Filling the Gap in Parenteral Packaging

Introduction
The primary packaging market for parenteral formulations is dominated by a few established and well-characterised containers. Each container type has a number of benefits and drawbacks, as further outlined in the following sections of this article. When overlaying these pros and cons, a clear gap in parenteral packaging options becomes obvious. Fleximed® is a new parenteral packaging option, designed to fill this gap by addressing the unmet needs centred on ease of use and cost of goods.

Ampoules
Ampoules are available in many different sizes and shapes, and are also made from several materials; however, specifically for parenteral applications, glass is by far the most common material. The main benefit of ampoules is their low cost of goods. Especially in developing economies, the glass ampoule is therefore the most common type of primary packaging for parenteral formulations. Due to the good barrier properties of glass, ampoules provide a high level of protection at minimum cost.

The main disadvantage is user handling, as ampoules have to be cut and broken to be opened, and the drug has to be transferred into a syringe using a transfer needle. In addition to this being a cumbersome procedure, cutting and breaking glass creates small glass particles which may enter into the bloodstream, and if the break is not clean, dangerous glass sharps are generated. Moreover, ampoules are mostly made from thin-walled glass, which easily breaks when dropped. Due to their tall, narrow shape ampoules easily fall over, leading to costly and sometimes dangerous spillage of contents once the ampoule has been opened. Further on, the opening is large, posing a risk of contamination if not handled with utmost care.

Ampoules should thus only be considered as a viable packaging option if cost of goods is the only selection criterion. Ampoules are not ideal if the drug is administered to patients very frequently due to high time-consumption for the care-giver. In case of drugs requiring particular care when handled, such as cytotoxic drugs, ampoules should be ruled out as a primary packaging option altogether.

Crimp Vials
As for ampoules, crimp vials exist in many different sizes. The main difference from ampoules is the rubber septum used to close the vial. This design aspect resolves the main disadvantages of ampoules and in addition allows for multiple administrations from the same container. Cost of goods is higher due to the additional number of components and the thicker glass required, ensuring that the crimp sealing process does not cause the glass to break.

Crimp vials are predominantly made of glass, except for the rubber septum, the latter component leading to more challenging drug compatibility characteristics compared to ampoules. Crimp vials entirely made from plastic are becoming more popular, for parenteral applications plastic vials are predominantly made from cyclic olefin copolymer (COC). This material does, however, not provide the same level of barrier properties as glass, especially for oxygen and water vapour permeation.

The handling procedure for crimp vials is clearly improved compared to ampoules, but still requires numerous steps as the drug has to be transferred into a syringe requiring a dedicated transfer needle. Crimp vials are thus a viable packaging option for many types of drugs. But as for ampoules, the complex handling procedure is a limiting characteristic of this primary packaging option. Crimp vials are therefore a suboptimal choice for drugs administered very frequently and/or to a very large number of patients.

Pre-filled Syringes
Over the last 20 years, the popularity of pre-filled syringes has increased significantly. The main reason for this trend is the substantially higher level of convenience for the user. If equipped with a staked-on needle, a pre-filled syringe requires minimal preparation and can easily be used by care-givers as well as patients themselves. As for crimp vials, pre-filled syringes are to date also mainly made of glass, with COC versions slowly gaining market acceptance. There are, however, also some clear drawbacks of pre-filled syringes, the main ones being comparatively high unit costs, especially for delivery volumes above 2 ml, and the need for silicone lubrication. Also the fact that a rubber plunger is required poses challenges for certain ingredients. And tungsten residues on the inner glass surface have caused some undesirable interactions in the past.

Pre-filled syringes are thus a viable packaging option for drugs which are frequently administered. To compensate for the comparatively high cost of goods, pre-filled syringes are mainly used for high-priced pharmaceutical preparations, and this is especially true for larger delivery volumes. In addition, special attention needs to be paid to compatibility aspects related to rubber materials and silicone oil.

Cartridges
A cartridge is basically a combination of a pre-filled syringe and a crimp vial. The cartridge is typically used for multidose applications, e.g. for administering anaesthetics in dental care and for the self-administration of hormone replacements such as insulin, growth hormone etc. They allow for accurate deliveries of small amounts of liquids (<0.5 ml). As for the other parenteral containers, glass is by far the most widely-used material for the cartridge barrel. Similar to pre-filled syringes, the drawbacks are mainly related to comparatively high unit costs, the need for siliconisation inside the barrel, and compatibility aspects due to the use of rubber components.

Cartridges are thus a viable packaging option for drugs which are frequently administered in small doses and which have a sufficiently high price tag to absorb the higher total cost of goods. As for pre-filled syringes, special attention needs to be paid to compatibility aspects related to rubber materials and silicone oil.
Material Considerations
As already stated in this article, glass is by far the most common material used for parenteral packaging. This is for good reason, as the barrier properties of glass are unmatched by anything else, and the material is inert to a wide range of ingredients. However, besides obvious drawbacks of glass such as the risk for breakage, glass can pose substantial challenges such as delamination e.g. due to acidic pH or protein adsorption for biologic APIs. Therefore polymer-based packaging materials such as COC, COP or PP are becoming more and more widely accepted as primary packaging materials for injectable drugs. However, these materials provide insufficient barrier properties for a large range of sensitive ingredients. And especially for larger containers, the cost of goods is prohibitive for many applications.

Liquid Unstable Drugs
Formulation scientists are confronted with special challenges if drugs are not stable in liquid form over prolonged periods of time. The goal for any new drug must be to achieve liquid stability, as this is always the better option in terms of cost of goods, packaging complexity and logistics, and most of all user handling. However, despite all modern formulation technologies, liquid stability cannot be achieved in many cases. Therefore, the primary packaging should reduce the formulation-related challenges and drawbacks. Unfortunately, to date very few viable primary packaging options exist. In most cases the dry component is filled either as a powder or granulate into a crimp vial, or as a liquid followed by lyophilisation. The liquid components have to be stored in a separate crimp vial, resulting in a particularly complicated and time-consuming handling process. To simplify this process, special add-on devices are available, but these devices are not reducing the actual number of steps but still add further delivery costs. The most convenient option to date are dual-chamber cartridges and syringes, which clearly reduces the number of steps and makes drug delivery almost as easy as for liquid stable drugs. But for many applications, the resulting high total cost of goods is prohibitive, and in addition due to their comparatively large size, dual-chamber cartridges and syringes are rarely used for delivery volumes > 1ml.

Filling the Gap
From the above considerations, it becomes clear that current parenteral packaging options do not fully cover current market needs. The greatest need is apparent for frequently administered drugs which cannot be sold at a sufficiently high price to absorb the costs for a pre-filled syringe. In addition, certain characteristics of drug ingredients can also be problematic with today’s primary container selection, e.g. if ingredients are interacting with silicone lubrication or causing glass to delaminate.

Even more dramatic is the need for suitable packaging options if parenterally administered drugs cannot be formulated as liquids for stability reasons. To date most such drugs are therefore packed in suboptimal primary containers.

To meet this substantial need, the innovative Fleximed® tube has been developed. Fleximed® provides a combination of packaging characteristics which is absolutely unique in the field of parenteral packaging:
- Ease of use: requiring substantially fewer handling steps compared to ampoules and crimp vials; no need of a transfer needle.
- Multi-layer laminates for tailor-made barrier properties.
- Different protein adsorption behaviour compared to glass.
- Packaging does not break when dropped.
- Low cost of goods, especially for larger fill volumes (> 3 ml).
- By adding a frangible middle seam, two or more components can be stored in one tube. State-of-the-art bulk freeze-drying technologies also allow Fleximed® to be used for lyophilised drugs.

The following illustration visualises how Fleximed® completes the cap for parenteral containers when considering the key challenges and demands in the parenteral world.

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