The market for sophisticated self-injection devices really began in 1984 with the introduction of the first insulin pen injector. Pen injectors are essentially sophisticated syringes, which were developed for the reliable and accurate injection of the first wave of biotech molecules, mainly hormone replacement therapies, such as insulin and human growth hormone (hGH).

Today, insulin still dominates the market for self-injection devices, followed by hGH and newer therapies such as fertility treatment (FSH – follicle stimulating hormone) and osteoporosis (PTH – parathyroid hormone) for which pen injection systems have recently been introduced.

The pen injector is a cartridge-based device designed for the frequent (usually daily) manual injection of hormone replacement therapies. These therapies often require weight-based dosing or dose titration and injections are repeated until the cartridge is empty - usually after one or two weeks. The drugs in the multiple-dose cartridges require the use of preservatives, while individual doses are typically 0.5 ml or less in terms of injection volume.

Pen injector patients are accustomed to injecting themselves manually with 29-31G pen needles and the need for automated needle insertion or injection has traditionally been outweighed by the patient's desire for discreet and easy-to-use devices. The market for pen injectors continues to grow significantly (see figure 2) while the whole market for self-injection systems is changing with the increased use of prefilled syringes and auto-injection devices in new therapeutic areas.

**NEW-GENERATION AUTO-INJECTORS: TAKING SELF INJECTION BEYOND PREFILLED SYRINGES**

The market for prefilled syringes continues to grow for the convenient injection of anti-coagulants and a range of biotech products. One area where their convenience is particularly appreciated is by patients who need to self-inject. In this article, Ian Thompson, Manager of Business Development at Ypsomed AG, describes how prefilled syringes are becoming more widespread for self-injection and how Ypsomed has developed and is continuing to perfect auto-injectors to facilitate injections using prefilled syringes in new and existing therapeutic areas.
Auto-injectors, as their name implies, automatically insert the needle and perform the injection, and are usually designed for use with fillable or prefilled syringes. Auto-injectors have been on the market as long as pen injectors but their use until the 1990s was restricted to emergency situations such as epinephrine for treating anaphylactic shock (EpiPen®) where the prime focus was less on a painless delivery of the drug, but rather on simply ensuring that the injection was completed. The first prefilled syringe-based reusable auto-injector was launched in the 1990s by Glaxo for treating migraine (Imigran®/Imitrex®).

Reusable auto-injectors have also been used since the late 1980s for syringe-based hormone replacement therapies and increasingly for newer waves of biotech molecules such as alpha-interferon for treating multiple sclerosis (MS). Some of these drugs are injected daily, but many therapeutics – particularly those for treating autoimmune diseases such as rheumatoid arthritis (RA) and psoriasis – are now injected weekly or less frequently.

Most of these newer therapies involve drugs that do not have a preservative (mono-dose formulations) and comparatively large injection volumes of up to 1 ml. One of the key market changes that has increased the interest in auto-injectors is the development of liquid-stable formulations in prefilled syringes. Other influencing factors are listed in figure 4.

Not only is there more interest in auto-injectors, but their operation and safety features are being improved. Currently marketed auto-injectors do not have complete needle safety as they are generally used with standard prefilled syringes with pre-attached needles. But, in the normal clinical environment, it is the need for needle safety, which has given rise to new safety syringes and other safety devices, which are being fitted to prefilled syringes. Increasingly, patients who self-inject are also concerned about the risks of needle-stick injuries to friends or family in their midst and for the easy and safe disposal of the used product. They look for safety – whether it is a syringe or an auto-injector that they are using.

The first-generation safety syringe devices were “active”, requiring the user to make them safe after injection, whereas the newer “passive” devices automatically provide needle-safety after the injection has been completed. Passive devices not only provide needle-safety but they are injection aids, which make it easier to perform injections.

The passive devices, with their low activation forces, can also be used in conjunction with new-generation reusable auto-injectors. For this reason Ypsomed has teamed up with Safety Syringes, Inc (SSI), based in Carlsbad, California, US, to develop reusable auto-injector technology which is compatible with SSI’s UltraSafe® PassiveTM Delivery System safety technology (figure 5).

The UltraSafe® Delivery System has the advantage that they can be used by healthcare professionals and patients alike and thus only require the drug company to offer a single stock keeping unit (SKU) for both. If the patient is still fearful of performing a manual injection then a compatible reusable auto-injector can be made available. Recent patient studies performed by SSI confirm that in a daily self-injecting MS patient population, approximately 50% use a prefilled syringe on its own and 50%...
The obvious gold standard for auto-injectors – where ease of use and convenience are ‘king’ – is the fully disposable device, where the prefilled syringe is already packaged in the auto-injector (figure 6). The patient only needs to remove the rubber needle cap and press the device against the skin. The device performs the injection and the needle is automatically covered and made safe as the device is removed from the injection site.

Although there has been increased interest in fully disposable auto-injectors, there are none on the market today for use with therapeutic proteins. A key prerequisite is the need for reliability (i.e. a very low incidence of failures), particularly when injecting expensive drugs. Another is that the majority of the injections should be self-administered – healthcare professionals may require needle safety when performing injections, but not a fully disposable auto-injector.

If the injection frequency is greater than weekly the device costs can become a relevant factor, since such auto-injectors consist of more than ten components and cost significantly more than a basic safety syringe. For weekly or less frequent injections the annual costs for the devices become negligible compared with the annual therapy cost.

To summarise, we believe that a “scale of convenience” is being created by prefilled syringes, safety syringes and auto-injectors (see figure 7) with “1” corresponding with the lyophilised drug in a vial and “10” with the fully disposable auto-injector.

A simple prefilled syringe alone can bring much convenience to an injection therapy: this has been well illustrated over the last year following the successful launch by Abbott of Humira® in a prefilled syringe for the treatment of RA. But auto-injectors in combination bring an additional degree of ease-of-use and safety. Therefore, Ypsomed is developing auto-injector platforms that are compatible with increasing levels of convenience which are, in turn, dependent on the drug formulation, the competitive environment, the proportion of patients self-injecting and their specific needs (see figures 8 and 9).

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**Ypsomed Disposable Auto-Injectors**

Main pre-requisites:

- Safety mechanisms: safe activation and locking needle-cover
- Patient feedback: intuitive handling and visual feedback of injection process
- Reliability: injection must be completed every time, very low failure rate required
- Patient population requires close to 100% self-injection
- Costs can be prohibitive: weekly injection or less frequent

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**Patient Considerations**

Main patient considerations regarding self-injection devices

- Lifestyle flexibility, less dependence on healthcare professionals
- Safe, easy and reliable
- Obvious and intuitive handling
- Know that the injection is complete and accurate
- Size, shape and design for use, discreet
- Needle covers to counter needle phobia
- Avoid inadvertent injections or injury
- Safe disposal
- Minimal waste

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### "Scale of convenience"

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lyophilised formulation</td>
</tr>
<tr>
<td>6</td>
<td>Luer syringe</td>
</tr>
<tr>
<td>7</td>
<td>Pre-attached needle syringe</td>
</tr>
<tr>
<td>8</td>
<td>Safety syringe</td>
</tr>
<tr>
<td>9</td>
<td>Reusable auto-injector + safety syringe</td>
</tr>
<tr>
<td>10</td>
<td>Disposable auto-injector</td>
</tr>
</tbody>
</table>

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Figure 6: Ypsomed Disposable Auto-Injector

Figure 7: The “scale of convenience” created by prefilled syringes, safety delivery systems and auto-injectors

Figure 8: Main patient considerations regarding self-injection devices

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Different patients have different needs

- Visual:
  diabetes, elderly patients

- Motor disabilities:
  MS, RA, cancer

- Age issues:
  hGH, osteoporosis

- No handicap:
  psoriasis, allergies

- Short therapy duration:
  lmw-heparin, infertility

- Emergency situations:
  anaphylactic shock, migraine

- Needle issues:
  HCV, aids and 10-15% of all patients

Figure 9: Different patients have different needs

...tion indication-specific patient characteristics. In particular, patient groups with motor disabilities or cognitive impairments are particularly challenged when having to perform self-injections. To minimize the risk of poor compliance dedicated device ergonomics are developed to make the injection process as easy and intuitive as technically possible.

At Ypsomed our injection devices are exclusively customised for our partners based on patent-protected technology. We develop new platforms and work strategically with our partners to customise technical solutions that complement the lifecycle planning for the individual drug product.

The production of sophisticated injection devices requires a deep understanding of the technical design and manufacturing processes. At Ypsomed we have more than 15 years of experience working with state-of-the-art moulding and assembly equipment. Our long-term working relationships with contract fillers and syringe and cartridge suppliers are also key with the development of more disposable devices (combination drug/device products). Ypsomed is therefore ideally positioned to provide pharma and biotech partners with a complete service for the growing demand for both pen and auto-injector systems.

Ypsomed develops and manufactures its custom-made injection pens, compatible pen needles and auto-injectors for a wide range of pharma and biotech partners. All products are developed and manufactured in Switzerland, where internal capabilities include R&D, tool making, injection moulding, clean-room production and assembly facilities. Ypsomed provides not only the marketing and technological expertise, but also the production expertise according to the latest regulatory requirements for both low- and high-volume production. Ypsomed manufactures in FDA-registered facilities, is inspected regularly, and supplies devices approved for all leading markets including the US, Europe and Japan.