Our injectable medicines are most often available in a glass vial closed by a rubber stopper and a crimp seal, an arrangement more than a century old. Is it true to say that the pharmaceutical industry has lacked innovative power during that time? On the contrary, this simple packaging format has led to numerous progresses in the past decades. However, recent studies, new regulations and emerging products suggest that there is still a significant potential for improvement in fill and finish operations.

Comparing the picture of a 1919 vial of vaccines to a similar vaccine in 2011 may suggest that primary packaging for parenteral medicines has evolved little over the past century. Indeed, the most common presentation for injectable drugs remains a container closure system composed of a glass vial, an elastomeric closure and an aluminum crimp seal. This reality masks a tremendous evolution of sterile drug presentations from multidose vials to unit dose format, then unit dose in syringes, and the emergence of plastic material as a replacement to glass, such as COP (Cyclic Olefin Polymers) to address closure systems and demanding drug compatibility issues between container and the emergence of plastic material as a replacement to glass, such as COP (Cyclic Olefin Polymers) to address compatibility issues between container closure systems and demanding drug products.

However, fill and finish operations remain substantially unchanged since the early 1900s and involve the key steps of filling, stoppering, freeze-drying (where applicable) and crimp-sealing. Significant progresses have been made in the manufacturing environment and in the reduction of preparation steps for packaging components. On the manufacturing environment side, isolators and RABS (Restricted Access Barrier Systems) have replaced standard cleanroom processing and thus transformed the concepts of risks as related to microbial contaminations. As for component preparation, the manufacturers of elastomeric closures initiated a significant change in the manufacturing of sterile products by taking ownership of the preparation of the stoppers in the 1980s. Nowadays all stoppers are provided pre-cleaned with specifications of cleanliness, and are offered in formats compatible with fill and finish processes (steam sterilisable bags, bags with rapid transfer port).

Component preparation by the suppliers was first acknowledged by the FDA in 2004 and since the introduction of pre-cleaned aluminum caps and combisales, and the recent inroads for vial pre-processing all primary components are now available ready-to-sterilise or ready-to-use. In addition, the introduction of automated inspection to eliminate defective components and the possibility to have specified leachable profiles contribute to achieving the ultimate goals of quality for packaging elements, and more importantly, for the drug products.

With the emergence of disposable downstream and upstream processing components, the roadmap to a reduced involvement of the pharmaceutical industry in manufacturing operations is well defined, where it is not already implemented.

Current Issues related to Vial-based Container Closure Systems
Are we then close to the end of the road?

Recent regulations, literature and recalls suggest that this common packaging format which we thought grandfathered for decades is yet to be scrutinised and prone to generate significant work in packaging development, quality assurance and engineering. According to Guazzo, 140 million containers were recalled between 2003 and 2007. 40% of which related to container closure integrity issues, and 45% to vial issues. Lam & Stern and Simianu demonstrate in separate studies that standard vials and standard closures may not always have the geometric compatibility to give a perfect fit for freeze-drying applications or where an inert gas headspace is required. Their studies provide a rationale for the issue of stoppers that raise between the lyophilisation and crimping processes, either through modelling of the impact of stacked tolerances on the robustness of the seal, or by actual visualisation of the sealing surfaces hidden by the flange of the vial. While other elements such as surface treatment for both vials and stoppers may also be involved, they appear to touch a potential problem ignored for decades: the possibility that standard vials may not always be compatible with standard elastomeric closures! In addition, headspace studies also demonstrate that container closure integrity may not be assured by the stopper alone and lead to vacuum loss and oxygen ingress between lyophilisation and crimping.

Regulatory agencies have acknowledged the issue. EMEA Annex 1 to Good Manufacturing Practices specifies new requirements for Class A air supply protection of the vial until the final seal (crimping) is achieved, and the control of containers packaged under vacuum. At the same time that Annex 1 was in preparation, a PDA (Parenteral Drug Association) task force on risk management also investigated the transfer of lyophilised vials from...
the freeze-dryer to the crimp-sealer, and concluded the same needs that are now regulations in Europe14. An open question remains: knowing that risks exist for container closure integrity before crimping, are these risks such that Class A air supply is enough, or such that it is a first step to full Class A with cleaning and sterilisation of the caps, as is already the practice when isolators are used? PIC/S published a recommendation in 2010 that adds that unless it is verified that the stoppers are correctly set, and that misplaced or missing stoppers are rejected, aseptic conditions should apply15.

Beyond regulation, the issue of raised stoppers is critical for several reasons:
- Prevention of vacuum loss for lyophilised products packaged under vacuum.
- Prevention of vial rejects because of imperfect land-seal and raised stoppers.
- Prevention of false positives when alternate methods are used for sterility testing.16

Class A air supply crimping resulted in recent years in many practical issues. On the manufacturing side, automatic loaders and down loaders for freeze-dried products found application to facilitate transfers in the Class A environment requirements. Crimp-sealers were upgraded to meet Class A air supply requirements. On the control side online raised stopper detectors have been developed, and headspace analysers complement the existing offer for online container closure integrity testing. In-line controls meet the regulatory requirements, but still fail to fully address two issues:
- Sorting production into quality does not meet the emerging concept of quality by design17.
- The Annex 1 statement that “crimping of the cap should be performed as soon as possible after stopper insertion”13.

Risk and Compliance Management: Early Container Closure Integrity.
It appears that many of the current issues discussed above are related to the fact that the components used require the dissociation of the two operations that ultimately achieve container closure integrity. In most manufacturing set-ups, stoppering and crimp-sealing are separate in time and space.

Bringing these two operations together, in a single operation or in two immediately consecutive processes, addresses the risk of raising stoppers and the compliance objective.

Freeze-Dried Drug Products
For freeze-dried products the earliest possibility to achieve final container closure integrity is inside the freeze-dryer, immediately after the insertion of the stopper.

Products such as LyoSeal® were specifically designed for that purpose. An all plastic cap LyoSeal® is designed to snap on the flange of the vial when pressure is applied. Placed on the vial-stopper system before loading of the vials in the freeze-dryer, the cap uses the pressure of the shelves to insert the stopper to achieve simultaneous stoppering and final crimping. Picture 2 shows a LyoSeal® 20mm after placement on the stopper, before lyophilisation, and Picture 3 after the stoppering cycle of the freeze-dryer. The overall process is summarised in Diagram 1.

LyoSeal® has the attributes to become a standard component for industrial manufacturing:
- Compatibility with standard neck finishes (ISO, GPI)
- Compatibility with validated lyophilisation cycles (18)
- Compatibility with most industrial freeze-dryers.

In addition, it resolves another frequent issue of freeze-drying operation when coated or flange-coated closures are not used: the sticking of stoppers to the shelves of the freeze-dryer. Initial work with pharmaceutical laboratories assesses the validity of the concept 19.

Sterile Liquid Products
The use of all-plastic caps in crimping operations, for both lyophilised and liquid drug products, is expected to eliminate the downsides of aluminum components: particle generation, variability of the crimping process and easy promotion of cosmetic defects. In particular, the possibility to use plastic components in the immediate vicinity of the filling operation allows for crimping immediately after stoppering, thus bringing final container closure integrity for liquid products in the filling core in association with ready-to-use
vials and closures (Diagram 3, Picture 4), the concept satisfies both the compliance issues discussed above and the possibility to further reduce the number of pharmaceutical fill and finish operations.

Production Management: Reduction of the Number of Manufacturing Operations

A closer look at the evolution of fill and finish operations in the past decades shows that the number of processes managed on the production floor is decreasing. For standard liquid processing, up to 12 steps are involved, depending on whether cleanroom processing or isolation technology is used (Tables 1 and 2). Lyophilisation adds two additional operations (Table 3). Ready-to-sterilise and ready-to-use elastomeric closures, now common in the industry, have reduced by one or two the number of operations on the fill side. The recent introduction of clean and sterile aluminum crimp seals has had the same consequence on the finish side. Plastic caps and ready-to-use vials have the potential to further reduce manufacturing steps down to five or seven.

Conclusion

Fill and finish operations for the manufacturing of sterile products in vials has evolved in the past years due to the fact, now well documented, that container closure integrity is not achieved until the final crimp is in place. The requirement for Class A crimping requirements and the new control tools now implemented address the risks that a container closure system loses integrity between stoppering and crimping, but do not address the root cause, which is the separation in time and space of the stoppering and crimping operations. LyoSeal® has been developed to address that very point. In addition it provide ■

Bibliography

MANUFACTURING


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Philippe has over 20 years of industry experience in both primary packaging for sterile parenterals and pharmaceutical compliance. He participated in the early development and marketing of ready-to-sterilize elastomeric closures before opening the European branch of a pharmaceutical compliance and engineering firm. He joined Biocorp in 2008 as director, sales and marketing. Email: plegall@biocorp.fr

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