Challenges and Development Perspectives of Primary Packaging for Parenteral Drugs

When talking about parenteral drugs, we usually refer to the administration of drugs by injection through the integument or directly into the circulation.

The parenteral route – it could be intradermal, subcutaneous, intramuscular or intravenous – indeed allows a rapid effect, the administration of orally inactivated drugs, rapid intervention in emergencies, and the administration of nutritional solutions to patients who cannot feed themselves normally.

The most common parenteral drugs are injectables, therapy drugs administered by professional users in healthcare facilities, such as vaccines or IVs, and infusionals, mostly complementary solutions used as an adjuvant for such therapies.

When it comes to packaging to contain such drugs, it is composed by an integrated system featuring the primary packaging properly said, a vial or a bottle, a rubber stopper, and a basic or tear-off aluminum gear.

Vials are manufactured in glass, with different material specs and manufacturing technologies available, and different features that can better adapt the drugs characteristics and challenges.

Glass specs depends from the characteristics the material should have to better contain drugs: Type I is a borosilicate glass, featuring an enhanced mechanical resistance and a high degree of hydrolytic stability, making it ideal to contain all types of injectable products with an acid, neutral or slightly alkaline pH.

Type II is a soda-lime glass that achieves the performances required by the international pharmacopeia for parenteral applications through appropriate surface treatment, and it is particularly suitable for packaging injectable and non-injectable preparations with acidic and neutral solutions.

Finally, Type III is a low alkaline sodium-calcium glass with good hydrolytic resistance, particularly when it comes to sudden temperature changes. These features make it ideal for non-aqueous or powdered injectable preparations, excluding drugs that must undertake a freeze-drying process.

As said, glass used to contain parenteral drugs might come from two different manufacturing technologies: premium molded glass and tubing glass.

The first ones are obtained from an improved molding process known as press-and-blow. Glass is melted into a furnace at over 1600° C, extruded and then blowed into a high precision mold by using mechanical tools (a piston) and a jet of hot air. In just one single process, the melted glass is transformed into a parenteral vial ready to be supplied to pharmaceutical companies or CMOs.

This process is intended to the production of premium borosilicate glass, the golden standard for parenteral and injectable pharmaceutical application.

On the other hand, tubing glass containers require a two-step process. They are produced by transforming a glass pipe into a vial by means of localised flames and through a number of steps to give the desired shape.

Given these different possibilities, the pharma manufacturer might choose the better option for any application, considering multiple elements such as:

- The heat used when forming the vials directly affects the level of extractables at the surface due to the vaporisation of the more volatile elements of glass and to the condensation of vapors on the inner and colder surface, which produces "rough spots", chemically different from the rest of the surface
- Premium molded vials are mechanically and chemically superior, while tubing vials perform better in terms of the aesthetic quality of the surface. Differences in other tested aspects are negligible.
- The bigger the format in which the drug must be contained, the more molded glass vials are to be considered as an option due to its mechanical performances; the smaller, the more tubing glass vials are to be preferred

Primary packaging for parenteral use also has extensive variation when it comes to format sizes, with the injectables championing in smaller formats and infusionals that require the bigger ones. More in detail, size spans from 2 to 1,000 milliliters.

The bigger formats could also be marketed with level marks print, and with a special design allowing a perfect fit with the infusion bottle hangers used in the hospitals.

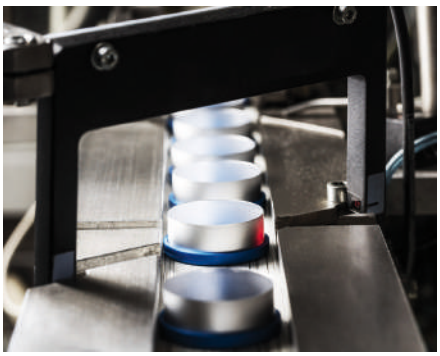
Additional services could be provided to parenteral primary packaging upon client request, such as the ready-to-use and the ready-to-sterilise options that could be chosen in order to let the pharmaceutical manufacturer concentrate on its own core activities, or additional controls to address every customer need, up to the visual inspection on 100% of production and customised post-production second quality check.

Moreover, in-depth, data-based information could be provided to streamline the customer validation procedures, as well as additional, certified analysis about extractables testing and helping companies to address different regulatory frameworks.

The packaging integrated system is completed by a rubber stopper, manufactured with highest quality rubber able to minimise interaction with the drug, and by aluminum classic or tear-off gears.

While classic aluminum gears mostly rely on a mechanism similar to the ones used in soft drink cans, tear-off gears are composed of a pre-drilled aluminum closure together with a plastic cap, providing usability advantages for professional users, as well as customisation capabilities to enhance the drug distinctiveness in a healthcare facility.

This is what a primary packaging for parenteral drugs looks like today. While long-term future could see a convergence towards wearable devices, especially when it comes to chronic diseases treatments requiring a continuous therapy administration, the



short-term future could see an evolution of packaging engineering according to multiple directions: as for the improvement of container features, the driver of innovation is primarily the characteristics of the raw material: the glass.

More specifically, the continuous improvement of the treatments used on the internal surface of the glass containers, allowing for low levels of hydrolytic cutoffs, making the bottles ideal for drugs that are administered through an IV.

A second area of improvement is the enhancement of container resistance and, in particular, of the external glass surface through continuous research into new technologies, such as – among others – the use of layers of silicon, CVD and plasma. As containers are subject to intense processes such as sterilisation and depyrogenation, the aim is to reduce the risk of breakage along the production chain due to mechanical and thermal stress, as well as impacts and scrapes.

Thirdly, the identification of new technologies and processes to reduce leachables and extractables, with continuous tests being run to closely analyse the elements that are extracted to address the need for stability with drug formulations that are becoming increasingly chemically aggressive. This need for enhanced stability also applies to closures, searching for innovative, cutting-edge treatments for primary closures aimed at enhancing compatibility with drug formulations.

Another important pillar is the development in terms of materials, with the set-up of brand-new generation of glass bottles that are capable of offering superior chemical neutrality, shock absorption and assembly line flow characteristics.

Yet our innovation goes far beyond R&D for the improvement of materials. It also applies to a general rethinking of containers as complex systems, integrating brand new characteristics and features. For example, allowing for enhanced integration within the pharmaceutical value chain, or making administration easier for professional users, such as doctors and nurses.

The Covid-19 pandemic has shown us that caregivers and professional users may face sudden, unprecedented workloads and pressure, which consequently enhance margins for error and injury risks. Packaging can make their jobs a little easier, through improved usability, guaranteeing simpler, faster and safer drug administration.

Since 2019, several products or concepts have been presented that address these emerging needs and facilitating parenteral drug reconstitution and administration by professional users, enhancing their safety thanks to luer-lock systems and minimising product waste. These are applicable to both multi dose or single dose containers. Pharmaceutical companies have shown a growing interest in these products and the first tests to scale up their industrial production are underway.

The second pillar of this redesign process is the transformation of single containers to ensure enhanced traceability across the supply chain. This is a huge theme in the pharmaceutical sector and investigating new solutions to track and trace drugs through primary packaging could be a real breakthrough, particularly when it comes to high value-added drugs.

According to the WHO, the counterfeit medicines market is worth 73 billion euros per year and causes serious reputational risks for companies and health risks for patients in terms of safety and therapy efficiency. That's why a non-modifiable, non-counterfeitable, technologically-advanced tracking solution is increasingly required by pharmaceutical companies. Put into practice, containers would be marked with a unique code, providing new ways of marking complex codes into glass, with multi-layer information stored with blockchain technologies that can then be verified throughout the supply chain.

Now more than ever, the new challenges brought about by the Covid-19 pandemic call, on one hand, for an increasingly scientific approach to supporting the evolution of single packaging elements in order to anticipate the needs of new drug formulations and guarantee a more enhanced, measurable and stable level of performance. On the other hand, forward thinking is increasingly required when it comes to parenteral packaging as a system, integrating additional functionalities thanks to a structured and controlled innovation process.

In order to develop these processes smoothly and efficiently, new, closer partnerships between pharma companies and packaging manufacturers are required. Continuous dialogue and long-term planning are key to making these new partnerships effective, as is a new shared responsibility model, in which both parties strongly commit to ensuring the success of the entire system and, as a result, of the therapeutic drugs on the global market.

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