federal Regulations. https://en.wikipedia.org/wiki/Title_21_of_the_Code_of_Federal_Regulations (Accessed on June 25, 2015).
24. USFDA.Combinationproducts:http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm118332.htm (Accessed on June 26, 2015).
25. Andrea Wagner. Advances in Prefilled Syringe Technology. IPTonline – Innovations in the Pharmaceutical Technology Journal 2007 http://www.iptonline.com/articles/public/ipt_24_p73nonprint.pdf (Accessed on June 27, 2015).
26. Michael Gross. Combination Product Quality Systems: http://chimeraconsultingna.com/wp-content/uploads/2014/12/2009- December.pdf). (Accessed on June 28, 2015).
27. Meddev medical devices guidance document. Borderline products, drug delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative: 2009.
28. Suzette R. Regulatory Submission Strategies for Pre-filled Syringes 2015.
29. Ambrosio T. Packaging of Pharmaceutical dosage forms. In: Banker GS, Rhodes CT, eds. Modern Pharmaceutics. New York: Marcel Dekker, 2002: 510-540.
30. Borchart S.J et.al J. Parenteral Sci Technology 43,67,1989.
31. ISO 11040-4:2015 Prefilled syringes -- Part 4: Glass barrels for injectables and sterilized sub assembled syringes ready for filling.
32. Stanaszek W and Ing-Hsiung P, Comparison of drug stability in glass versus plastic containers: analysis of prefilled syringe admixtures Proc. Okla. Acad. Sci. 58: 102-105 (1978).
33. Blue Book Memos - ODE Guidance Memoranda; 2015.
34. ISO 10993-5:2009 Biological evaluation of medical devices -- Part 5: Tests for in vitro cytotoxicity.
35. Medical Devise & Diagnostic Industry (MDDI).Making Sense of Plastics and Their Properties.http://www.mddionline.com/article/making-sense-plastics-and-their-properties.
36. Andrea Wagner. Advances in Prefilled Syringe Technology. IPTonline – Innovations in the Pharmaceutical Technology Journal 2007.
37. Amgad Khalil; Cyclic Olefin Copolymer (COC) in the pharmaceutical industry; Rochester Insti of Technology, 2004.
38. On Drug Delivery. Prefilled Syringes: Shantanu Kale et al., World J Pharm Sci 2015; 3(10): 2095-2110.
39. Gert Blankenstein. Microstructured arrangement for the bubble-free filling with a liquid of at least one system for draining off liquids, apparatus having such an arrangement and filling method US 20050169778 A1 04 August 2005.
40. Jenni Hollinsworth. Challenges and key considerations for the sterilisation of prefilled syringes Ondrugdelivery magazine, Oct 2010.
41. International Organization for Standardization ISO 14937:2009. "Sterilization of health care products – General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices".
42. International Organization for Standardization ISO 17665-1:2006. "Sterilization of health care products – Moist heat – Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices".
43. International Organization for Standardization ISO 11137-1:2006. "Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices".
44. FDA, Draft Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. April 2013.

45. Hosa A. Dowlat. Prefilled Syringes and Related Biologic Drug/Devices: Market Trends and Regulatory Acceptability. Pharmaceutical outsocuring. Nov 2013.
46. Drug Development & delivery, Prefilled Syringes & Parenteral Contract Manufacturing: Anticipating the Needs of the Future - http://www.drug-dev.com/Main/Back-Issues/SPECIAL-FEATURE-Prefilled-Syringes-Parenteral-Cont925.aspx#sthash.Pphw9T9C.dpuf (Accessed on August 5,2015)
47. Drug Development. Special Issue: http://www.drug-dev.com/Main/Back-Issues/SPECIAL-FEATURE-Prefilled-SyringesParenteral-Cont-925.aspx#sthash.Pphw9T9C.dpuf (Accessed on August 5,2015)
48. Romacker M., Dr Schoenknecht T., Dr Forster R., The rise of prefilled syringes from niche product to primary container of choice: a short history on drug delivery.
49. U.S.patent number EP0847770.
50. Shandilya H., Sewa Medicals Limited, Understanding the complexities involved in manufacturing and meeting customer's expectations in delivering prefillable syringes.
51. Kubo, Tomohiko (1-30-1108, Sibukawa 1-chome, Kusatsu-shi, Shiga-ken, JP), patent no. EP0847770
52. G Heffernan, A Welsher - US Patent App. 10/921,678, 2004.
53. Process for the manufacture of prefilled syringes, WO/1997/008054, WIPO
54. G N Smith, J C Tanner, C John - US Patent 5,597,530, 1997
55. Polin J B., The ins and outs of pre-filled syringes, Pharmaceutical and medical packaging news, Vol. 11, No. 5, May 2003.
56. Bradley F. Otto, I. Made Suarnawa, At-birth immunisation against hepatitis B using a novel pre-filled immunisation device stored outside the cold chain.
57. Thorpe G.A, Prefillable syringes – Trends and growth strategies.
58. Turco S, King RE. Sterile dosage forms their preparation and clinical application. 3rd ed. Philadelphia: Lea & Febiger; 1987.
59. Romacker M, Schoenknecht T, Forster R. The rise of prefilled syringes from niche product to primary container of choice: a short history. ON Drug Delivery. Prefilled syringes: the container of choice for today's injectables. 2008:4–5.
60. Jones LS, Kaufmann A, Middaugh CR. Silicone oil induced aggregation of proteins. J Pharm Sci 2005; 94: 918–927.
61. Liu W, Swift R, Tirraca G, et al. Root cause analysis of tungsten induced protein aggregation in pre-filled syringes. PDA J Pharm Sci Technol 2010;64:11–19.
62. Wright JM. Developing containers and devices to meet emerging and evolving parenteral needs. ONDrugDelivery. Prefilled syringes: with the patient and safety at its core, the market re-aligns. 2011:22–24.
63. Kettelhoit S. Industrielle Herstellung von Glasspritzen. Pharm Ind 2008; 70: 1261–1269.
64. Novak W. Fertigspritzen aus Glas - Herstellen, Befullen, and Verschliessen. Pharm Ind 2010; 72:1059–1068.
65. Barker KN, Flynn EA, Pepper GA, et al. Medication errors observed inb36 health care facilities. Arch Intern Med. 2002; 162: 1897-1903.
66. Doherty C, McDonnell C. Tenfold medication errors: 5 years' experience at a university-affiliated pediatric hospital. Pediatrics. 2012; 129: 916-924.
67. Folli HL, Poole RL, Benitz WE, et al. Medication error prevention by clinical pharmacists in two children's hospitals. Pediatrics. 1987; 79: 718-722.
68. Ghaleb MA, Barber N, Franklin BD, et al. The incidence and nature of prescribing and medication administration errors in paediatric in patients. Arch D is Child. 2010; 95:113-118.
69. Hoyle JD, Davis AT, Putman KK, et al. Medication dosing errors in pediatric patients treated by emergency medical services. Prehosp Emerg Care. 2012; 16:59-66.
70. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA. 2001; 285: 2114-2120.
71. Maidment ID, Lelliott P, Paton C. Medication errors in mental healthcare: a systematic review. Qual Saf Health Care. 2006; 15: 409-413.
72. Harrison B, Rios M. Big Shot: Developments in Prefilled Syringes; 2007. Available at: http://www.pharmtech.com/big-shot-developments-prefilled-syringes. Accessed March 30, 2015.
73. Makwana S, Basu B, Makasana Y, Dharamsi A. Pre-filled syringes: an innovation in parenteral packaging. Int J Pharm Investig. 2011; 1(4):200.
74. Prefilled Syringes Market (Glass and Plastic): Global Industry Analysis, Size, Volume, Share, Growth, Trends and Forecast, 2013e2019. Technical report. Albany, NY: Transparency Market Research; 2013.
75. Pre-filled Syringes Market Forecast 2015-2025. Technical report. London, UK: Visiongain; 2015.
76. Basu P, Blake-Haskins AW, O'Berry KB, Randolph TW, Carpenter JF. Albinterferona2b adsorption to silicone oil-water interfaces: effects on protein conformation, aggregation, and subvisible particle formation. J Pharm Sci. 2014; 103(2):427-436.
77. Gerhardt A, Bonam K, Bee JS, Carpenter JF, Randolph TW. Ionic strength affects tertiary structure and aggregation propensity of a monoclonal antibody adsorbed to silicone oilewater interfaces. J Pharm Sci. 2013; 102(2): 429-440.
78. Gerhardt A, Mcgraw NR, Schwartz DK, Bee JS, Carpenter JF, Randolph TW.
79. Protein aggregation and particle formation in prefilled glass syringes. J Pharm Sci. 2014; 103(6):1601-1612.
80. Basu P, Krishnan S, Thirumangalathu R, Randolph TW, Carpenter JF. IgG1 aggregation and particle formation induced by silicone-water interfaces on siliconized borosilicate glass beads: a model for

siliconized primary containers. J Pharm Sci. 2013; 102(3):852-865.
81. Krayukhina E, Tsumoto K, Uchiyama S, Fukui K. Effects of syringe material and silicone oil lubrication on the stability of pharmaceutical proteins. J Pharm Sci. 2014; 104: 527-535.
82. Walder R, Schwartz DK. Dynamics of protein aggregation at the oil-water interface characterized by single molecule TIRF microscopy. Soft Matter. 2011;7(17):7616-7622.
83. Roach P, F arrar D, Perry CC. Interpretation of protein adsorption: surface induced conformational changes. J Am Chem Soc. 2005; 127(22):8168-8173.
84. Ostuni E, Grzybowski BA, Mrksich M, Roberts CS, Whitesides GM. Adsorption of proteins to hydrophobic sites on mixed self-assembled monolayers. Langmuir. 2003; 19(5):1861-1872.
85. Mehta SB, Lewis R, Bee JS, Randolph TW, Carpenter JF. Gelation of a monoclonal antibody at the silicone oil-water interface and subsequent rupture of the interfacial gel results in aggregation and particle formation. J Pharm Sci. 2015; 104(4):1282- 1290.