Secondary Seals for Injectable Drug Vials

Secondary seals are the first line of protection for injectable drugs and have an important role to play in helping maintain an integral sterile seal, thus securing the drug supply chain and ensuring patient safety.

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Identifying effective and innovative delivery systems and components for injectable drugs – whether a serum, lyophilised or dry powder drug – is a challenge for pharmaceutical packaging engineers. Selecting an appropriate secondary seal is just as critical to product success as selecting an appropriate vial and stopper. End-users of drug products also need increasing assurance that the product has not been tampered with, and that it was made by the original drug manufacturing company.

This article explores the increasing importance of pharmaceutical vial (secondary closure) seals, as related to product and – ultimately – patient safety. We will examine the many uses of secondary seals, present industry best practices via case study analyses and address issues related to product and patient safety. We will also cover secondary seal considerations when developing a packaging programme and new technologies applied to secondary seals that can help manufacturers, distributors and healthcare professionals identify, authenticate and use drugs safely.

SECONDARY SEALS

Secondary seals – seals that do not come into contact with the packaged drug – have an important function in helping to maintain an integral sterile seal, thus securing the drug supply chain and ensuring patient safety. Secondary seals are the first line of protection, followed by primary closures – that is, packaging components such as vials and elastomeric stoppers that directly contact the packaged drug product.

Seals ensure the safety and efficacious delivery of injectable drugs. By incorporating overt, covert and forensic technologies, seals protect against counterfeiting and also provide vital information that can help identify drugs as genuine, and provide instructions for proper storage, as well as cautionary statements and dosing information that can help prevent dosing errors.

Until the late 1970s, secondary seals were either two- or three-part aluminium shells. In the late 1970s, it was reported that haemophiliacs were cutting themselves on three-piece aluminium seals while trying to gain access to a drug that would stop a bleeding episode; in response to this, West Pharmaceutical Services, in conjunction with Baxter Healthcare, developed the aluminium shell and plastic tear off (flip-off) button. At this time, it was also determined that providing instructions embossed on the seal improved user compliance. Today, most secondary seals applied to injectable drug vials generally consist of an aluminium shell and an attached plastic button that is assembled to the shell, usually in a heat-staking process. When the button is removed, the injection site of the stopper is revealed. In the manufacturing process, the seal is applied after the vial has been filled and stoppered.

A capping machine rolls or crimps the skirt of the aluminium shell under the flange of the vial, serving two purposes. First, it holds the stopper firmly in place and second, it creates a tight seal for the vial and elastomeric stopper interface that helps prevent contaminants from entering the vial.

The plastic button provides important protection for the drug package by protecting the stopper injection site to ensure that the elastomeric stopper is not accessed until the time the drug is to be administered. The aluminium shell
has a hole in the top that is revealed when the button is removed. The hole allows the person administering the drug to access the contents of the vial by inserting a syringe or IV spike through the stopper. As well as ensuring that contaminants do not settle on the injection site during shipping and storage, the plastic button also provides evidence of tampering. When the button is removed, a portion of the aluminium shell tears away and stays attached to the plastic. Buttons that have been removed cannot be reattached properly to the aluminium shell and the shell will remain in place, keeping the stopper secure in the vial.

The plastic button can be imprinted and moulded with conspicuous cautions, warnings and instructions which can prove useful during manufacturing, storage and at the point of use. The importance of this feature during manufacturing cannot be understated. Drug vials are frequently labelled after they have been filled and a manufacturer may ship the filled vials to another plant for labelling. Information printed on the plastic button or seal, such as bar codes, can help identify products during manufacturing so that they are processed in the correct labelling and packaging line.

PROMOTING PATIENT SAFETY
Information at the Point of Use

Printing cautionary and warning statements on plastic buttons and aluminium shells can help reduce medication errors and promote proper handling and storage of drug products to help assure drug efficacy.

For some drug products, cautionary statements printed on the button and seal are required. For example, the warning statement, ‘Must Be Diluted’ is required on buttons and aluminium shells used to secure vials of potassium chloride for injection. Cautionary statements such as ‘Paralysing Agent’ are frequently used for neuromuscular blocking agents, a class of drugs used during surgical procedures. Other statements may include warnings such as ‘Must Be Refrigerated’ or ‘Store Frozen’. These statements can be imprinted on both the plastic button and the aluminium shell or, if a clear plastic button is used, on the shell only.

Unique Package Identification

Applying the unique characteristics of a vial’s contents to the plastic button and aluminium shell can help reduce medication errors and prevent drug mix-ups in the clinical setting. Application can be accomplished by printing directly onto the button and shell, and by moulding type and other characters into the button, as well as by embossing type into the shell.

The button and shell provide two layers of identification. The overt messages on the plastic button are the first check on a product’s identity. Because the button covers the top of the aluminium shell, messages printed on this surface provide a covert layer for adding additional information. Examples of the type of information that can be applied to the button and shell include:

- The strength of the packaged drug
- Storage instructions
- Dosing instructions
- The manufacturer’s name and logo
- The drug product’s brand name and logo
- Manufacturing lot and date information

In addition to printed, moulded and embossed information, drug manufacturers frequently select unique colour combinations for the button and shell to help identify their products. The use of unique colour schemes can help differentiate drugs during the manufacturing process, which can in turn help prevent incorrect labelling.

Some manufacturers also print bar codes, using lasers to etch coding onto the button and shell during the filling process. The coding can also be used to track vials through the manufacturing process.

COMBATING COUNTERFEITING

Drug counterfeiting is becoming a major threat to the drug supply chain and ultimately a threat to consumers. Once a problem limited to under-developed nations, drug counterfeits are now found in the US, Europe and Japan. Counterfeiting is defined as the intentional dilution, mislabelling or adulteration of prescription drugs.

The importance of using the overseal to help protect against counterfeiting can be seen in an examination of the drugs included in the National Specified List of Susceptible Products released by the National Association of Boards of Pharmacy® (www.napb.net) in December 2004. The NAPB is the only professional association that represents the State Boards of Pharmacy in all 50 US states, the District of Columbia, Guam, Puerto Rico, the Virgin Islands, New Zealand, eight Canadian provinces, two Australian states and South Africa. Of the 32 drugs on the list, 17 are injectables packaged in vials. Of these, seven are currently packaged with the overseal used as one layer of anti-counterfeit protection. The manufacturers of four other injectables are considering adopting such measures.

The proliferation of counterfeit drugs can be seen in the number of cases tracked by the FDA, which has grown from five in 1998 to 58 in 2004. The FDA’s counterfeit investigations include all dosage forms. Some
examples of recent injectable drug counterfeiting cases are shown in Table 1.

Custom-designed packaging components introduced by the suppliers of two erythropoietin products that have been counterfeited – Procrit® and Epogen® – demonstrate how oversears can help protect drug products and identify them as genuine.

Pfizer adopted a colour coding and covert printing scheme for Procrit to help protect against counterfeiting. The colours of the seals and buttons match the colour coding on the label, which helps to identify the drug as genuine. Further, printing on the button identifies the product as single- or multi-dose, and printing on the seal identifies the brand name and dosage strength. The printing remains hidden until the plastic button is removed.

Amgen is using a custom button as an anti-counterfeiting measure for its erythropoietin product, Epogen; the buttons are moulded with the Epogen logo and colour coding on the label, which helps to identify the drug as genuine. Further, printing on the button identifies the product as single- or multi-dose, and printing on the seal identifies the brand name and dosage strength. The printing remains hidden until the plastic button is removed.

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SECURING THE DRUG SUPPLY CHAIN
Other technologies are being incorporated into secondary seals as measures for protecting against drug counterfeiting, providing manufacturers with track-and-trace capabilities and providing covert authentication capabilities from manufacturing to end use.

In a February 2004 report issued by the FDA’s Counterfeit Drug Task force, radio frequency identification (RFID) technology was cited as having the potential to provide a methodology to track and trace the movement of every package of drugs from manufacturing to administration. According to the FDA report, reliable RFID technology will make copying medications either extremely difficult or unprofitable. The FDA report strongly suggests that pharmaceutical manufacturers incorporate RFID technologies as appropriate by 2007.

Product authentication data embedded into an RFID tag cannot be altered; the electronic profile provides a higher degree of security than the paper documents because documents can be altered, forged or counterfeited themselves. Secondary seals with RFID tags moulded into the plastic button are now coming onto the market. RFID tags have the potential to provide pharmaceutical manufacturers with the ability to improve inventory management, assign an item-level serial number to each drug vial that passes through a filling line, and enable rapid product authentication in the field.

Moulding the tag into the plastic button, rather than placing it within the label, also overcomes a problem inherent in RFID technology – that is, a tag in close proximity to a liquid, such as a serum drug, reduces the reliability of the information to be decoded by an RFID reader because the liquid interferes with the radio wave transmitted by the tag.

Other item-level technologies that can be incorporated into the overseas to thwart drug counterfeiting include printing with spectroscopic inks and applying high-quality, full-colour graphics. Information in the form of bar codes, for example, can be printed on buttons in spectroscopic inks that can be seen only under special lighting conditions; the bar coding can be read with a scanner.

High-quality graphics can help identify and authenticate drugs as genuine; because of the sophistication of the printing and the moulding process, this technology may be difficult for drug counterfeiters to duplicate.

THE MOST IMPORTANT OF PURPOSES
Pharmaceutical oversears serve as the first line of protection for serum, lyophilised and dry powder drugs packaged in vials. The seals provide protection by:

- Preventing particles from entering the vial and contaminating the drug
- Maintaining the stopper firmly in place
- Protecting the injection site on the stopper
- Providing evidence of tampering
- Incorporating overt, covert and forensic technologies that can help protect against counterfeits, provide track-and-trace functionality from manufacturing to end-use, aid in product authentication, and provide written instructions for storage and use

In performing any or all of these functions, the seal serves the most important of purposes: to aid in the safe and efficacious delivery of drug products.

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