Aseptic Vial and Syringe Filling

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Like the preparation of a fine dinner, aseptic filling of vials and syringes is best performed with the highest quality components, equipment and personnel available. Establishing and maintaining an aseptic environment is equipment, labor, and management intensive, but not technically challenging. The expense is large and mostly fixed. It is directed to personnel training and the maintenance of equipment and quality systems. The variable expense after establishing aseptic procedures is minimal, and thus favors a facility operated close to capacity. Constant vigilance is required to assure that equipment and environmental parameters stay within established guidelines, and rapid intervention may be necessary to avert catastrophic events. The game is to recognize acceptable levels of risk and to guard against the consequences of an adverse event. It is rare that fills of different product would have the same filling batch record. There are, however, commonalities which present opportunities for product contamination by viable or non-viable materials. A brief introduction to the operations, and thus the pitfalls, of aseptic filling is presented.

Preparation of Components

Components need to arrive with adequate acceptance criteria from qualified vendors. Engineering specifications and cleanliness are very important. Outliers in dimensional tolerance can cause washing equipment to malfunction. At best such instances may lead to broken glass, thus introducing a greater than zero risk of glass particles being carried through the process. The aseptic filling company has validated cleaning methods for components, but those methods are not infinitely robust. Dirt, meaning organic and inorganic contaminants as well as associated unidentified particulates, can be difficult to quantify on incoming components. Laboratory testing for these unknown contaminants is nearly impossible. Yet testing for a validated parameter is unlikely to find an extraordinary event for which the washing procedure is not validated.

Stoppers can be more problematic than vials to clean and sterilize. Vendor certification for low particulate shipment is essential because elastomer surface adhesion makes particles difficult to remove. The use of detergents and emulsifiers in stopper washers has the inherent hazard of inadvertently adsorbing the detergent or emulsifier into the rubber. Sterilization of the stoppers (as well as drying times) is time limited without risk of damage to the component. There are also unique problems with stoppers of various shapes which can be distributed in such a way that there is rubber to rubber contact which prevents steam penetration. Experienced manufacturers recognize and control for such risks.

The Vial Fill

Having managed to marshal sterile components and sterile product into an aseptic environment, the feat of maintaining sterility over six to ten hours while real people operate imperfect equipment to achieve filled vials is just short of miraculous. Yet it is achieved in numerous clean rooms and aseptic filling chambers every day. Indeed, most of the situations which may threaten a fill operation are mechanical and only indirectly related to sterility. Of course, if aseptic conditions were not imposed, then these supposed threatening situations would be true non-sterile events. Clean baked glass has a high amount of friction. In many fill operations, vials are fed onto a rotating equipment in-feed table where they contact other vials, leading to scratched and overturned vials. Overturned vials are a sterility hazard and must be removed. Meanwhile, there are hundreds, if not thousands of open top vials on the table, awaiting the arrival of any wayward microbe. Assuming that the fill is being performed in laminar flow, there is also a downward directed steady stream of air to assist in getting a microbe into a vial.

Perhaps the central activity in filling is the placement of liquid into the bottle. As an aseptic event, filling is low risk. The liquid comes out of the fill nozzle inside the vial and in most instances dispenses completely inside the vial as the needle is simultaneously lifted. Unless the liquid is contaminated, or a nozzle becomes contaminated, there is little opportunity for a sterility breach at the site of dispensing.

Stoppering

Most vial fill operations perform stoppering with equipment that is integral to the filler. The conveyor distance from dispensing to stoppering is usually less than two linear feet. Again, aseptic breach is an unlikely event, due to the short

exposure time. However, stoppers are typically placed into a vibrating bowl that is used to align them for mechanical placement. While one can sterilize for microbials and be assured that they will not spontaneously generate, the same is not true of non-viable particles. Rapid, vigorous vibration, as must occur for the "vibratory bowl" to function, is an anathema to particulate control. Many types of stoppers also require an application of silicone for adequate machine transport. That layer of silicone eventually comes into contact with liquid products and sometimes causes problems. There are only three standard size stoppers, 13mm, 20mm, and 28mm in common use for sealing vialed parenterals. Furthermore, the 28mm stoppers are uncommon for small volume parenterals, which encompass 99% of aseptic filling. Large volume parenterals can usually be terminally sterilized. A misconception is that 13mm and 20mm stoppers will fit into any 13mm and 20mm vials. In fact, the vial dimensional neck geometry needs to be designed with a particular stopper in mind. Due to the lack of fit, stoppers will sometimes not completely seat. That becomes an aseptic concern because part of the sterile barrier is meant to be direct contact of the rubber stopper with the top flange of a vial. Relying on the cap to compress the stopper and form that barrier is unwise.

Capping

It was only a few years ago that the aseptic vial fill industry formed a consensus that capping needed to be performed in class 100 conditions. The reason was that if the stopper fits, and is correctly placed after dispensing, then the container is closed to bacterial entrance and capping can be done under any class of air. However, it is not correct to assume that every stopper is correctly seated and some units may be presented to the capper which have a stopper seated high enough to permit contamination. The capper could then compress the elastomer and trap a microbe between the stopper and glass flange. Trapped microbes are unlikely to replicate, but prudence dictates that capping be performed under class 100 conditions. Capping ensures that a properly seated stopper does not move. Within the industry vial closures are validated by a "container closure" test, which demonstrates efficacy for the microbial barrier. However, it is important to link the validation to the set-up of the capping machine as that operation is critical to the installation of an efficacious cap.

Pre-sterilized Syringes

Pre-sterilized syringes are filled through the large end (opposite of the needle end). On some equipment, the insertion of a stopper (called a plunger for syringes) occurs immediately after dispensing, analogous to vials. In order to place the plunger, since air is in the syringe above the product, it is necessary to push the plunger through a metal straw and let it extrude at the point of placement inside the syringe. That method of setting the stopper may limit the distance between the plunger and the liquid product, creating a gas gap (bubble) between the plunger and product. Some development is necessary with each product to determine how close the plunger can be placed without getting product into the plunger rings. An alternative method of placing plungers is to evacuate the inside of the syringe, either individually or as a group, then place the plunger and readmit the gas. In that method, there is a risk of low pressure product boiling which may limit proximity of the plunger to the product, creating a bubble. Syringes may also be vulnerable to minor changes in pressure, causing movement of the plunger. Such conditions might be encountered in an unpressured airline cargo hold.

Post Fill Activities

With the exception of products intended for use in an operating theater, post fill activities can be conducted with less concern for sterility. Non-sterile containers are caused by a break in the container integrity. These can be hidden to visual inspection, such as hairline cracks in the neck of a vial or the luer tip of a syringe. Careful handling throughout the packaging operation is essential to a satisfactory aseptic product.

Vibratory stopper bowl is used to orient vial stoppers so that they can be fed into automated placement equipment.

Pre-filled syringe, showing plunger and associated rings. The rings are clear of fluid, which would cause a rejected unit. There

is a typical bubble on the plunger as a consequence of placement.