Innovative Manufacturing Technologies

With soaring scrutiny from regulators on drug delivery systems' safety and effectiveness, addressing industry requirements has become increasingly challenging. Like with other obstacles, there is almost always a way to overcome it. Perhaps laser-assisted cutting technology and X-ray inspection systems are the answers

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Since the mid-2000s, the pre-filled syringe market has grown rapidly. An increasing number of drugs have been developed and presented in a subcutaneously injectable format because of the significant benefits in comparison to traditional glass primary packaging, such as vials or ampoules. This trend is fuelled by an ageing population and, as the number of chronic disease sufferers increases, so do therapies.

Pre-filled syringes – particularly when used with auto-injectors – enable people with lifelong conditions to safely and conveniently self-administer their medications, thus improving their quality of life and treatment compliance. This also positively contributes to decreasing overall healthcare costs by shifting patient care from hospitals to the home.

Ready-to-use (RTU) sterile syringes account for approximately 80% of the global consumption of these primary containers. The remaining 20% are bulk ones which still need to be washed, siliconised, assembled and sterilised before they can be processed on a fill and finish line. Although there are still firms sourcing the latter, there is a clear trend toward switching to RTU syringes and, therefore, outsourcing operations to primary packaging suppliers.

There are several reasons why these activities are contracted to external partners. When comparing RTU primary packaging to traditional bulk containers, the advantages are clear: lower investment costs and smaller footprint equipment for fill and finish upstream processes such as syringe washing, drying, siliconisation and assembly. They can also reduce the complexity of the overall process which, in turn, yields superior quality performances. All of this enables organisations to focus and deploy resources on their core business activity: developing and manufacturing innovative, safe and effective drug products to treat patients.

Packing Up

With this outsourcing trend comes a growing reliance on primary packaging suppliers to address increasingly stringent regulations for safer drug products. Since 2006, nearly 50 medications have had glass breakage or particulate issues serious enough for FDA recalls, impacting over 100 million units of medication. While the risk to human health is paramount, glass particulates contribute to other global healthcare issues like drug shortages.

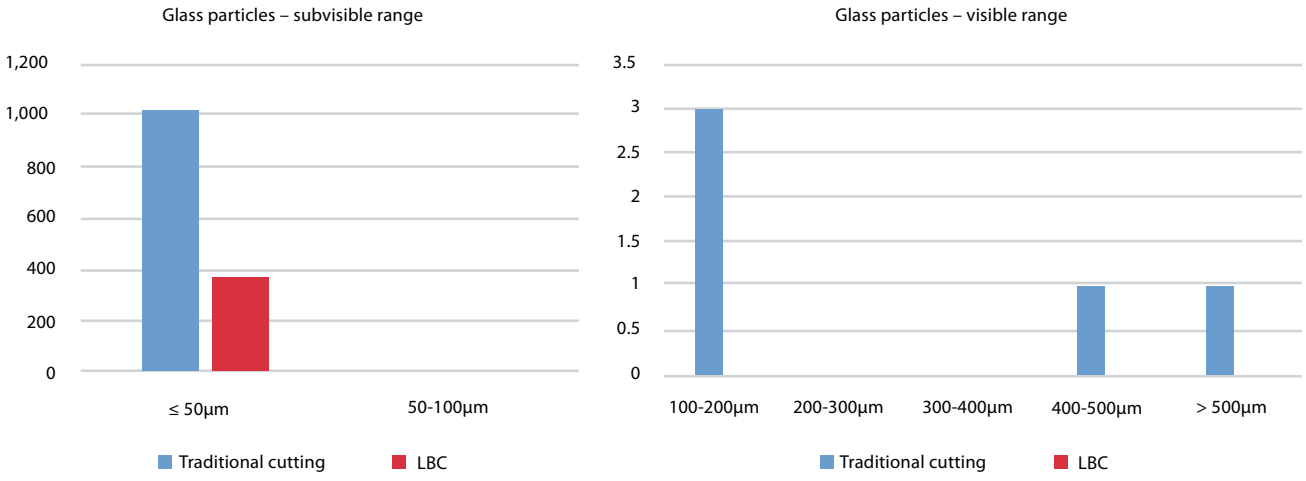


Figure 1: Glass particle generation – traditional thermo-shock cutting versus laser-beam cutting (LBC)

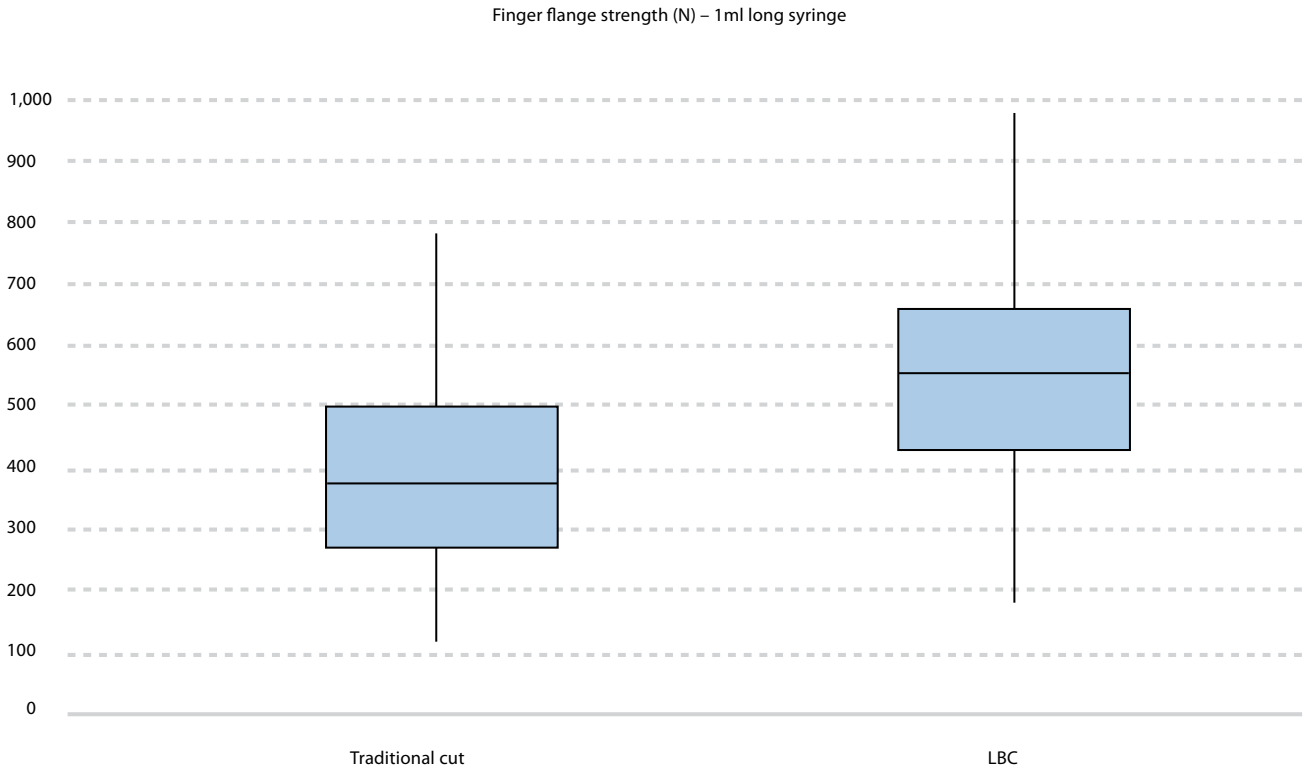


Figure 2: Finger flange strength – traditional thermo-shock cutting versus LBC

The formulation of parenteral drugs is highly demanding and complex. It is crucial to guarantee the sterility of the product and the container closure integrity (CCI) at every step. To comply with the expectations of companies and regulators, manufacturers must invest in state-of-the-art production and inspection technologies, which enable the fulfilment of such high-end requirements. There are two possible creative innovations that can mitigate the aforementioned liabilities:

1. The implementation of laser-assisted cutting on a syringe manufacturing line. This has been shown to decrease glass particle generation during the cutting process and positively contributes to better dimensional and mechanical properties of the final product
2. A ground-breaking in-line X-ray needle shield inspection technology that provides a superior assurance over CCI by overcoming the limitations of commonly used inspection systems. This method enables direct control and measurement over the actual embedding of the steel cannula into the rubber pre-fillable syringe component and needle inclination after shield assembly

Glass Particle Generation

Several factors may contribute to an increased risk of glass particle generation such as breakages at the manufacturer's end and at the fill and finish site; glass cutting during tube drawing and syringe converting operations; and delamination, among others. The FDA reported that 22% of recalls for sterile injectable drugs in the period of 2008-2012 were associated with particle issues, including contamination from delaminating glass primary containers, breakage and particulates, which resulted in more than 100 million units of drugs packaged in vials or syringes to be withdrawn from the market.

If present, glass particulate poses a safety risk for patients. There is the potential for intravenous drugs containing these fragments to cause embolic, thrombotic and other vascular events. Those delivered subcutaneously can also lead to the development of foreign body granuloma, local injection site reactions and increased immunogenicity. A company facing a recall may find its bottom line affected by investigations, loss of market share, replacement costs and reputation damage in the market.

In a document released by the FDA in 2011, the Agency advises firms to re-examine their supplier's quality management programme in order to ensure that they are not encountering this problem. It is clear that demand for the quality and integrity of packaging systems is on the rise. The selection and qualification of materials should include a risk assessment during the development phases in close communication with the packaging manufacturers.

One company has taken a proactive approach by introducing an innovative laser-based cutting (LBC) technology.

Figure 3: X-ray inspection system – overcoming traditional inspection technologies' limitations

This is a major influencing factor on the generation of glass particles and the mechanical properties of the syringe's finger flange, as well as on the dimensional consistency of the glass. Both internal and external investigations can prove that this practice contributes positively to the parameters mentioned above.

The conventional method employed to cut bulk glass syringes to length is a three-step procedure. First, an industrial grade diamond grinds the glass tube, followed by a flame-heating process. Finally, a fine cold water nozzle causes a thermo-shock which breaks the glass, while the grinding line assures a full 360° cut.

The innovative new technology replaces the traditional heating step by introducing a precise laser beam to cut the glass barrel. As the laser beam only heats up the very narrow grinding area and exposes it to a fine cold water spray resulting in a very sharp and clear cut, it yields additional benefits such as a highly reduced particle count and a stronger finger flange.

A study was set up in collaboration with the German Center for Glass and Environmental Analysis to examine the particle load on 60 glass syringes created on bulk syringe converting lines through the traditional flame technology compared to LBC. The samples were taken straight after the cutting process without any water or air flushing.

The bulk syringe samples were collected and rinsed with distilled water, subjected to ultrasonic treatment and then went through a second rinsing. After this, the suspension obtained was poured over a 0.2µm mesh size filter and glass particles were counted under a microscope. The syringes taken from the conventional flame-heating production line showed significantly more and larger particles (see Figure 1). In the sub-visible region – or particles less than or equal to 50µm – the total number was three times lower compared to the conventional production technology. For the number of visible particles (those greater than or equal to 100µm) the results were even more apparent with no visible particles counted in those samples produced on the bulk converting lines equipped with the LBC.

As highlighted earlier, glass cutting is one of the main contributing factors to the mechanical properties of the syringe's finger flange. Therefore, their strength was also analysed on both production lines. Eighty 1ml long syringes with round flanges were tested according to Annex C of the ISO 11040-4 standard. The minimum and average breakage values of those made with LBC were 57 and 40% higher respectively than the conventional method (see Figure 2, page 43). This is a direct result of the sharp and clear cut, which is obtained with the LBC technology.

Container Closure Integrity

Biologic drug products cannot be subjected to terminal sterilisation due to the sensitive nature of the large molecules they typically consist of. For this reason, they need to be manufactured under strict aseptic conditions to assure the sterility of the final product. Like primary container closure systems, RTU syringes used in combination with compatible rubber closures must provide an integral barrier ensuring stability and sterility from product conception to injection.

With industry syringe requirements shifting from bulk to RTU, primary packaging suppliers are now responsible for a crucial CCI step that was previously commonly under the responsibility of pharma companies in the past: needle shield assembly and inspection. Through this process, the tip is embedded into the shield rubber whereby a sealing interface is created, which assures microbiological barrier integrity and protects the drug product from leakages or losses during its shelf life.

To mitigate the risk of incorrect shield assembly – potentially resulting in CCI failure – syringe products have to be inspected. Today, manufacturers rely on a short list of in-line inspection systems, which can only indirectly detect potential CCI deficiencies through, for instance, laser- or mechanical-based systems for dimensional control, cameras for shield inclination and pressure decay or high voltage practices for detecting pierced shields. Such commonly used inspection technologies do not provide any direct control or measurement capabilities over the actual degree of tip embedding into the shield rubber after assembly.

X-Ray Inspections

While pressure decay and high voltage are widely used, reliable methods for detecting pierced needle shields, they are not capable of discovering when the tip is fully embedded into the elastomer but with a narrow distance between it and the outer edge of the shield. In such cases, there is an intrinsic risk of downstream CCI failure as physical stresses occurred during

transportation, fill and finish processes, assembly and final product distribution and handling operations are likely to lead to the tip piercing the elastomer.

To overcome traditional inspection technologies' limitations, a novel system based on a 100% in-line pulsed, low radiation X-Ray needle shield inspection that emits flashes lasting only a millisecond has been introduced. This has led to the minimising of radiation exposure and the prevention of motion blurs (see Figure 3, page 45).

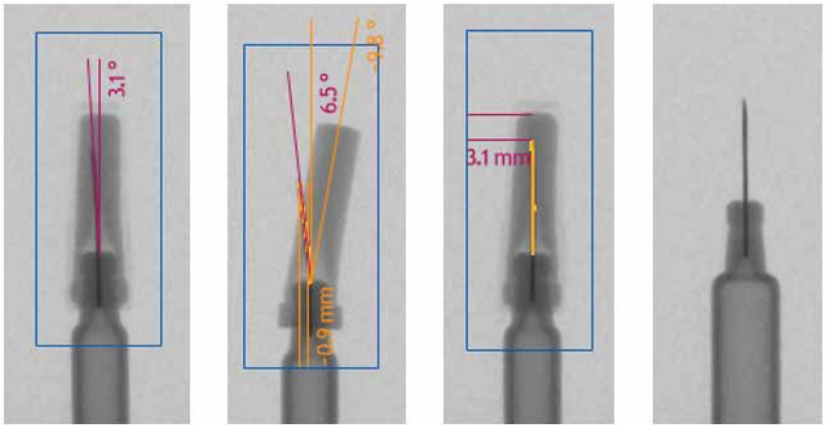
With a resolution on needle position of 0.1mm, this technology is capable of measuring the axial needle deviation – the distance between the tip and outer edge of the shield – and the embedding of the needle into the elastomer after shield assembly, thus providing a comprehensive control over CCI key quality attributes (see Figure 4). Axial needle deviation is becoming an increasing concern as a result of the industry trend to shift from regular-wall 25G or 27G needles to thinner-wall 29G or even 31G needles. While providing a nearly pain-free injection to patients, these are more likely to be bent and permanently damaged during shield assembly.

Advanced Technologies

Control over needle embedding into the elastomer is critical to ensure product sterility as well as to prevent any product loss or leakage, which might lead to crystallisation and clogging of the needle, particularly for increasingly common highly concentrated formulations.

Being able to measure the distance between the tip and the outer edge of the shield as well as define acceptable thresholds has become even more important as pre-filled syringes are widely used in tandem with auto-injectors. Assembly operations whereby syringe tips are integrated within auto-injectors' caps apply mechanical forces that press needle shields down in a way that could potentially result in the tips piercing the elastomers, hence the CCI failure.

By providing a robust and comprehensive approach, these technologies enable companies to reliably outsource shield assembly and inspection operations, thus reducing the overall process complexity. Enhancing the quality of primary container closure systems also ensures that the X-ray technology yields superior fill and finish process performances by decreasing the rejection rate of filled syringes during final CCI inspections. This certainly has a strong cost impact whenever high-value drug products are manufactured.



Axial needle deviation | Pierced needle shield | Distance needle tip to outer edge of the shield – embedding of the tip in the elastomer | Missing needle shield

Figure 4: Needle/needle shield interface key quality attributes

About the authors

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