BioPharma Solutions

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Considerations and Options for Prefilled Syringes

Baxter

Introduction

A prefilled syringe is a convenient primary packaging option for delivery of a parenteral medication. The packaging option is easy to carry and ready to administer without the need to dilute before injecting. Medications filled into vials require preparing the vial by sanitizing with an alcohol swab and using good aseptic technique to remove the medication from the vial. The reduction in steps required for syringe filling can reduce the risk of contamination versus a vial.

A prefilled syringe requires less overfill volume than a vial. An overfill of the drug solution is required to ensure the entire dose can be removed from the primary packaging. A vial requires more overfill than a prefilled syringe because solution is retained in the vial by the stopper and retained by the syringe and needle used to remove the solution from the vial. The overfill volume can result in losses of the drug solution when manufacturing tens of thousands of vials. Substantially less overfill is needed for prefilled syringes. Less overfill leads to more sellable units and less waste of the expensive drug product.

Convenience, product differentiation, and less waste are great reasons for developing a product in a prefilled syringe. This document describes the options available for prefilled syringes and provides some considerations for developing and manufacturing the product.

Syringe Components and Options

All syringes have similar components that include the barrel, flange, plunger, and plunger rod. The possible differences include a luer lock or slip-tip cone for attachment of the needle, development of a prefilled syringe with a pre-staked needle, and manufacturing the syringes out of glass or polymeric materials (Figures 1 through 3).

Syringes are available from multiple suppliers (Table l) that offer a range of sizes manufactured of type 1 borosilicate glass or different polymers such as polypropylene (PP), polycarbonate (PC), cyclic olefin polymer (COP) and cyclic olefin co-polymer (COC). The syringes can be combined with needles that are offered in a wide range of gauges and lengths. The length of the needle is chosen based on the site of delivery. Intradermal and subcutaneous injections use the shortest needles with the narrowest gauge size. Intramuscular and direction intravenous injections use longer needles to reach the site of injections.

Figure 1. Comparison of a Syringe with Luer Lock Tip and a Syringe with Slip-Tip Cone.

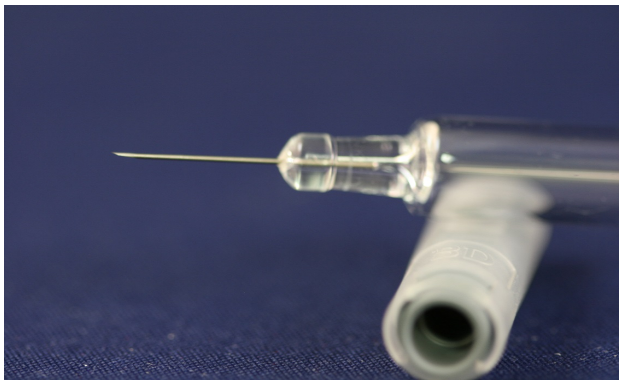

Figure 2. Appearance of a Syringe with a Pre-Staked Needle.

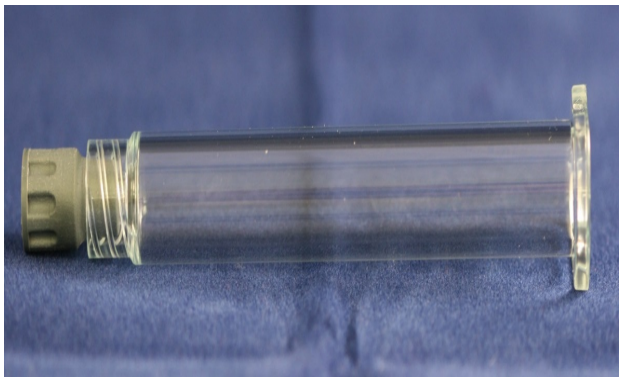

Figure 3. Appearance of a Polymeric Syringe.

Table I. Manufacturers and Options for Glass Syringes.

Manufacturer	Pre-Staked Needle (mL)	Slip Tip Cone (mL)	Luer Lock (mL)
Schott	0.5-1	0.5-3	0.5-3
Becton Dickinson	0.5-20	0.5-20	0.5-20
Gerresheimer	0.5-10	0.5-10	0.5-10
Nipro (MGlas AG)	0.5-1	0.5-10	0.5-10
Nuovo Ompi	0.5-20	0.5-20	0.5-20

Source: Syringe specifications in Table I are taken from manufacturer websites and/or specifications.

Glass used for prefilled syringes mainly contain silicon dioxide, but also include metal ions to alter the physical-chemical characteristics (Table II). Silicon dioxide is typically non-reactive, but the metal ions can interact with the solution filled in the syringe and cause a shift in pH. Some molecules may absorb to the charged surface of the glass resulting in decreased potency of the drug solution. The syringes are coated in a layer of silicone to allow movement of the plunger through the barrel. Free silicone can interact with large molecules and lead to aggregation. The free silicone may appear as particles when the solution in the syringe is examined for particle size and content using a light blockage instrument for release testing.

Table II. Components of Type I Borosilicate Glass.

Component	*Percentage of Formulation*
SiO_2	70-80
B_2O_3	12-13
Al_2O_3	2
Na_2O K_2O	<7

The possible interactions with glass and the potential for breakage have made polymeric syringes an attractive option. Some polymeric syringes can be manufactured without silicone, but still provide smooth surfaces for easy movement of the plunger. The polymeric syringes are available in a wider range of sizes and are more customizable than glass syringes (Table III).

Table III. Polymeric Syringe Options and Manufacturers.

Manufacturer	*Material*	*Sizes (mL)*	*Options*
Becton Dickinson	Crystal Clear Polymer (CCP) COP	5-50	Pre-staked, Slip Tip, Luer Lock
Schott	TopPac® COC	1-50	Pre-staked, Slip Tip, Luer Lock
Gerresheimer (Tasei Kako)	ClearJect® COP	0.5-5	Slip Tip, Luer Lock Tamper evident lock system
West (Daikyo Seiko)	Crystal Zenith® COP	1-100	Pre-staked, Slip Tip, Luer Lock
Merit	Medallion® COP and PC	1-20	Luer Lock
Aguettant	PP	4-50	Luer Lock

Source: Syringe specifications in Table III are taken from manufacturer websites and/or specifications.

A potential benefit of using a polymeric syringe is better dimensional tolerances because they are manufactured using injection molding. Better tolerances may lead to fewer problems with stopper placement.

Filling Operations and Sealing Operations for Prefilled Syringes

Some important information is needed in preparation for the filling operations. The retention volume of the syringe and needle are needed along with the expected variability in filling weight for the equipment. This information is needed to ensure sufficient volume is available in the syringe to provide the expected injection volume. The retention volume is calculated using approximately 15 filled syringes. The contents of each syringe are ejected into a container on a balance to obtain the deliverable volume. The empty syringes are weighed, disassembled, and rinsed with purified water. The rinsed syringes are dried with their respective plungers and caps and weighed again. The weight of the dried syringe components is subtracted from the weight of the empty, wet syringe components to determine the retention weight. The weights are averaged and the volume is calculated using the density of the drug solution.

Most manufacturers receive syringes pre-washed, pre-siliconized (if needed), and pre-sterilized. The syringes are aligned in a polymeric nest that sits in a polymeric tub (Figures 4 and 5). The tubs are sealed and double bagged. Glass syringes are sterilized using ethylene oxide and polymeric syringes are sterilized using gamma irradiation.

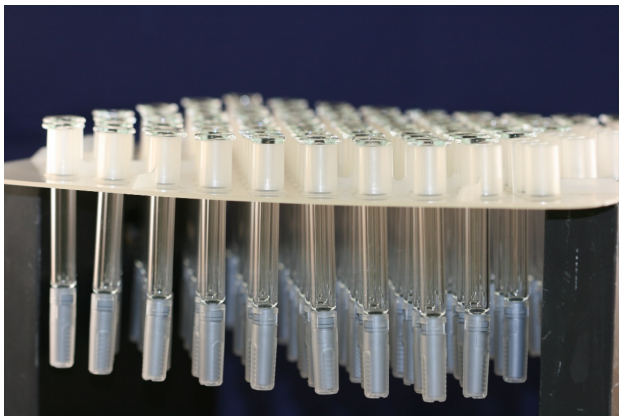

Figure 4. Nest Holding Pre-Staked, Glass Syringes.

Figure 5. Nest of Syringes in a Tub with Opened Seal.

The bags surrounding the tubs of syringes are removed progressively as the tubs are transferred to the more controlled areas of the manufacturing suites. The first bag is often removed in the grade C (ISO 7) area and placed in a transition zone where the second bag is removed before transferring the sealed tub to the grade B (ISO 5) area. An operator will place the sealed tub in the grade A (ISO 5) area and the Tyvek seal is removed manually or automatically. The tub with exposed syringes is conveyed into the syringe filling equipment where the nest is lifted from the tub by the automated syringe filling machine.

The solution is delivered to the filling equipment using a filling pump such as a diaphragm pump, peristaltic pump, rotary piston pump, or a time/pressure filler. The solution is used to fill the syringes as the nest of syringes is conveyed through the equipment. A set of filling needles fills a row of syringes directly followed by stopper placement (Figure 6). Stoppers are placed in the syringes using one of the two methods. One method is vacuum plunger placement and the other uses a stainless-steel tube to hold and slightly compress the stopper as an ejection rod pushes the stopper into place in the barrel of the syringe.

Figure 6. View of Filling Syringes Followed by Stopper Placement Using on Insertion Tube.

It is important to determine which filling method is needed for the specific syringe type planned for the product and to determine which method is used by the manufacturing site. Vacuum placement and placement using an insertion tube are compatible with most types of syringes. The polymeric syringe from West (Daikyo), known as the Crystal Zenith® is only compatible with the vacuum method.

A prefilled syringe is a nice option for a medication that is delivered in a single injection. The choice of syringe type and size require research and discussions with the syringe and plunger manufacturers to

identify the best option for the product. It is also important to become familiar with the methods of filling and stopper placement at the manufacturing site. This type of planning and gathering of information will help the scientist develop studies to support successful stability, scale-up, and technical transfer.

More detailed information on prefilled syringes, visible inspection of prefilled syringes, and packaging materials for parenteral products are available in the following publications:

Gregory A. Sacha, Wendy Saffell-Clemmer, Karen Abram, and Michael J. Akers, *"Practical Fundamentals of Glass, Rubber, and Plastic Sterile Packaging Systems"*, Pharmaceutical Development and Technology, 2010: 15(1): 6-34

Gregory A. Sacha, J. Aaron Rogers, and Reagan L. Miller, *"Prefilled Syringes: A Review of the History, Manufacturing and Challenges"*, Pharmaceutical Development and Technology, 2015; 20(1): 1-11

Gregory A. Sacha, *"Prefilled Syringes – Prefilled Syringe Automated Inspection & End-Product Testing"*, Drug Development and Delivery, Issue April 2018

Baxter Healthcare Corporation
One Baxter Parkway
Deerfield, Illinois, USA 60015
United States: 1-800-4-BAXTER International: 1-847-948-4770
Email: biopharmasolutions@baxter.com www.baxterbiopharmasolutions.com

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