The aseptic filling of injectable drugs has always been very challenging for the pharmaceutical industry. Contamination accidents, despite being rare, are still recorded among the 20 billion injections and infusions made every year in the world. In a recent market study, six per cent of hospital professionals in Europe and the US reported that they had already faced at least one incident of contaminated vials. In recent years, the authorities have taken a radical turn to strongly support the most advanced aseptic filling technologies, such as the use of isolators. The use of classical processes in an ISO5 class A cleanroom are, however, becoming more and more challenged due to the risks from the presence of the operator close to the open containers. The emphasis on the quality of aseptic filling has also been increased with a recent request from the authorities to withdraw preservative agents whenever possible from injectable products. This article reviews a new filling technology that has initially been developed to further increase vial quality for the patient, but also to simplify the filling process for the manufacturer when compared with the classical glass vial. In addition, new features have been introduced to secure the supply chain, such as on-line coding by RFID or laser-coding.

**The Closed Vial**

The closed vial is a container made of five elements:

**The Vial Body**

Cyclo-olefin copolymer (COC) is used for this part of the container. This polymer was selected because of its excellent barrier and transparency properties, making it one of the most popular plastics for containers in the pharmaceutical industry. The vial bodies are produced by injection moulding for the smaller vials, or by injection blow-moulding for vials exceeding 3ml in volume.

**The Stopper**

A thermoplastic elastomer with particular laser absorbance properties was selected to enable laser re-sealing. With laser-heating, melting of the elastomer occurs and the two sides of the puncture trace fuse to restore the closure integrity.

**The Top Ring**

This ring secures the closure integrity of the assembly of the vial body and stopper with non-return right-angle snap-fits.

**The Bottom Ring**

This ensures very good stability of the vial and a firm hold during piercing and needle withdrawal.

**The Cap**

The polyethylene cap protects the piercing area by keeping it under Class 100 until use by the health professional. This last feature, obtained by a circular rib pressing onto the stopper surface, avoids contamination of the stopper surface during vial storage.

The manufacture of the vials is also completely innovative as they are moulded and stoppered by robots.
in a cleanroom Grade A/ISO 5. The manufacturing process comprises the following steps:

- The vial bodies and stoppers are moulded at the same time in two moulds installed in a cleanroom Grade A/ISO 5.
- Immediately after mould opening, two robot arms pick up the vial body and stopper, and bring them in front of each other. The assembly is performed by simple pressure of the two elements.
- The vials, now being closed, are then transferred by one of the robot arms to an adjacent clean room Grade C/ISO 8 where the addition of top and bottom rings is performed by a fully automatic machine.
- The vials are packed in corrugated polyethylene boxes, and six boxes are doubled-wrapped in polyethylene foils.
- The vials are gamma-irradiated at a minimum of 25 kGray.

This process provides vials with extremely high levels of quality in terms of sterility and particle and endotoxin contamination. Consequently, any additional steps such as washing and depyrogenation are not necessary, and the vials are in a ready-to-fill state for supply to the pharmaceutical manufacturer.

THE FILLING LINE

Filling of the vial is performed on a dedicated filling line equipped with specific technologies. As shown in Figure 1, the complete filling process – from delivered vials up to filled and capped vials – comprises five steps.

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Loading
The operator loads the vial from polyethylene boxes using semi automatic opening equipment; the risk of contamination by the operator is thus kept to an absolute minimum.

Top Surface Sterilisation
Despite this, as the loading is a manual step, the risk of contamination as a result of human error cannot be excluded. For this reason, an e-beam (beta-irradiation at 25 kGray) is used to re-sterilise the most critical surface – that is, the top of the vial which will be in contact with the filling needle during piercing. Immediately after this, the vials enter directly through a barrier which maintains a Class 100 environment during all filling operations.

Filling
Filling is performed by a 13 G needle which pierces the stopper, dispenses the volume of liquid and exits by lifting (see Figure 2). The needle has a pencil point to eliminate any coring effect in the stopper, and to minimise the generation of particles during piercing. The injection holes on the needles are located along the side and oriented at a 30º angle to allow a smooth flow of liquid coming into contact with the vial walls and not with the bottom. The side wall of the needle is grooved in order to vent the over-pressure generated during filling, ensuring that there is no pressure increase inside the vial after the filling.

Laser Re-Sealing
To fully restore the closure integrity, the re-sealing of the pierced stopper is performed by a laser dispensing 6.3 watts during one second. This laser shot increases the temperature of the stopper surface to 165ºC to melt the material, which then fuses and restores the closure integrity on cooling down. The re-sealing depth is greater than 0.3 mm and is generally observed around 0.5 mm. The melted stopper material fully recovers its initial characteristics in terms of elasticity and resistance. By using a low energy laser, the energy does not reach the product and no temperature change is recorded in the liquid after a laser shot.

Capping
By using plastic caps with snap-fit technology, capping is easily performed without the need for crimping.

The first two steps – loading and e-beam irradiation – are performed under a laminar airflow delineated by soft walls. The three last steps are made in a Restricted Access Barrier System (RABS), with access only through gloves and rapid transfer ports. As the doors cannot be opened, and direct access is forbidden for operators, a high quality Grade A/ISO 5 environment is permanently ensured. For specific products – such as cytotoxins, radioactive products and other potent products – an isolator can be installed to protect the operator from contamination by the product.

KEY BENEFITS
Compared with the classical glass vial technology, the closed vial technology provides a number of key benefits; these can be classified into three major groups:

Better Sterility Assurance and Reduced Particle Presence
The most important benefit is an increase in quality for the patient in terms of both levels of sterility assurance and particle presence. The higher sterility assurance level is obtained by keeping the vial continually closed, so that there is no risk of contaminant penetration inside the vial resulting from exposure to the environment. By contrast, the traditional glass vial is frequently exposed for periods of more than 20 minutes between the sterilisation tunnel and the stoppering station under HEPA filters; this exposure is totally eliminated with the closed vial technology. With regard to the presence of particles, the full closed vial process generates very limited amounts of particles, less than half the amount generated during a classical glass vial filling process.

Another advantage for the patient is provided by the newly designed capping technology. The entire stopper surface is protected by the circular rib located on the inner face of the cap, thereby creating additional closure integrity.

Simplified Filling Operations
The filling operation is much simpler as several elements of glass filling equipment become obsolete with the closed vial technology:

- The washing stations for both the vial bodies and stoppers are unnecessary
- Consequently, there is no need of water for injection on the filling line, eliminating a major source of expense, validation work and risk of batch rejection
- The sterilisation tunnel – with its high consumption of energy and difficulties regarding validation – is also eliminated, as is the cooling zone
The stoppering station – a source of frequent stoppages – is also eliminated. Using simple snap-fit technology, the capping station is simplified compared with the crimping process used for aluminum caps.

There are only two new technologies added to the filling process which are not present on traditional glass vial filling lines: the e-beam sterilisation and the laser re-sealing stations. These new technologies have been designed to ensure full compliance with the most advanced cGMP requirements, such as process analytical technology (PAT). As shown in Figure 3, a filling line can be installed in a building equipped just with electricity. A source of water for injection is only needed to prepare the filling equipment in the washing room and for the autoclave.

Security of Supply Chain and Easier Handling

The vial is designed in such a way as to improve the security of the supply chain until the product reaches the patient. First, by using COC, the vial body is very resistant to shocks and cannot be easily broken. This confers a higher safety assurance, not only for the operators but also for the medical staff, especially when potent or radioactive products are used. In addition, for final users, the stopper has been designed to have a large and flexible piercing area, and to ensure the complete collection of liquid by avoiding recess areas, thereby allowing a significant reduction of expensive overfill.

The design of the vial allows on-line coding of the vials prior to any operator having access to them. Two ways of coding can be selected:

- RFID coding – an RFID chip can be installed under the cap. When the cap is placed in position, the RFID is fully secured by the snap-fit assembly of the cap with the top ring. A coding machine can be installed inside the line; each vial will then be definitively marked before exiting the line.
- Laser coding – thanks to the large vertical surface of the top ring, a laser coding can be made either with alphanumeric characters or with a 2D matrix. Again, this coding can be made inside the filling line.

The key difference is that the coding can be done online, whereas coding on traditional glass vials (either by RFID or by laser) is usually performed on the labels. Two issues arise as a result of this delayed coding: first, a mix-up could occur in the stock before labelling; and second, a label with coded information could be easily transferred to another vial.

CONCLUSION

Initially designed to significantly improve sterility assurance, closed vial technology brings much more to pharma vial-filling by offering a higher level of quality for the patient, a dramatic simplification of the filling process and increased security of the supply chain. The new technology will help biopharmaceutical manufacturers improve their capability to supply high-quality injectable drugs, within a stable production environment and in full accordance with the most recent regulatory requirements.

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