New Directions in the Development of Pre-Filled Syringes

By Bob Sharp and Paul Whyte at Future Injection Technologies (FIT) Ltd

An increase in the number of viscous biopharm products reaching the market, plus new requirements for absolute needle safety, is driving the development of novel PFS/auto-injector combination devices.

The past five years have witnessed major growth in the pre-filled syringe (PFS) market as the benefits of increased safety, improved security, accurate dosage and the anti-tampering and counterfeit protection provided by such devices have become widely recognised. From a commercial perspective, PFSs offer franchise protection and marketing differentiation, particularly when delivery route is a key product differentiator; they also represent an important way of adding value to new and existing products.

Syringe manufacturers are reporting exponential growth in PFS demand – a trend that is set to continue, with two thirds of new injectable products and many already on the market being formulated or reformulated in a PFS format.

PFS-BASED AUTO-INJECTORS

Most older drugs are aqueous with a viscosity similar to that of water and are easy to inject. In contrast, the newer biotech-based drugs often have high viscosity, and cannot be easily self-administered due to the high forces required to push a viscous fluid through a fine gauge needle. This has led to the development of auto-injector devices that combine with a PFS to allow the easy administration of such products.

The continued emergence of these new viscous therapies means that the next five years will not only see growth in the use of PFSs, but also in the use of associated auto-injectors and needle-safe devices. These will incorporate or be used in conjunction with a PFS for reasons of safety, reduced cost and increased ease of use by patients.

The most important factors currently driving the market for auto-injectors that incorporate a pre-filled syringe or cartridge can be summarised as follows:

- The viscosity of new biopharm products means that they are impossible to self-administer safely by ordinary injection, making auto-injectors a requirement for this category of injectable therapeutics
- Needle-stick regulatory requirements will require needle-safe devices
- Patients and healthcare providers and funders are increasingly demanding low-cost self-treatment away from the expensive primary healthcare environment, which would also optimise patient-compliance and quality of life
- Certain new compounds need to be delivered at a pre-determined depth in order to be effective, and this is not consistently achievable without an auto-injector
- Auto-injectors that can incorporate a PFS without changing the primary packaging offer a fast, low-cost and low-risk solution, as the drug does not have to be resubmitted for regulatory approval

In fact, we believe that the use of such devices will become mandatory as the regulatory authorities demand auto-injectors that prevent needlestick injury, and healthcare providers demand devices that reduce primary healthcare costs by allowing patients to self-medicate.

REGULATORY REQUIREMENTS

Needlestick regulations, and the moral, financial and legal duty of healthcare providers to protect their staff and third parties, mean that the days of needles and syringes will soon be over. Needle safety has become a priority and this is affecting all facets of healthcare provision.

Major international imperatives are underway to further regulate the requirements of healthcare environments in an attempt to reduce the incidence of needlestick injuries. In the US, 500,000 sharps injuries are reported each year (with probably another 50 per cent going unreported), with similar numbers in Europe. In general, healthcare workers report 0.5 to 3.4 sharps injuries per year. Similarly, patients who self-medicate have voiced concerns over the safety of family members in a home environment where there are unprotected needles.

Figure 1: Auto-injectors

European, US, Australasian and Japanese statutes now exist, and employers or healthcare providers not meeting such requirements expose themselves to punitive financial penalties in this increasingly litigious field. The legal requirements are evolving as more information on the benefits of auto-injectors emerges; in Queensland, Australia, for example, the CHRISP study identified auto-injectors as the single biggest factor in the reduction of such injuries and their use is now mandated where available.

COMMERCIAL FACTORS

New biotech-based drugs – such as monoclonal antibodies and immunomodulators – are revolutionising the treatment of many diseases, offering unparalleled control of symptoms and possibly also the ability to reverse the progression of disease. While biotech-based drugs have been widely used in the treatment of rheumatoid arthritis for 15-20 years, their use is now expanding into areas such as dermatology, gastroenterology and transplantation, and they are soon likely to play a role in many more disease categories. Two thirds of all drugs currently in clinical development are biotech-based, and many pharmaceutical companies have active acquisition programmes for such products. It is predicted that 15 per cent of gross revenue will be attributable to this therapeutic sector by 2012, and while not all of the 1,400 biopharm products in clinical trials will reach market, it is clear to see where the future of medicine lies.

Two thirds of biopharm drugs are already formulated in pre-filled syringes, but administration challenges remain in that many are too viscous to allow self-injection through a narrow gauge needle. Wide-bore needles offer an alternative but are painful for the patient. Imagine a patient with rheumatoid arthritis trying to apply the force and control required to inject drugs as thick as treacle through a fine needle; not only is a high level force and control required, but the needle must be inserted to an exact depth. This example makes the clinical impetus for auto-injectors clear.

Some of the blockbuster biopharm products – for example, in the treatment of rheumatoid arthritis, transplantation, viral disease and endocrine manipulation – will come off patent in 2012, presenting a new opportunity for generic or biosimilar equivalents. For such products, route of administration will be one of the key differentiators in market success – highlighting the value of an auto-injector incorporating a pre-filled syringe.

FINANCIAL BENEFITS

Studies have shown that auto-injectors provide a 95 per cent reduction in injectable drug costs compared with administration of injections by healthcare staff or clinicians based in a primary care setting. Patients, employers, healthcare providers and others have realised the importance of self-treatment in both reducing primary healthcare costs and improving a patient's well-being – not least because patients no longer have to attend hospital to receive their medication. Auto-injectors also optimise drug usage as they reduce

Image: Future Injection Technologies (FIT) Ltd

administration errors and enhance drug compliance, thus lowering the risk of disease complications. In our experience, a comment by one patient sums up the situation: "Not only did the auto-injector probably cost less than the car parking to attend hospital, but I no longer have to take half a day off work once a fortnight".

The recent increased awareness of pandemic management and a realisation that Western healthcare resources could never meet emergency demand for mass treatment have similarly highlighted the benefits and cost-savings of self-treatment. This area too is now incorporating the concept of drug provision in PFS with auto-injection.

THE ROLE OF THE SYRINGE SUPPLIER

Communication between the biopharma company and component supplier early in the life cycle of a product is essential. Errors in compatibility that are not discovered early in the product development life cycle can lead to disastrous complications later on. Areas where potential problems can arise include: elastomer or glass interacting with the drug, potential involvement of extractables and leachables, glass absorption parameters, permeation, gassing, pH changes, air gaps, glide force, flange strength, drug viscosity and needle diameter. All these factors require early clarification at any early stage in the product development life cycle.

Formulation of an injectable product involves complex interactions with syringe components, packaging and the needle manufacturing process; this, together with the need for product tracking and process validation, has led to advances in the synergistic relationship between pharma companies and their supporting suppliers. What a few years ago was a simple supplier-customer relationship is now a partnership in which all parties share responsibility for product safety. For example, glass manufacturers have made huge strides in quality control, syringe-marking, glass consistency and optimisation of manufacture and assembly in order to minimise any structural, chemical or mechanical damage or variances. In the US, pre-filled syringes are considered as medical devices, whereas in Europe they are considered to be a pharmaceutical component. In either situation, the glass and component suppliers share responsibility with pharmaceutical companies for the integrity and performance of a product.

PFS/AUTO-INJECTOR COMBINATIONS

The convergence of PFSs with auto-injectors has raised new issues for syringe manufacturers to consider as differing structural requirements and tolerances will be required. One issue is that most syringes were not designed to cope with the forces required for the injection of viscous drugs. For aqueous drugs, this causes few problems – but for the newer viscous biopharm drugs, huge forces will need to be applied in order to deliver the drug through a fine-bore needle.

The use of auto-injectors for viscous drugs will mandate not only the redesign of syringes and components, but also the revision of quality control processes by responsible syringe manufacturers. Such design parameters specifically concentrate on the absence of structural abnormalities on the finger flanges, reduced variances in the distance beneath the flange to the syringe (so as not to affect the volume of drug delivered by most injectors) and consistencies in front wall thickness that in the majority of auto-injectors can affect the depth of needle insertion and volume of drug delivered. With some of the new biopharm drugs costing £300 per ml, leaving 0.1ml behind in the syringe is not only potentially deleterious for the patient but will also waste £30 worth of drug.

Enhanced partnerships in the early stages of drug development will be required to optimise product performance. Syringe manufacturers, fillers, pharmaceutical companies and auto-injector and other device manufacturers will need to exchange information from an early stage to optimise the safety and efficiency of the drug development process.

THE FUTURE

Earlier designs of auto-injectors were derived from insulin pens or simple tubes with recoil springs. While, historically, these have been adequate for most aqueous products, they now face two key problems:

- New regulations are likely to mandate that leaving needles external to the main body of the device will no longer be permitted, and devices will require full needle protection. Devices with no needle protection or simple plastic needle sheaths will probably be viewed as not complying with regulatory requirements
- The demanding physical characteristics of newer biopharm medicines with regard to viscosity and lyophilisation means that new auto-injector solutions will be required for PFSs

For pharma companies currently marketing products in existing devices, the likely outcome will be an expensive

change of device mid-way through the product life cycle, with all the regulatory hurdles and timelines that this would entail. The message is clear: PFS components need to be matched with the correct injection device at an early stage in the process.

Companies are also having to wake up to the fact that there is limited auto-injector intellectual property available for an expected 1,200 drugs coming to market; with most auto-injector companies currently signing exclusive deals in disease-specific areas, some companies may be left with no available devices for their products. The market has seen a rash of licensing and take-over activity in recent months in the race for the development of auto-injectors with viscous capabilities. Demand for devices with lyophilised capabilities will follow a similar pattern as more vaccine and immunomodulatory drugs come to market.

One new range of auto-injectors (SafeClick™) has been designed to cope with the requirements of viscous drug delivery and lyophilised presentations, while retaining the ability to deliver aqueous drugs. The device incorporates a unique mechanism that was specifically designed from first principles to cope with the potentially huge forces required for the reliable and successful delivery of viscous and lyophilised drugs via an existing PFS with a fine-gauge needle. Key features include the following:

- The novel design prevents syringe breakage as no force is transmitted through the vulnerable glass syringe
- The device is fully automatic and protects the needle inside the rigid tough body of the device before and after injection
- Any drug of any viscosity can be administered to any depth and a version for lyophilised drugs in dual-chamber cartridges is also available
- The correct dose is administered only at the correct needle depth without ejecting drug during the needle insertion process
- The device offers a low-risk and low-cost solution that uses any conventional syringe or cartridge presentation; this is achieved without altering the primary packaging and so minimal regulatory action is required, resulting in a rapid path to market
- Primary healthcare costs can be reduced by up to 95 per cent as patients are able to self-medicate at home; the risk of needle-stick injury is also eliminated, as required by emerging regulations
- The device is designed to be easily assembled using automated pathways and has only five plastic parts – reducing the potential for error and minimising costs

CONCLUSION

With as many as 1,400 potential biopharm drugs expected to be launched by 2012, and with many existing drugs being formulated into auto-injectors for therapeutic and marketing reasons, the market for auto-injector/PFS combination devices looks set for rapid growth. At the same time, new requirements for absolute needle safety and the need for an ever-increasing number of viscous biologics drugs to be injected through finer and finer needles means that commercial success will depend on access to the best auto-injector/PFS combinations.

As production and filling lines are consolidated into dedicated 'one-stop shops' to minimise the number of manufacturing and regulatory steps, it seems clear that they will need to incorporate auto-injector assembly around the pre-filled syringe format in order to produce a market-ready product from one assembly line. This highlights a need at an early stage in the product development process for cooperation between the syringe manufacturer, auto-injector supplier, filler, assembler and pharmaceutical company in order to achieve the development and marketing of commercially successful injectable products.

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