



Tightly Sealed

Global supplier of industrial components, Datwyler Sealing Solutions, considers the role and importance of crimp caps – in particular, flip caps – when it comes to vial-based parenteral packaging systems

Vial-based parenteral packaging systems consist of a vial or bottle – usually made of glass – that is closed with a rubber stopper after filling with the medicinal product, before being crimped with an aluminium cap. The preferred execution of such a cap comes in the form of a flip cap, consisting of an aluminium shell combined with a plastic disc that must be flipped off with the thumb to access the stopper penetration area. Flip caps therefore consist of two parts – one of aluminium,

one of plastic – that are shaped through separate manufacturing processes before being mechanically assembled to make one product.

Product Differentiation

The shaping of the aluminium shell takes place in a high-speed deep drawing process involving an aluminium strip that is lacquered on one or both sides with a coloured epoxy lacquer. This lacquer

will protect and preserve the aluminium when it is exposed to steam sterilisation and swabbing with disinfectant. Other surface coatings may be used for specific purposes – in particular, to reduce the shedding of aluminium particles that is associated with aluminium caps handled on pharmaceutical filling lines.

At the same time, the plastic flip button is made of polypropylene in a plastic injection moulding process. This material is used as it can withstand the temperatures that are typically involved with moist heat sterilisation processes. With the use of colour masterbatches, the plastic parts can be toned in different colours to create a variety of customised designs that can be paired with distinct products.

Other factors in the differentiation of flip caps include the design and size of the plastic button, and the way in which the aluminium and plastic components are joined together. With respect to the flip button design, the top surface of the cap may be flat or domed. Since the contact surface of domed plastic parts is more limited in comparison with completely flat tops, these caps are less scratch-sensitive, which may result in a cosmetic advantage for the complete vial presentation.

Manufacturing and Assembly

Different possibilities exist for the assembly of aluminium shells and flip cap buttons. The plastic part can be shaped so that it constitutes a number of plastic 'fingers' that can be put through the central hole of the aluminium shell. This is followed by the combined application of heat and pressure which bends these fingers in a radial direction. One benefit of this is that later, on activation of the cap, the plastic and aluminium parts can be separated without any breakage. This can prevent particulate contamination of the rubber stopper at the time of use. A further plus lies in the fact that tampering is made more difficult as the fingers cannot be pushed back between the cap and stopper.

An alternative means of assembly sees a cylinder that is smaller in size being led through a correspondingly smaller central hole in the aluminium cap. This is then bent to form one mechanically interlocked part. On activation of the cap, when lifting the flip button, the bent plastic will exert a force on the top surface of the aluminium shell that will eventually lead to the removal of its central part, as this area has been made weaker. Unless the manufacturing of caps is well controlled, this breakage can give rise to aluminium particles ending up on the rubber stopper and the formation of sharp edges at the score position. This is undesirable when it comes to swabbing the top surface of the stopper with a disinfection agent prior to piercing the stopper with a needle.

Today, manufacturing of flip caps is to a large extent automated. Current standards require that deep drawing, injection moulding and assembly take place in well-designed separated areas where the necessary measures – such as sound facility design, gowning rules, and appropriate material and operator flow – are in place to keep bioburden at an acceptable low level. Manufacturing of high-end flip caps is then completed with 100% in-line camera control of assembled caps. This permits the rejection of defective parts – for example, caps that are not well assembled, caps or discs in the wrong colour, or deformation of the aluminium part.

Aseptic Processing

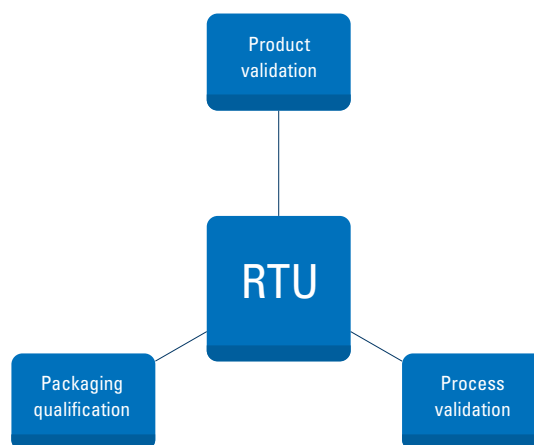
The majority of flip caps are used in packaging for sterile parenterals. Typically, as per US and European guidelines, these packages are terminally sterilised. However, in reality, most caps are subjected to aseptic filling systems in which Good Manufacturing Practices



offer the choice to perform vial crimping either as an aseptic process using sterilised caps, or as a clean process outside the aseptic core (1). In the latter case, filled and stoppered vials should be protected by the aseptic core's Grade A conditions up to the point where they leave the processing area, and thereafter protected by a Grade A air supply until the cap has been crimped.

If crimping is being undertaken as a clean process, from a risk management perspective the bioburden of the cap should be minimal – even if the

Figure 1: RTU caps: three main validation areas



cap is not exposed to the filled drug. If crimping takes place as an aseptic process, then caps must be rendered sterile before introduction to the aseptic processing area. Steam sterilisation can be used for this or, alternatively, ready-to-use (RTU) caps can be chosen. Sterilisation of these is performed by radiation.

Validation Work

Prior to production, manufacturers should engage in an appreciable amount of validation work that will eventually lead to a guaranteed sterility assurance level (SAL) of 10^{-6} for their caps. Using ISO 11137-2, a minimum irradiation dose must be determined to guarantee a SAL level of 10^{-6} (2). A maximum dose must be identified, at which it is shown that the radiation does not have a negative effect on the cap performance. Negative effects could range from discolouration of the plastic flip button to breakage of the button on activation of the cap.

The second level of validation comes from the evidence that is obtained via the industrial irradiation process – when carried out in the industrial packaging configuration of caps – which shows that irradiation doses are effectively between the established minimum and maximum doses. This irradiation process validation is often referred to as 'dose mapping'. Mapping throughout the entire packaging configuration of caps ensures that the dose is high enough to guarantee a SAL level of 10^{-6} and, at the same time, is low enough not to run into functionality issues.

The third level concerns the primary, secondary, tertiary or even quaternary packaging of flip caps. Tightness of seals of primary and secondary packaging caps must not be affected by irradiation at doses encountered in the validated irradiation process, and the robustness of the tertiary or quaternary packaging of caps must be tested in suitably chosen transport simulation tests.

Ready-To-Use

The sterility of RTU caps must be guaranteed all the way through to the pharmaceutical customer. Sterility can be ensured through both irradiation process validation and packaging validation, but verification of the integrity of the flip cap packaging right before entrance into the aseptic core should be made possible through adequate design of the packaging – for example, demonstration of preservation of an under-pressure between the primary and secondary packaging of the flip cap.

An under-pressure that is intentionally applied between the primary and secondary bag in which the caps are packed must still be present at the end of shelf-life. Its absence can be indicative of non-integral packaging, therefore introducing a non-sterility risk. From a risk management perspective, such packaging must not enter into the aseptic processing area.

Functionality Assessment

The most obvious functionality of a flip cap is that it should easily open at the time of use, with the plastic flip button separating from the aluminium shell with an acceptable force. Opening forces for injection vials are described in ISO 8362-4 and ISO 8362-5 for caps with and without overhanging plastic parts, and in ISO 8536-7 for infusion bottles (3,4).

Another function of the flip cap is to work together with the vial or bottle and rubber stopper to form an integral package. Vials and stoppers are named primary packaging components since they are in direct contact with the medicinal product. Crimp caps are termed secondary components as they are not intended to come into contact with the drug.

The principal action of the cap, however, is to exert a force on the stopper that keeps it tightly in position and permits the elastomeric closure to form an integral seal on the vial or bottleneck over the entire shelf-life of the medicinal product. As a result of

ongoing changes to US Pharmacopeia 1207 (Sterile product packaging: integrity evaluation) the scope of container/closure integrity is likely to extend to other areas, namely the restriction of product loss and the prevention of entry of detrimental gases or other substances that can affect the physicochemical quality of the packaged drug. Flip caps, therefore, in spite of being secondary packaging components, play a primary role in the preservation of packaged drug quality.

Depending on their design and construction, flip caps may also exhibit tamper-evident and/or anti-counterfeiting features. If tamper evidence is well designed, it will be obvious to the healthcare worker whether the packaging is being opened for the first time or not, while overt or covert anti-counterfeiting features will make it difficult for criminals to bring black market drugs into the supply chain, thereby protecting patients from false medicines.

References

1. EU Guidelines for Good Manufacturing Practice – Medicinal Products for Human and Veterinary Use – Annex 1: Manufacture of sterile medicinal products, November 2008
2. ISO 11137, Sterilisation of Healthcare Products – Radiation, Part 2: Establishing the sterilisation dose
3. ISO 8362, Injection Containers and Accessories
4. ISO 8536, Infusion Equipment for Medical Use



The Datwyler Sealing Solutions Division is a leading supplier of sealing solutions to global markets. Within the healthcare segment, its focus lies on delivering innovative solutions for vaccines, diabetic care and biotechnology. Celebrating our 100th anniversary, we are your partner for the future.