glass WORLDWIDE

Innovative solutions for a vital process

Carole Grassi discusses SGD Pharma's innovative solutions for implementing aseptic filling with ready-to-use moulded glass vials.

Use of the parenteral route of administration has risen sharply in recent years, with parenteral drugs now representing approximately 32% (by volume) of the global market[1]. Parenteral drug delivery, via injection or infusion, is essential for many biologics but is also commonly used for small molecules, low solubility drugs and delivery of nutritional and vitamin therapies.

These products are commercialised in both liquid or lyophilised forms and are available in a broad range of dosages and containers including vials, bottles, ampoules, cartridges, flexible bags and pre-filled syringes. In all cases, aseptic filling of the container is a key step in the manufacturing process, with significant investment involved in safeguarding the quality and cleanliness of the primary packaging.

There is growing recognition that preparing primary packaging for filling is Capex, Opex and time-intensive and that the first steps of the aseptic filling process, though critical to product quality and safety, are not value-added activities.

Rising demand for parenteral drugs comes at a time of intense pressure to reduce costs, across an industry that is seeing a transformation in its structure. Pharmaceutical companies are scaling back on operational ownership, with a network of contract research organisations (CROs), contract manufacturing organisations (CMOs) and by aquiring biotech start-ups. A new segment of the market shifts from yesterday's blockbuster small molecule drugs, requiring large, dedicated product filling lines, to the manufacture of smaller batches of biotech products, in facilities handling multiple products in different container presentations to treat smaller disease populations.

These changes call for agility and a lower asset base, creating an appetite for standard, transferable solutions for aseptic filling to facilitate a focus on core activities of drug development. One notable trend is the growing usage of ready-to-use (RTU) primary packaging for 'fill and finish' operations. Due to the success of prefilled syringes, RTU primary packaging has become a preferred option in the aseptic manufacturing process to enhance flexible filling and reduce the total cost of ownership to pharma companies. Increasingly, outsourcing the non-core activities of washing and sterilisation is becoming common practice for vials and cartridges. RTU options for small volume vials are largely in place but flexible processing solutions for larger sized containers, in the 50-250ml volume range, are not yet fully established; access to larger moulded vials in RTU format is critical for key applications.

The introduction of Sterinity by SGD Pharma makes the manufacture of RTU moulded glass vials commercially accessible for the first time. Powered by the well-established EZ-fill platform from Ompi, this product extends the commercial and practical benefits of RTU to a wider range of applications.

Understanding aseptic filling

Parenteral drug products are delivered directly from their packaging to the patient, making rigorous preparation of that packaging essential for patient safety. The process of aseptic filling consequently extends from the packaging, through preparation, to filling the drug and securing closure, ready for storage/shipping. A detailed discussion on each of the steps involved lies beyond the scope of this article but they are described briefly below.

Clean, inspected glassware, as received from a supplier, is subject to washing, sterilisation and depyrogenation processes to ensure the removal of:

- Inert particles, which present a risk of thrombotic effects for the patient. These may be airborne or arise during glass production and transport.
- Micro-organisms, which are endemic within the environment and can trigger serious illnesses such as septicaemia.
- Pyrogens, substances that induce a fever in the patient, a prime example being endotoxins produced by dead bacteria. There is extensive regulatory guidance in this area, including FDA guidance detailing Current Good Manufacturing Practice (CGMP)[2] and recently updated (2017) EU GMP documentation[3]. As 21 CFR 211.113 makes clear "appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilisation processes." Establishing a new aseptic filling line is an extensive and significant undertaking.

Trays may be the optimal configuration for certain applications but nest and tub offers the flexibility for a single unit to support multiple filling machines using different packaging types.

Washing/rinsing processes are critical steps in the preparation of glassware for aseptic filling. Used primarily to remove inert particles, they also reduce contamination and endotoxin levels. Using water that meets the same quality standards as that injected into the patient – Water for Injection (WFI) – is crucial. Sterilisation processes further reduce micro-organisms - to a defined sterility assurance level - and may include steam heating, dry heating (in an oven or sterilising tunnel), ethylene oxide treatment, the application of radiation (gamma or electron), filtration and/or other techniques. Depyrogenation is typically a higher temperature treatment than sterilisation, carried out for a longer period in a dry oven or (sterilisation) tunnel.

RTU minimises the assets associated with aseptic filling at a specific site and at the same time can offer significant savings in both Capex and OPEX relative to the installation of a bespoke, dedicated system.

The time and money associated with bringing an aseptic line onstream is considerable. Beyond Capex for a washer and dry heat sterilising tunnel, there is substantial ongoing expenditure associated with maintenance, ongoing validation and routine operation. Any manual tasks call for exemplary clean room practice, supported by rigorous training. Against this backdrop, switching to RTU can offer significant advantages, depending on the level of complexity and customisation required.

Choosing parenteral packaging

Pharmaceutical glass packaging is produced in three glass types, as defined by the major pharmacopoeias both USP <660> and EP 3.2.1 specifying performance standards for Type I, Type II and Type III glass containers. Glass containers used for parenteral packaging are differentiated by their chemical composition (Type I, II or III) and with respect to how they are manufactured, with both tubular or moulded products in widespread use. The performance of these containers is quantified in terms of:

- Hydrolytic resistance (a measure of chemical stability).
- Dimensional stability and mechanical resistance.
- Cosmetic quality.

Identifying the most appropriate packaging is therefore an essential element of product development and crucial for safe and cost-effective manufacture.

Type I is the designation assigned to borosilicate glass, which contains significant amounts of boron oxide (~10%) and has a relatively high hydrolytic resistance level. Hydrolytic resistance, as measured by pharmacopoeial tests, is quantified in terms of the amount of alkali released by a glass vial filled with ultra pure water, when tested at elevated temperature[4]. A high level of hydrolytic resistance is associated with low release rates and indicative of high chemical stability. Type I glass also exhibits higher resistance to thermal shock. These attributes make it highly valued within the industry and extremely suitable for parenteral products.

Type III, soda-lime-silica or regular soda lime glass contains significant quantities of both sodium oxide (~15%) and calcium oxide (~10%) and has lower hydrolytic resistance than Type I. It can be used for parenteral products if stability testing specifically confirms suitability, with powder applications being the most common. Hydrolytic resistance can be raised by treating the inner surface of the glass with ammonium sulphate to produce Type II glass, which has a similar hydrolytic resistance to Type I but with lower chemical durability.

When it comes to the impact of manufacturing method, moulded vials offer high mechanical resistance and low risk of breakage, making them particularly suitable for larger volumes - from around 50-3000ml - and for lyophilised products. Moulded products are also often selected for high pH formulations. Tubular vials are most popular in the 1-20ml volume range, offering high cosmetic quality, high dimensional stability and thin walls – a lighter product.

All these factors and others affect the packaging chosen for a specific parenteral drug, which in turn directly impacts the aseptic filling technology selected. A dedicated manufacturing facility for an established, commercialised drug may handle just one type of vial but CRO, CMO or R&D departments need the flexibility to switch easily between packaging types to assess/handle different volume vials. This requirement for flexibility significantly complicates the development of optimised aseptic filling processes.

RTU solution

SGD Pharma's Sterinity offer, through Ompi EZ-fill, provides an off-the-shelf solution for aseptic filling. Sterinity vials are delivered ready for direct introduction into an aseptic fill-finish operation, leveraging the advantages of Ompi EZ-fill secondary packaging, which has already been tested and adopted in a wide range of fill-finish equipment platforms.

Parenteral glass vials are delivered ▸

directly to the process area, which may be at the pharmaceutical manufacturing site or remote, at a centralised or contract facility, serving multiple laboratories and/or production sites. Vials are produced and 100% inspected in a clean room environment at the SGD Pharma plant and then subject to the following processes:

- Washing with WFI followed by drying in a clean room environment.
- Depyrogenation in a pharmaceutical grade tunnel.
- Packaging in a nest and tub or tray configuration.
- Covering with Tyvek sheet.
- Sealing with a Tyvek lid followed by steribag bagging (single or double).
- Sterilisation by ethylene oxide using a process validated in accordance with ISO 11135[5].

RTU glass vials can then be stored with a five year shelf life. The technology decouples the preparatory stages of the aseptic filling process from the final fill and finish process, thereby introducing significant opportunities for outsourcing/process management. Levering this proven solution eliminates the development, design, construction and validation work associated with a bespoke in-house design, accelerating the time required to complete a project.

This is a crucial gain, in both the clinical and industrial settings, whether the goal is a new line or the retrofitting/expansion of existing capacity that can help to speed a product through to commercialisation. Furthermore, off-the-shelf designs are rigorously optimised with respect to ease of operation, automation and maintenance. These advantages allow customers to lower associated Opex significantly.

These options mean that the TCO of an RTU platform - Capex plus Opex across the lifetime of the unit – are often much lower than for in-house solutions. This is particularly the case where there is a requirement for combination lines, aseptic filling lines with the flexibility to handle multiple types of parenteral packaging (cartridges, syringes or vials) without module resetting. This is specially valuable in small batch filling operations.

Beyond cost saving, RTU offers other practical advantages. Firstly, there is the reassurance of high quality that can easily be replicated, from site-to-site, or by external suppliers if the activity is outsourced. Scale-up is straightforward and issues associated with method transfer are reduced. In certain geographies, using an RTU solution will be economically beneficial even for large-scale manufacturing, simply because it alleviates quality concerns associated with services such as electricity and water supply, including maintenance of the quality standards required for WFI. In addition, the use of RTU offers the flexibility to manage the footprint associated with aseptic filling operations – to minimise the amount of equipment at a certain location, for example, which may be critical for some organisations.

Nominal capacity	Design	Neck finish	Type of glass	Type of pack	Number of pcs per pack	For Human Use with 5 years shelf life
20 ml	EasyLyo	20 mm	Type I	Tray	60	Available
25 ml	EasyLyo	20 mm	Type I	Tray	60	Available
50 ml	EasyLyo & ISO	20 mm	Type I	Tray	28	Q4 2019
100 ml	ISO	20 mm	Type I	Tray	/	On going (2020)
20 ml	EasyLyo	20 mm	Type I	N&T	24	2020

Table 1: The Sterinity platform will extend to a portfolio of moulded glass vials answering directly to a wide range of parenteral applications.

RTU moulded glass vials

The Sterinity offering powered by Ompi EZ-fill uses moulded glass vials made from Type I glass of exemplary quality. A steadily expanding portfolio of products in a range of sizes will be commercialised over the next two years, focusing on two core designs: A premium quality ISO design and an optimised EasyLyo product (table 1).

The ISO vials provide a high quality moulded glass RTU option, compliant to ISO 8362-4. The EasyLyo product is a latest generation moulded glass vial that combines chemical and physical strength with superior cosmetic quality, relative to conventional moulded alternatives. The external dimensions of these vials are equivalent to tubular designs of the same volume, while vial weight is around 30% lower than for standard moulded alternatives. Essentially, they combine the strength and resistance to breakage associated with moulded vials with the superior packaging/transport characteristics of a tubular product, advantages that are particularly beneficial for lyophilisation applications. An optimised bottom to aid heat transfer and an ISO 20mm neck finish for secured stoppering answer directly to lyophilisation requirements.

Both types of vials are currently available for use in tray format; nest and tub configurations are currently in development. In a tray format, RTU vials are packaged upside down in trays, with dimensions according to Ompi Ez-fill/R secondary packaging, specified for use with defined filling technology. This configuration offers the benefit of maximising the number of vials in a tray increasing packaging density, thus optimising the throughput of fill and finish operations. Nest and tub is homogenised between all vial formats and with syringes and cartridges to allow adoption of the same handling points in combination lines. Both the tray and nest and tub configurations are designed to completely avoid glass-to-glass contact to preserve the integrity of the product through transportation.

Looking ahead

The growing parenteral market is looking for proven solutions to streamline processing, to focus effort on value added/core activities and to cut production costs, particularly as the structure of the industry changes. With many products now developed and manufactured in collaborative partnership between pharmaceutical companies, biotech start-ups, CROs and CMOs, there is a growing need for flexible processing solutions that facilitate safe and reproducible technology transfer. RTU is a cost-effective, efficient approach for aseptic filling, a safety critical but non-core activity for many organisations with moulded vials essential for many applications. ●

EZ-Fill is a registered trademark of Ompi, Stevanato Group. Sterinity is a brand owned by SGD Pharma.

References:

1. IQVIA MIDAS, Actual 2018 – Global market database covering 93 countries and over four million pharmaceutical packs.
2. FDA guidance for industry: Sterile drug products produced by aseptic processing - Current good manufacturing practice, September 2004.
3. Revision of Annexe 1 'Manufacture of sterile medicinal products', December 2017.
4. USP 40 Physical Tests /<660> Containers – Glass. Available to view at: https://hmc.usp.org/sites/default/files/documents/HMC/GCs-Pdfs/c660.pdf
5. ISO 11135:2014 Sterilisation of health care products – Ethylene oxide – Requirements for the development, validation and routine control of a sterilisation process for medical devices.

About the author:
Carole Grassi is Chief Innovation and Development Officer at SGD Pharma

Further information:
SGD Pharma, Puteaux Cedex, France
tel: +33 1 40 90 36 00
email: marketing@sgdgroup.com
web: www.sgd-pharma.com