Here, Claudia Petersen, Director of Business Development at Gerresheimer Bünde, provides an excellent insight into some of the most significant regulatory, technological, clinical and market trends affecting the parenteral drug delivery industry.

With a share of approximately 27%, injectables were the number two in the US$860 billion (£559 billion) global pharmaceuticals market in 2010, preceded only by oral medication. Double-digit growth rates, mainly triggered by biotech-derived products, and the rise of injectable generics, show that the importance of this segment is still on the rise. Besides prefilled glass syringes vials are still the most common primary packaging containers for modern injectables. However end user requirements and even marketing related reasons have led to a growing market for innovative devices such as safety syringes, pen systems and needle-free or intradermal injectors.

Various glass container systems are traditionally used for the storage of parenterals. All of them are standardised to facilitate processing on automated filling lines. The most common, a selection of which are pictured in Figure 1, include:

- Ampoule DIN EN ISO 9187-1
- Vial DIN EN ISO 8362-1
- Dental Cartridge DIN ISO 11040-1
- Insulin Cartridge DIN ISO 13926-1
- Prefillable Syringe DIN ISO 11040-1

With the exception of ampoules, all glass containers have pharmaceutical rubber closures. The so-called container closure systems (c/c system) are designed to protect the drug product from quality-diminishing environmental influences such as light, moisture and microbial contamination. However, the c/c system is not just a container. Over the product shelf life it also has to ensure that functionality and drug delivery accuracy always comply with the specifications. Available container c/c systems and devices include vials, reconstitution kits, disposable or prefillable syringes, ampoules, auto-injectors and pen systems. Several factors have to be considered when choosing the right c/c system, such as drug product formulation properties, dosage, type of application and end-user friendliness. Examples of drug product formulation-related factors observed especially with prefillable syringes are high metal ion sensitivity and viscosity. A high sensitivity to metal ions may necessitate the use of new alternative primary packaging materials. In the case of high-viscosity syringe systems, features such as needle diameter have to be considered.

Furthermore, the dosage regime can influence device decisions, driven by the type of application, frequency and volume and fixed or variable dose. In connection with end-user friendliness, factors such as the place of application (clinic, home or emergency setting), the length of therapy, the target patient group and the dexterity of the operator have to be considered. It may be necessary to develop different packaging solutions for one product to satisfy different patient group needs.

“In 1997, the European Pharmacopoeia included 19 pages on primary packaging materials”

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So, the offering from the parenteral primary packaging industry is diverse and complex, requiring manufacturers to consider a variety of factors. Not only this, but it is also an industry which has changed significantly in recent years, and will continue to do so. We have identified four of the key trends affecting companies involved in the development and manufacture of primary packaging for parenteral products. They are outlined here.

**TREND 1 – OUTSOURCING OF CLOSURE PRODUCTION STEPS**

A dominant trend in primary packaging is the evolution from simple bulk packaging materials towards ready-to-sterilise (RTS) or even ready-to-use (RTU) primary packaging containers. Process steps in the pharmaceutical production process such as washing, siliconisation and even the sterilisation of container system components are outsourced to suppliers which have to ensure that these processes are qualified and validated in accordance with current global regulatory requirements.

Even when pharmaceutical manufacturers opt for ready-to-sterilise products, they have a significantly lower investment in machinery and qualification/validation. The requirement of washing and siliconising equipment is eliminated and products are supplied with a certified endotoxin, bioburden and particle load. When rubber components and prefilled syringe systems are outsourced, this also includes the necessary siliconisation process.

Ready-to-use (RTU) quality is the next logical step. Pharmaceutical manufacturers outsourcing RTU components can thereby also eliminate the need to invest in sterilisation and the regular revalidation of this process. The sterility and shelf life of the products are certified by the primary packaging supplier.

While prefilled syringe systems are always EtO-sterilised, plunger stoppers undergo mainly gamma irradiation. A validated gamma sterilisation process has to provide a minimum sterility assurance level (SAL) of $10^{-6}$. Dose mapping and setting have to conform to ISO 11137-2. In general, a package transport simulation and integrity validation should be performed on the sterilised goods and an expiration date has to be stated (Figure 2).

Ready-to-fill syringe systems have already been available for many years. In recent years pharmaceutical rubber suppliers have recognised this trend and now offer a broad range of ready-to-use (either gamma or steam-sterilised) rubber components. Glass suppliers have now begun working on RTU glass vials. It remains to be seen whether a packaging standard such as the tub packaging for prefilled syringe systems will be established for vials.

**TREND 2 – INCREASINGLY STRINGENT QUALITY REQUIREMENTS**

Regulatory authorities all over the world are paying greater attention to the use of appropriate primary packaging materials with the consequence that standards have become very comprehensive and detailed. In 1997, the European Pharmacopoeia included 19 pages on primary packaging materials. Fifteen years later the number of pages had nearly tripled to 53. Within the same time frame, regulatory authorities around the globe issued new guidelines dedicated to primary packaging materials such as the Container Closure Guideline published by the US FDA in 1999 and the EMA Guideline on Plastic Immediate Packaging Materials dated 2005. Another example is the DIN ISO standard 15378: “Primary packaging materials for medicinal products – Particular requirements for the application of ISO 9001:2000, with reference to Good Manufacturing Practice (GMP)”, dated 2006.

The primary packaging industry has coped with these increasingly tough regulatory requirements by enlarging quality departments, installing dedicated regulatory affairs officers and intensifying technical support. ISO 15378-compliant production is standard practice nowadays in the European and US primary packaging industry.

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*Figure 1: A selection of the Most Common Glass Containers for Parenterals.*

*Figure 2: Comparison of Bulk versus Ready-to-Fill Prefillable Syringes.*

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Quality requirements for glass containers, which are likely to be tightened further, include specific requirements regarding the particle load, lower rates of cracks or cosmetic defects and smaller dimensional tolerances. Prefillable syringes are associated with specific requirements such as low hold-up volumes and reduced tungsten or siliconisation levels.

The tungsten oxide contamination resulting from the forming process of the bore inside the syringe cone can, for example, be avoided using pins made from other metals in the forming process. No official tungsten limit exists as yet. An upper limit of 500 ppb is under discussion. Superior quality requirements on the cosmetic and dimensional side can be met by improved manufacturing processes, the introduction of comprehensive process control with camera systems and packaging inside clean rooms. Automated visual inspections to check for dimensional and cosmetic defects allow constant sorting performance with high reliability and output.

Inevitable negative side effects are the cost of the equipment and a proper sorting process qualification to avoid an excessive scrap rate due to false rejects. Rubber component suppliers have developed similar visual inspection procedures.

**TRENDS 3 – GROWING SYSTEM COMPLEXITY**

Relentless progress in medical technology, the cost pressure of increasingly expensive healthcare systems and the necessity to operate profitability in a globalised economy all contribute to the complexity of decisions in the primary packaging market. Medical factors which must be taken into consideration include demands for simpler and safer administration and increased dosage accuracy.

Economic factors include the total cost of a system and the retail price of drugs. It is also necessary to consider that developed nations face an aging population which will double the percentage of people aged 60 and over by 2050.

Other factors are demands for optimised production processes or enhanced product value, specific regulatory frameworks or a company’s IP position. There are currently four major factors which are controversial in some respects in the drug delivery device market:

• More standardised, simpler and more robust packaging solutions to address the increasing cost pressure.
• Modern drug delivery systems as means of differentiation from competitors.
• Modern drug delivery systems as a reflection of modern lifestyle.
• New regulatory and legislative requirements such as dose counting for metered dry-powder inhalers and needlestick legislation for injectables to be considered during device development.

In this complex situation, the requirements of the drug product, syringe/container and device are all interlinked which necessitates the close collaboration of all project participants. Pharmaceutical and primary packaging/drug delivery device manufacturers should share their expertise to specify system requirements and achieve a common understanding.

**TRENDS 4 – NEW MATERIALS**

There are a number of reasons why packaging and device suppliers should develop enhanced primary packaging solutions or even use new materials.

New, complex devices may require primary packaging which cannot be made from glass due to the limitations of its technical and material properties. As mentioned previously, modern biopharmaceuticals which are mostly based on large proteins are more likely to interact with traditional c/c system components. Also, biopharmaceuticals are often quite expensive so low overfills and excellent container drainability are essential.

Primary packaging manufacturers are responding to these challenges with new or modified materials. For example, elastomeric components such as plunger or injection stoppers can be coated with fluoropolymers. The FluroTec® closures manufactured by West are partially covered, whilst Duettwyler’s Omniflex closures have a completely coated surface. Acting as a barrier, the coating improves compatibility with drugs and minimises extractables/leachables. This eliminates or drastically reduces the need for additional siliconisation of plunger stoppers for lubrication purposes while maintaining the functionality of the syringe system.

In cases where the technical limitations of glass prevent its use, modern plastics such as cyclic olefins can be a solution. They offer far greater design flexibility, facilitate tighter dimensional tolerances and are more break resistant than glass.

Surface treatments such as ammonium sulphate treatment can be applied to glass containers to minimise sodium ion leaching and a subsequent pH shift. The use of low alkali borosilicate glass, called low extension glass (LEC), has the same effect (Figure 3).

Another approach is based on thin-film technology. Pure silica (SiO2) coatings are applied to the inner surfaces of glass containers. The silica layer acts as a diffusion barrier, preventing interaction of the glass matrix with the drug without impairing compatibility with standard filling lines and sterilisation procedures.

In the past, the high cost and complexity of meeting regulatory requirements discouraged manufacturers from considering materials other than the well-established combination of borosilicate glass and pharmaceutical elastomers. That has now changed and, as new types of drugs with unique properties are entering the market, innovative materials are being scrutinised more closely.

The polymers of choice are cyclic olefin polymers/copolymers (COP/COC) which have some properties comparable with those of glass. Both materials are transparent, durable and solvent-resistant. Cyclic olefins also have some properties which are superior to glass such as higher break resistance, broader pH-range tolerances, and achieve a common understanding.
ance and no leakage of metal ions. One particularly important feature relating to the storage of biotechnological drugs is the excellent drain-ability of cyclic olefin containers which limits the need for excess overfill.

However, cyclic olefins also have some downsides. Compared with glass they are more susceptible to scratching, which requires a special handling on filling lines. Another parameter to consider during primary packaging material selection is the gas and water vapor permeability of cyclic olefins. Compared with other plastics, they have much lower permeation values. Glass, though, is gas impermeable.

Prefillable plastic syringes such as ClearJect™ from Taisei Kako Co Ltd (Osaka, Japan) are manufactured in “lights out” factories. In other words, the entire production process, providing highest injection molding accuracy, is fully automated and takes place inside clean rooms. Camera inspection systems are used for 100% quality control of dimensions, cosmetic defects and other product parameters such as the siliconisation. These syringe systems are gamma-sterilised. They offer the advantage over glass prefilla-ble syringe systems that the tip cap and plunger stopper are made of the same modern latex-free, chlorobutyl-based pharmaceutical elastomer.

OUTLOOK

Present trends indicate that the future of pharmaceutical primary packaging will be characterised by continuous change. Although traditional disposable syringes with vials or ampoules will remain in use, the trend in biopharmaceuticals towards prefillable syringes, auto-injectors and pen systems as well as customised delivery systems will continue. Primary packaging containers will be made from either glass or plastic. Alternative coatings to standard siliconisation are being developed and will gain in importance.

For the primary packaging industry, this means an expanding market for more convenient and easier-to-use injectable products. This trend is closely related to rising demand for complex services that cover more stages in the supply chain. Primary packaging suppliers will assume an increasing number of production steps relating to closure preparation for the fill and finish process. As a result, they will evolve from component providers to system suppliers and product development project partners.

REFERENCES:


ABOUT GERRESHEIMER

Gerresheimer is an internationally leading manufacturer of high-quality specialty products made of glass and plastic for the global pharma and healthcare industry. Its comprehensive portfolio of products extends from pharmaceutical vials to complex drug delivery systems such as syringe systems, insulin pens and inhalers for safe medication dosage and application. Together with its partners, it develops solutions which set standards and have role model status in their respective market sectors.

The Group realises revenues of around €1 billion and has 10,000 employees at 45 locations in Europe, North and South America and Asia. It uses first-rate technologies, convincing innovations and targeted investments to systematically consolidate a strong market position.
Our comprehensive offering: RTF® syringe systems

| High-quality ready-to-fill syringes
| Innovative accessories
| Proprietary baked-on siliconization

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