The parenteral route of drug application has significantly gained in importance over the years. A great number of newly developed drugs, in particular the many new biological molecules such as proteins, pushed this trend as they almost always require application by injection or infusion. New, highly potent drugs have increased the pressure on the pharmaceutical industry to provide safe and efficient delivery systems. One container form that enables parenteral application either through injection or infusion and combines easy administration with safety for the patient as well as the healthcare professional is the prefilled syringe.

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THE RISE OF THE PREFILLED SYRINGE

Prefilled syringes are not a recent development but have actually been in use since World War II. The growth the prefilled syringe market has undergone in recent years, however, is tremendous and unparalleled by anything the sector has seen in the past. For many years the prefilled syringes application system was only chosen for specialty drugs – today the syringe market shows annual growth rates of up to 25% and there is no sign that this development may slow down over the next years. Syringes are now available in many different sizes and a variety of materials, making them an option for a great range of products – liquid and even lyophilized – in various stages of their life cycle.

THE ADVANTAGES

Undeniably, the great popularity of prefilled syringes today has its roots in some essential advantages this container type has over more traditional ones such as vials and ampoules (figure 1). The convenience and safety of the prefilled syringe makes it the preferred choice of healthcare professionals and in the end for the patients themselves. A great number of risky needle-stick injuries can be prevented as prefilled syringes simplify the application of injectables. The time-consuming procedure of transferring the drug product from its original container to a syringe is completely avoided. In emergency situations this can save lives.

Avoiding the transfer of the drug product means also that it can be more accurately dosed in the original container. This means no overfill is required and the valuable drug substance is not wasted – an important factor in times of rapid and continuing rate of growth of the prefilled syringes industry has exceeded the initial expectations of those who were involved in this sector in its early years. In this article, Dr Gerald Hofer, Senior Director of Global Manufacturing at Fresenius Kabi Product Partnering, outlines the advantages of prefilled syringes that drive this growth, and balances them with an examination of the challenges that companies wishing to benefit from employing prefilled syringes will likely have to face. Dr Hofer describes how Fresenius Kabi’s Product Partnering division is well placed to help its partners overcome the challenges and thus realise the benefits that this product presentation and delivery method can bring.

“SOURCING PREFILLED SYRINGES MEANS NOT ONLY PURCHASING AN EMPTY SYRINGE; PREFILLED SYRINGES INCLUDE A VARIETY OF COMPONENTS SUCH AS STOPPERS, PLUNGER RODS, TIP CAPS, AND NEEDLE SHIELDS”

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continuously increasing cost pressure in the public healthcare sector.

Prefilled syringes come ready to use, which guarantees sterility, and labeled, which prevents misidentification and mix-ups which are particularly dangerous when highly potent drugs are in play.

A variety of safety devices can be used in combination with prefilled syringes to make them even safer and minimise the risk of the needle coming into contact with medical personnel. A lot of development is going on in this field accounting for a product range from quite simple solutions to highly sophisticated devices. Safety devices are currently only mandatory in the US, but also in Europe it is becoming more commonplace to include them in prefilled syringe products.

This improvement in the safety of handling prefilled syringe systems, makes them a viable option for home-use products and self-administration. This trend is strongly supported by the increasing availability of self-administration devices such as auto-injectors and pens for use in combination with prefilled syringes.

From a marketing point of view, the use of the prefilled syringe as a container allows pharmaceutical and biotechnology companies to differentiate their drug products from the competition, opening up new opportunities for lifecycle management, not only for newly developed drugs but also for well established products.

During the last few years, innovations in plastic syringes have considerably broadened the possibilities for prefilled syringe products. The use of the previously predominant glass syringes is limited to small volumes of up to 20 ml. Also many highly sensitive drug products are not compatible with glass. Plastic syringes made of COC (cyclic-olefine-copolymer) or COP (cyclic-olefine-polymer) have the advantage that they are as clear as glass and can be used in larger sizes. They are starting to become commercially available from most of the established suppliers in sizes up to 50ml.

**THE CHALLENGES**

The advantages of prefilled syringes seem overwhelming; nevertheless there are also some drawbacks to be taken into consideration when assessing prefilled syringes. For one, prefilled syringes are complex medical devices and as such they are more expensive than simpler container forms. It has to be carefully evaluated whether the higher cost of the container can be compensated by the advantages such as the reduction of waste and product differentiation.

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An issue weightier even than the cost is the strained supply situation. There are only few well established suppliers in the market and due to the current big demand, prefilled syringes are not easily available. Extremely long lead times may have to be taken into account. Sourcing prefilled syringes means not only purchasing an empty syringe; prefilled syringes include a variety of components such as stoppers, plunger rods, tip caps, and needle shields. It is essential to be aware that these components are not equally available.

Prefilled syringes are not only sealed by a stopper but have a second opening closed either by a needle plus needle-shield or a tip-cap. Both the needle-shield and the tip-cap may be made from a material different to that of the stopper.

Testing material compatibility and leachables/extractables studies are far more complex and, with the needle, might even include a metallic component in addition to a variety of plastics and rubbers. Material compatibility may become a huge problem and mean a no-go for your prefilled syringes project. Incompatibilities have, for example, been reported for proteins and residues of Tungsten, the material used for fusing needle and glass. Also, the compatibility of the drug product with the silicone layer that is usually used to maintain break-loose and gliding forces may become an issue.

The good news is that the huge demand of prefilled syringes has pushed the rate of development in recent years, also changing some mechanical parameters. Now different technologies for siliconisation are available and the first syringes without any silicone at all are appearing on the market.

Nevertheless, the material compatibility as well as the functionality of the prefilled syringes has to be verified in addition to the stability of the drug product itself throughout the whole shelf life. The functionality concerns in particular the break-loose force and gliding force parameters; tests for which special equipment and know-how is necessary.

Related to the additional testing required for stability studies are the general regulatory requirements. If a drug is newly developed the situation is quite clear; the prefilled syringe is the primary packaging material and all the relevant data has to be supplied as in the case of a vial, with the additional emphasis also on the syringe functionality.

The situation is different if a variation from a vial to a syringe is planned in order to customise the product or to introduce the innovative container for lifecycle management reasons. In this case the requirements are different for Europe and the US. While in Europe it is recommended to contact the EMEA early on to clarify whether a supplement to the existing dossier is sufficient, the requirements in the US are clearly defined and differ from NDA to ANDA. In the case of an NDA it is possible to file a supplement for the change in container; in the case of an ANDA a new ANDA has to be submitted.

"A PREFILLED SYRINGE IS USUALLY A VERY ATTRACTIVE OPTION. AT THE SAME TIME IT IS A FACT THAT HIGHLY SPECIALISED KNOW-HOW IS NECESSARY FOR THE SUCCESSFUL IMPLEMENTATION OF SUCH A DEVELOPMENT PROJECT"

for all materials and the complete range of sizes. Despite the fact that recent developments in plastic materials have increased the volume range of available syringes significantly, the filling volumes of commercially available empty prefilled syringes are still restricted to a maximum of 50 ml (starting at 0.5 ml).

The strained supply situation is particularly problematic if a prefilled syringe product is still in the development stage and the different containers available are under evaluation. In these cases small quantities are required to produce small-scale trials to test and compare different options without knowing the outcome of such studies. For this purpose a strong relationship to all potential suppliers is an advantage not to be underestimated.

For pharmaceutical manufacturers to implement prefilled syringe technology new equipment is required. At first sight prefilled syringes may appear to be fairly similar to the conventional vial with glass container and plastic stopper, but the prefilled syringe being the primary packaging material adds a lot of complexity to the manufacturing processes and the testing of drug products. Not all stopper materials available for vials are also available for syringes. Prefilled syringes are not only sealed by a stopper but have a second opening closed either by a needle plus needle-shield or a tip-cap. Both the needle-shield and the tip-cap may be made from a material different to that of the stopper.

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Essentially, for parenteral products, the development of a drug in a prefilled syringe is usually a very attractive option. At the same time it is a fact that highly specialised know-how is necessary for the successful implementation of such a development project.

For the pharmaceutical industry specialised in drug development it therefore makes sense to work with a partner who has the required know-how and to choose a contract development/contract manufacturing approach.

Through its Product Partnering division, Fresenius Kabi is able to provide this service, having built up the required expertise in the course of the implementation of the prefilled syringes technology for its own portfolio.

Recently, the Fresenius Kabi facility in Graz, Austria, has been working with well established partners to set up a syringe-filling line laid out aseptically to process plastic and glass syringes with filling quantities ranging from 0.1 to 50ml. At Fresenius Kabi, the prefilled syringes technology teams up with long-standing experience in aseptic filling, preparation of complex aqueous solutions and fat emulsions, in oxygen control and purification technologies such as ultrafiltration and distillation.

The prefilled syringe technology complements a wide range of capabilities that may be of interest for your prefilled syringes development project. Fresenius Kabi Product Partnering may well be your solution to tackle the challenges faced in the world of prefilled syringes.
At Fresenius Kabi Product Partnering we offer over 40 years of experience in the manufacture and development of sterile liquids and medical devices world wide.

As a flexible outsourcing partner we understand all aspects of pharmaceutical projects from bench to product.

We balance the need for a rapid time to market with stringent quality and regulatory compliance.

Challenge us with your requirements - we will provide you with a solution!