European Journal of Parenteral & Pharmaceutical Sciences 2009; **14**(2): 35

Developments in the packaging of pre-filled syringes

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The pre-filled syringe is an increasingly attractive presentation for both new and established parenteral pharmaceuticals and vaccines. In this article, the author explores how innovative carton packaging solutions can enhance this presentation whilst meeting the stringent requirements of both product protection and environmental sustainability. He analyses recent developments in the packaging of pre-filled syringes for pharmaceutical products and considers trends for the future.

Key words: Pharmaceutical packaging, carton packaging for pre-filled syringes, top-load carton, tamper-evident packaging for pre-filled syringes, packaging machine for top-load cartons, sustainability

Introduction

Bio-tech products are becoming more and more important because of their extraordinary pharmaceutical potential. Even today, 45% of new approvals are for drugs that contain biotechnological components and the market is predicted to grow over the next 5 years at a compounded annual rate of over 10%. This trend will continue to strengthen in the future: in the same period, 200 new approvals in total are expected world wide.[1]

The active ingredients of bio-tech products are frequently too unstable to be incorporated into solid-dose forms (typically tablets or capsules). Well over 90% of these products are therefore packaged as liquids in syringes, vials or ampoules.[2] Since the products are substantially more expensive than other pharmaceuticals, they must be packed as securely as possible. Moreover, many products have to be transported at precisely controlled temperatures. Special "cold-chain logistics" must ensure that a product is maintained at the correct temperature from manufacture through distribution and storage to the point of dispensing.

Most pharmaceutical companies manufacture and deliver their products world wide. The different demands in the respective market and product segments therefore require a highly flexible packaging system that can handle a wide range of different items and at the same time provide optimal product protection. It is also always essential to guarantee efficient, low-cost packaging of small, medium and large lot sizes. Other requirements of a modern packaging system include item and code checks (vision systems), printing and checking of variable data, the shortest possible machine set-up times and compliance with GMP standards.

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The pre-filled syringe

Since its introduction in the mid-1970s, the pre-filled syringe has gained wide acceptance. This acceptance is based upon life-cycle benefits that can be identified as follows:

- The pre-filled syringe is simple for healthcare professionals to handle. The risks of spillage, contamination and ampoule cuts are reduced or eliminated. Furthermore, the potential risks of misidentification or dosage error are reduced.
- The potential risk of needlestick injury, associated with all methods of injection, is greatly reduced by the addition of a safety needle device to the syringe. The availability of such devices enables compliance with current and envisaged legislation.[3,4]
- Self-administration by patients on long-term therapies is practical.
- For the pharmacist, requirements for storage, preparation and ultimate disposal are simplified.
- For the pharmaceutical manufacturer, the pre-filled syringe offers advantages in both marketing and distribution.
- No overfilling of the pre-filled syringe is required. It is filled with less drug substance per dose than a vial or ampoule, thus yielding significant cost savings. As much as 5% of the total batch may be saved in this way, considering usual estimates.

The increasing popularity of pre-filled syringes greatly facilitates the administration of liquid pharmaceutical products by the physician, by nursing personnel or by the patients themselves. In the simplest case, it is necessary only to remove the needle protection before injecting the drug. There is no longer the need to snap open ampoules, with the attendant risk of injury, or for the more complex manipulation

Figure 1. Top-load carton of syringes and needles.

of a vial and syringe. The reduced logistical costs that can be achieved with optimised packaging solutions are another argument in their favour (**Figure 1**).

The requirements of the package

All packages must safeguard the product throughout its route from manufacture to final point of use. The package must also convey sufficient information that the product is used satisfactorily. Each package provides the vital link between manufacturer and consumer; it is an essential component of the product itself.

The pre-filled syringe is an example of a high-value product that must be safeguarded throughout a long shelf-life and yet be readily and accurately used whenever required. The proper selection of the package and the attention to its design will promote the benefits of the product in addition to fulfilling these fundamental functions. The syringe is not viable without a primary package.

The package must enable rapid access to each of the pre-filled syringes it contains. The package must remain intact until the last of the syringes has been removed if that last syringe is to be safeguarded. The printing of the package will clearly present essential product information. Further features may confirm that the syringe is untouched until required for use.

A reclosable package can be retained for subsequent use without difficulty. If the package contains a course of treatment for a single patient, features to assist dosage compliance are appropriate. If the contents are to be used over an extended period, opening features that release only one syringe at a time can assist the user.

Concerning the logistics of distribution, costs are affected by the volume of the package itself. Where the product must be held in a temperature-controlled environment, it is particularly important to adopt a package of minimum volume relative to its contents. Minimising package volume also benefits storage immediately prior to use; for example in a hospital pharmacy (**Figures 2 and 3**).

Focus on packaging costs: paperboard vs PVC

Inevitably, over the last few years, sober economic considerations have put the spotlight on packaging costs and on the packaging industry in general. It can be said that some companies only take the costs of packaging materials into account, whilst others have a more holistic approach, which also encompasses operating and investment costs, personnel, set-up times, the cost of packaging machine format parts and material losses.

A good example is from the Swiss, who have been able to demonstrate cost benefits in terms of the packaging material alone. The NeoTOP solution "wins out" against the polyvinyl chloride (PVC) or polyethylene terephthalate (PET) blister and the attendant end-load carton. The carton is made from a proprietary 315gsm carton board and fastened by hot-melt glue. The key principle is that the more product in the folding box, the greater the cost saving. One of the reasons for this is the low volume of the pack in comparison with the blister.

Figure 2. Top-load carton of single syringe and needle.

Figure 3. Example of a unit top-load carton for outputs of 240 cartons per minute.

One internal study by a Swiss pharmaceutical company has shown that savings of up to 30% in volume are possible using the NeoTOP concept for disposable syringes. If this is applied to the annual production of just one product, it corresponds to a considerable financial saving. If the product then has to be refrigerated until it gets to the patient, a smaller pack offers another major cost advantage.[5]

Additional advantages can be identified. By opening the packaging from the top, the user immediately sees the entire contents. The leaflet or patient information insert can be extracted without any problems, and can be read and replaced. The packaging is suitable for printing additional information on both internal and external panels. Needles or vials can also be integrated into the package without any problems. Evidence of prior opening is provided either by the opening mechanism itself or by means of relevant additional labels; the opening mechanism may offer re-closure if required.

However, looking at packaging costs alone is short-sighted; the greater benefit lies on the machine side – or rather the process side:

- Only one installation instead of a thermoforming machine and a cartoning machine.
- No thermoforming process (with typical heat input of 20kW).
- Fewer personnel required.

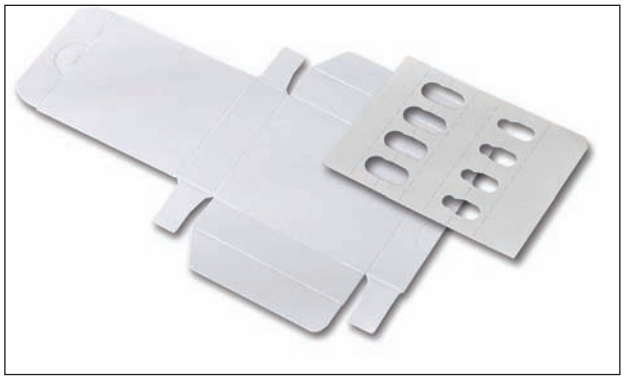

Figure 4. Examples of the flat blanks from which the top-load cartons are formed.

- Set-up in 30 minutes.
- Mono-material packaging independent of changes in the price of oil.
- Higher machine efficiency.
- Flexibility in machine allocation.
- Retrofitting/conversion of installations is practical as a result of the machinery's modular construction.

It is a far-reaching strategic decision by managers in the pharmaceutical industry to opt for mono-material solutions in preference to packages that combine a number of different materials. However, this decision will bring commercial advantages – in the day-to-day packaging process and in terms of greater systems flexibility.

One thing is absolutely clear: switching over existing products packaged in PVC involves considerable effort – this is without question (**Figures 4 and 5**).

Protection from counterfeiting or tampering

The Swiss have been concerned with guaranteeing originality for many years and have introduced the simple expedient of applying a spot of hot-melt glue at critical points on the carton. If the carton has been opened, this is immediately apparent to the user – and it involves virtually no extra machine costs and has no effects on performance.

Biotechnology products in particular are complex to produce and are therefore expensive to manufacture. The risk of these products being counterfeited or manipulated is unfortunately omnipresent and is regularly encountered in some parts of the world. Whether a counterfeit product is used for cancer therapy or for analgesia, the consequences for the patient can be severe.

The co-operation between two Swiss companies, one a specialist folding carton business, the other a security printing specialist, has yielded a solution that can be rapidly implemented on existing packages. An invisible code for the pack, product and information on usage ensures the necessary security – and also allows "Track and Trace".

Other anti-counterfeiting measures include the use of micro-text in the print of the carton or the application of holographic labels. Tamper-proofing may also be

Figure 5. Packaging machine for top-load cartons.

provided by means of label(s) that must be broken to open the carton as well as the glue spot and tear-out panel described above. These methods are already well established, but in the case of the top-load carton can provide evidence that is immediately visible (**Figure 6**).

Energy and environmental considerations

Until recent times, little attention was paid to the energy and environmental aspects of a packaging concept. Especially given the rigours for which a pharmaceutical package must be designed, these issues would take a lesser priority.

Today, it would certainly be inadvisable for a manager in the pharmaceutical industry to try to sweep this topic under the carpet – for the following reasons:

- Energy costs are rising – this variable cost is difficult to predict.
- Production costs (including packaging costs) are clearly a competitive advantage.
- Customers decide whether packaging is environmentally friendly.
- Costs of disposal are rising. Major consumers such as hospitals will exercise pressure.

For example, Germany's Federal Office for the Environment has made available figures that clearly show that merely to manufacture 1kg of PVC in granulate form generates the equivalent of 2.2kg of CO_2 and requires approximately 500 litres of water. Today these figures perhaps do not mean much to us, but in the medium term these values will also become an instrument for regulation of the industry.

It is the case that PET is preferred to PVC in the design of new thermoformed packages. Packages formed from PET are recyclable unless another material is sealed to the PET: an aluminium or a non-woven lidding to a thermoformed tray, for example. A trend in consumer products is to reduce the weight or gauge of packaging materials, especially of plastics. This, however, is generally difficult to achieve for pharmaceutical products where the needs for physical protection over a shelf life often measured in years are paramount and where the design parameters of the package may be registered.

Figure 6. End opening of top-load carton.

It must be stated, however, that there are some circumstances in which a thermoformed package has advantages that outweigh these considerations. A rigid plastic package may be required to contain the spillage of a toxic product in the event of catastrophic damage; a plastic package is particularly suitable for terminal sterilisation and is non-shedding when used in controlled environments.

Sustainability

The goal of sustainable packaging is to reduce environmental impact and the ecological footprint of a product's package. Eco-friendly packaging considerations go well beyond creating a recyclable package. Consideration must also be given to the amount of material used, the type of material, biodegradability, overall package volume and weight reduction to minimise transportation energy, printability of the material to eliminate separate labels, and even the amount of energy required for forming the package.

These "green" considerations are sometimes contrary to the unique needs of parenteral packaging features, including increased product protection, increased billboard space for patient compliance, tamper evidence, and unit dose packaging trends.

A well-designed green parenteral package starts with package material selection. Eco-friendly materials are derived from renewable resources, are easy to recycle, have relatively low energy requirements and are biodegradable.

Paper has the inherent advantage of coming from a renewable resource. Trees are considered a renewable resource because they can be replaced within a human lifetime. Paper is also commonly recycled, and can be directly printed, thus reducing the need for separate labels. Paper packages are formed easily by folding, using less energy than plastic packages, which must be heated before the forming process. Paper board packages are routinely used for cool-chain distribution of pharmaceutical products and indeed they have been successfully tested to temperatures as low as –50°C for short-term storage.[6] The risk of condensation damage to the paper board must be contained by avoiding rapid changes in temperature. The paper board package is not suitable for applications that require terminal sterilisation, for example by ethylene oxide, due to degradation of the material.

Laminated materials, commonly used in packaging, present challenges in recycling. Most must be physically separated before recycling, a process that is not always feasible.

One of the most important aspects of any sustainable package design is overall cost. The reality is that if any package design adds significant expense, it is doomed to failure. Overall cost can include package material (bulk or blanks), labour for forming, as well as shipping costs for inbound material and outbound finished products. Paperboard blanks can be shipped flat to minimise volume for inbound shipping, then formed, glued and filled using automatic machinery. State-of-the-art machinery is

Figure 7. Top-load carton of syringes showing ease of access for impaired users.

capable of erecting cartons, gluing partitions, and filling products at high speeds. Machines with a high degree of flexibility can produce different package formats with quick changeovers and high overall equipment efficiency. This further contributes to sustainability by reducing the overall plant floor space, resulting in less energy required for heating/cooling, and even construction and building materials.

Sustainable packaging is obtained by utilising an engineered approach that addresses the entire packaging and product life cycle, not merely the package itself. Paper-based engineered packages can offer significant advantages in achieving an eco-friendly and a high performance package while providing the least total cost of ownership (**Figure 7**).

Conclusions

We have seen that the pre-filled syringe is of increasing importance because of the range of benefits it confers throughout its life cycle. The packaging needs of the pre-filled syringe are rigorous if it is to perform safely and effectively. The top-load carton more than meets these packaging needs whilst enhancing the benefits of the pre-filled syringe.

The distinguishing advantages are the low volume, the easy handling by the user, the low production costs and the range of features available for information and patient compliance. Furthermore, reduced package volumes reflect in reduced distribution costs within the cool chain. The top-load carton can be produced from automatic packaging machines that provide a compact and integrated GMP solution.

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