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Pre-Filled Syringes: A New Concept

The administration of therapeutic drugs via injection is an indispensable delivery method for numerous drugs critical to patient health and well-being. Now this segment is evolving in response to changing patient populations, new classes of powerful therapeutic drugs and healthcare administration initiatives. Population demographics and efforts by managed care providers to control healthcare costs are driving the growth in drug self-administration, particularly for chronic conditions, introducing a new class of naïve users to parenteral drug delivery. User-friendly syringe and injection device designs and the availability of an increasing number of drugs in pre-filled insertable and disposable cartridges are propelling the growth of prefilled syringes for self-administration.

Features

Many of the innovative products like monoclonal antibodies, proteins and peptides need to be delivered via parenteral route, require accurate dosing and safe handling. Pre-filled syringes are now the primary container of choice for most parenteral drug delivery systems. Prefilled syringes have traditionally been made of a glass body formed from USP type 1 borosilicate glass, elastomeric plunger and plastic rod. The drug is packed in the glass body and is covered on both sides by elastomers. A plunger rod is fitted behind for the drug to be administered.

The definite advantages of using the system are:

- Prefills of syringe require less overfill. e.g. for a 0.5 ml vial, the USP recommends 20-25% overfill. In contrast, for a 0.5 ml BD Hypak dose, required overfill is less than 2%. Low risk of contamination e.g. Use of pre-filled syringes eliminates the possibility of cross infection arising from needle reuse.
- Accurate measurement of dosage
- Easier product identification
- Speed in emergencies
- Shorter preparation time
- Pharmaceutical product differentiation
- Improved product and company image
- Convenient to medical staff
- Boost to sales and marketing efforts

PRE-FILLED SYRINGE COMPONENTS

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



Figure 1 : Different pre-filled syringes

- 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.
2. 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.
 3. The plunger cover and tip seal are moulded from an elastomeric material, such as rubber, by any suitable molding

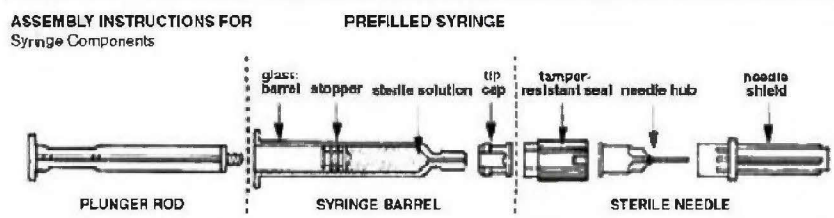


Figure 2: Components of pre-filled syringe

PREPARATION OF PRE-FILLED SYRINGES

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

(a) Preparation of components

1. Providing a barrel and plunger molded under conditions which are substantially free of pyrogens and viable and non-viable particulates,

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.

4. Maintaining said barrel and, optionally, tip seal and/or piston, under clean conditions for use in step (b).

(b) Filling and assembling the syringe.

The pre-filling and terminally sterilizing a syringe, consists of the following sequential steps:

1. 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;
2. Removing particulate matter from the interior of syringe barrel;
3. Sterilizing the cap and stopper, stopper being at the first and second opposite longitudinal ends;
4. Prior to filling empty syringe barrel, insert first end of stopper into the second open end of empty syringe barrel and move stopper toward first end of empty syringe barrel until first end of stopper reaches a position against first end of empty syringe barrel;
5. 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;
6. 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
7. 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.



Figure 3: Different pre-filled devices for lyophilized drug products

PRE-FILLED DEVICES IN THE MARKET

Dual-Chambered Syringe

To extend the advantages of a pre-filled syringe to manufacturers of lyophilized drugs, Vetter Pharma Fertigung offers the Vetter Lyo-Ject dual chambered syringe. This system is a glass-barreled syringe with a stopper in the middle to serve as a barrier between the two chambers. Vetter 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 then moves the center stopper into a bypass in the side of the glass. Elgard delivered by atrigel drug delivery technology is an example of the same.

Prefilled Diluent Syringe

While dual-chambered syringe or dual-syringe delivery systems are elegant, they are not compatible with many lyophilized drugs. Most of the freeze dried product must 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 reconstitution system consisting of a prefilled diluent syringe packaged with the drug vial, containing the lyophilized or dry powder drug.

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

Uniject is a plastic disposable injection device, pre-filled with 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,

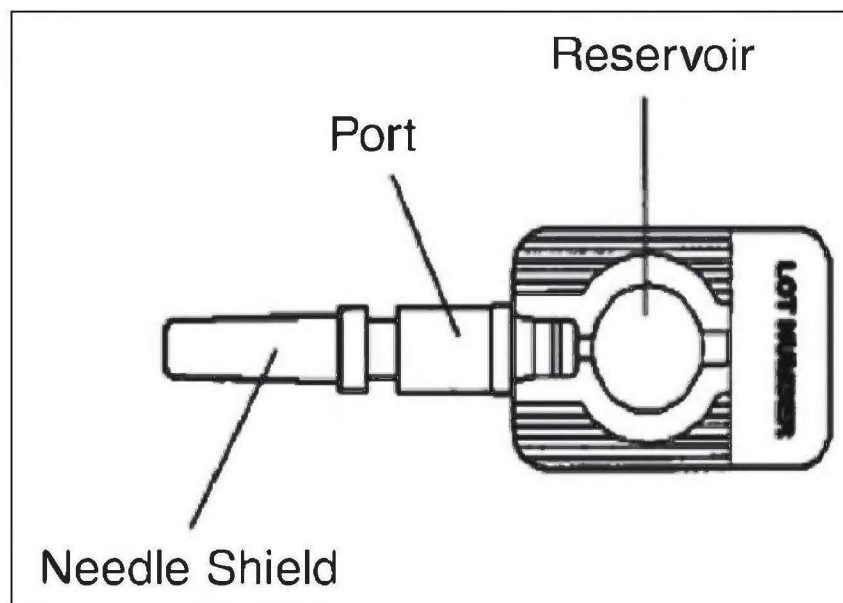


Figure 4 : Uniject pre-filled syringe

the needle inserted into the subject, and the dose is delivered by squeezing the blister until it collapses.

BD Hypak Physiolis™ 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, the BD Hypak Physiolis syringe needle is sharper and penetrates the skin more easily, which enhances patient comfort.

BD Readyfill™

The BD Readyfill™ syringe adds value

and innovation, differentiating it from those that need vials or ampoules.

Compared to alternative pre-filled devices, the unique combination of integrated features of the BD Readyfill™ syringe offers increased product differentiation, including:

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.

Rigid Needle Shield: A hard plastic shield promotes end-user safety and enables easy cap removal

Needle Isolation: Separating the liquid from the needle ensures that drugs sensitive to needle contact are not affected during

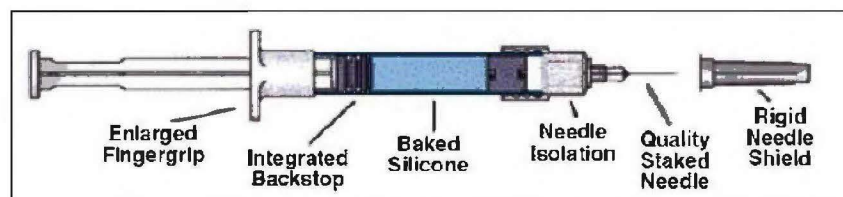


Figure 5: BD Readyfill™ pre-filled syringe

storage

Baked Silicone: Binding the silicone to the glass barrel through a proprietary technology reduces the level of free silicone. This is a 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 fingergrip means maximum ease of use for the end user and promotes overall injection safety.

BD Preventis™ Prefilled Syringe Automatic Needle Shielding System

The main features of the BD Preventis are:

- 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. The syringe comes prefilled with saline or heparinized saline in the posterior chamber. The clinician aspirates medication into the front chamber using conventional practices. 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



Figure 6(a)

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.

From figure 6 (a) 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 6 (b) 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

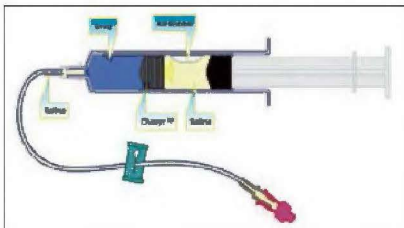


Figure 6(b)

the catheter. After opening the clamp, the syringe plunger is pushed thus infusing the saline pre-flush then the drug through the IV.

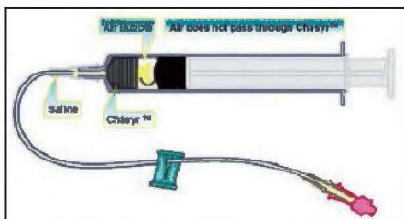


Figure 6(c)

From figure 6(c) it can be seen that the plunger is continually pushed until the valve in the first plunger is activated. Saline then flushes the hazardous medication from the Y-site and the IV catheter thus rendering the catheter free of medicant and filling it with the flush solution.

ACCESSORIES USED WITH PRE-FILLED SYRINGES

LEVA® Autoject

LEVA® is disposable and designed for subcutaneous injections of fixed doses. A skin sensor and automatic needle retraction



Figure 7 : LEVA® Autoject

assure a maximum safety. With an intuitive design, small size and few user steps; LEVA® provides a fast, easy and safe pathway to injection.

Flex Pen® Device

Product benefits

- Enhanced safety features
- Enhanced simplicity

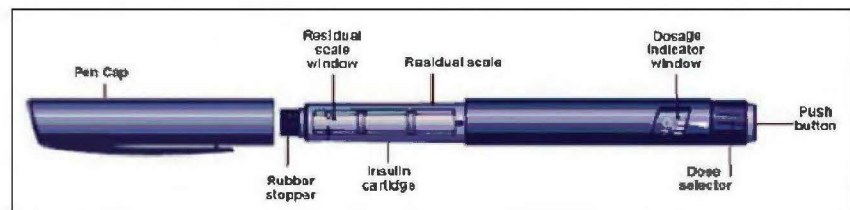


Figure 8 : Flexpen® device

- Discreetness
- Simple, single-step dose setting and delivery

FILLING PROCESS

There are three processes for filling and stoppering prefilled syringes.

They include:

1. Traditional filling and stoppering
2. Online vacuum filling and stoppering and
3. Online vacuum 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 expelled. Next, the syringe stopper is forced into 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 can cause the coating to wrinkle or tear.

In online vacuum filling and vacuum stoppering, syringes are first evacuated and filled under vacuum. Next, they are advanced to the stoppering position where a vacuum is again applied to the filled syringes, and a stopper is pushed into position by differential pressure. In this process, there is no compression of

the stoppers and insertion rods are not required. This process leads to bubble free filling of syringes.

Some of the notable advantages are:

- Reduction/elimination of stopper movement in reduced atmospheric

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