In this article, Ian Thompson, Vice-President, Business Development, Delivery Systems, at Ypsomed, focuses on the injection technology landscape for the development and manufacture of pens and auto-injectors, and introduces Ypsomed Delivery Systems’ range of Custom Products.

PHARMA DEVELOPMENT LANDSCAPE FOR INJECTION TECHNOLOGY

The number of new injectables in development and reaching the market continues to increase, as does the demand for the cartridge and syringe-based devices needed for their easy, safe and reliable administration. Over the last 25 years, self-injection devices, pens and auto-injectors have continuously been developed to meet the needs of patients in the key areas of diabetes (insulin / glucagon-like peptide-1 (GLP-1)), growth hormone and other hormone replacement therapies, hepatitis C, multiple sclerosis (MS), cancer treatment, autoimmune diseases and emergency injections for treating anaphylactic shock and migraine.

Many existing injectables are biotech drugs which are being reformulated and improved. Another trend is that biotech cancer therapies that are currently infused are being reformulated to allow subcutaneous self-injection. In addition, self-injectable therapies in new therapeutic areas such as Alzheimer’s and cardiovascular diseases are in development. Some injectable therapies are facing up to competition from substitution technologies; examples include dipeptidyl peptidase 4 (DPP-4) inhibitors versus GLP-1s in diabetes, and oral drugs for treating MS.

PHARMA NEEDS

As self-injection device technology has matured, the drive to customise platform products rather than develop completely new devices has intensified. Due to infrequent dosing or multidose drug presentations, many therapies require nominal device quantities even for relatively large patient populations. Apart from diabetes and certain autoimmune disease treatments, most injectable therapies require no more than several hundred thousands to a few million disposable devices per year. This means that the use of standardised device platforms that can be leveraged across a number of therapies is part of each pharma company’s strategy to maintain quality, minimise risk and reduce costs.

Improvements include liquid-stable formulations, long-acting formulations for less frequent dosing and multidose preserved formulations which help differentiate against generic / bio-similar competition.

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eral awareness of which devices are best to use for which therapies. This combined with cost pressures on big pharma means that they are looking for off-the-shelf solutions which reduce investment during Phase III clinical trials until it is clear that the drug is going to be launched successfully. Pharma companies want to be able to move into the clinic with a device which can be manufactured in the required volume with a minimum of modifications. It is therefore important for device suppliers to leverage platform products and minimise costs based on the use of common tooling, assembly and printing systems throughout the manufacturing process.

DISPOSABLE PREFERRED TO REUSABLE DEVICES

Pens and auto-injectors have reached a high level of patient-friendly functionality and there is a clear trend to disposable devices instead of reusable devices as this provides a higher level of convenience for patients. The main area of demand for reusable devices is for reusable insulin pens in developing markets that are moving away from vials to cartridge-based insulin injections and where disposable pens are not yet affordable.

INSULIN PENS – ESTABLISHED MARKET DRIVER

Currently approximately one billion insulin cartridges are filled each year with half being assembled into disposable pens and the other half used with reusable pens. Most insulin pens today have standard “dial-and-dose” functionality that is well accepted by clinicians, caregivers and patients allowing for easy dose selection and delivery. The key features of dosing up to 60 or 80 insulin units, easy-to-read dose displays, dose correction and clear injection control and feedback are a must for variable dose, multidose pens.

An in-depth understanding of pen gearing mechanisms, material selection and the patent situation is necessary to be able to develop and manufacture both reusable and disposable pens in the large quantities required by insulin manufacturers. The most recent insulin pen development activities have focused on moving from manual geared pens to spring-driven pens that further simplify the injection process for the patient.

Ypsomed Delivery Systems provides a range of state-of-the-art “dial-and-dose” reusable and disposable insulin pens to fulfil market demand in established and developing insulin markets (see Figure 1). The spring-driven reusable ServoPen features an attractive combination of user-oriented design and improved functionality based on a robust lightweight aluminium housing and a spring-assisted injection mechanism. The value reusable Ypsopen Twist is ideal for developing markets and non-insulin therapies where device cost is sensitive. The UnoPen disposable insulin pen has been developed for the new ambitious and fast-growing insulin providers.

PENS FOR OTHER INDICATIONS

Insulin pen technologies are ideally leveraged for use with other hormone-based therapies such as human growth hormone (hGH) and follicle stimulating hormone (FSH) requiring variable dosing. The move to spring-driven injection technology is ideal for patient populations which may have problems injecting themselves with manual geared pen technology such as MS patients or children treated with growth hormone.

AUTO-INJECTOR DEMAND CONTINUES TO INCREASE

While the market for traditional reusable auto-injectors is limited to frequently injected MS therapies and emergency injections for migraine, the market for disposable autoinjectors continues to grow driven by the demand for less-frequently injected drugs such as TNF-inhibitors for the treatment of rheumatoid arthritis (RA), psoriasis and inflammatory bowel disease (IBD). A positive development is also the introduction of needle safety mechanisms for the leading epinephrine emergency auto-injector.

AUTO-INJECTORS BRING REAL PATIENT BENEFITS

The “arms race” to develop full-feature auto-injectors, many of which are button activated, has been largely completed. Pharma companies are now recognising that there are a number of alternative devices in the “scale of convenience” between a bare prefilled syringe and the full-feature auto-injector. In particular, simpler two-step autoinjectors with push-on-skin activation are smaller, very patient friendly, and provide more scope for customisation than their button-activated cousins.

Auto-injectors based on spring mechanisms built inside the plunger rod help to reduce the size of the device. Most devices have good visualisation and clicks to provide the patient with excellent audible and tactile injection feedback. Very important is the need for an automated or patient-controlled dwell time at the end of the injection to ensure that the entire drug volume has been injected.

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Prefilled syringes are now being specified and manufactured for use with disposable auto-injectors. Ideally the syringe should be held on the front syringe shoulder rather than the finger flange as the latter could break. If the syringe has a rigid needle shield with a larger diameter than the syringe this makes assembly into the auto-injector’s syringe holder more difficult, but there are a number of systems available to accommodate this.

A key improvement of the prefillable syringe is the availability of different diameter thin-wall cannulae. By providing a range of needle sizes such as 29G, 27G up to 25G a broad range of drug viscosities can be covered by a standard auto-injector device. This avoids the need to develop bulky devices with high injection forces that require additional spring mechanisms that are external to the plunger rod.

Ypsomed Delivery Systems’ range of “push-on-skin” disposable auto-injectors provide intuitive handling, syringe visualisation and end-of-injection patient feedback. YpsomMate is Ypsomed’s latest 2-step push-on-skin autoinjector with a slim and easily customisable design. Ypsoscope is highly rated by patients for its patient-controlled needle retraction mechanism (see Figure 2).

Variable monodose injections from a cartridge or syringe are sometimes needed to accommodate weight-based dosing or dose titration. In some cases prefilled syringes containing different doses are provided to the patient, but it may be more practical to provide a simple standardised cartridge or syringe-based dosing mechanism that can be used by most patients, such as DuoPen (Figure 3).

Dual-chamber cartridges and compatible injectors designed for the simple reconstitution of lyophilised drug and diluent have been on the market for more than 20 years. Examples include multidose pens for therapies such as hGH and PTH. All insulin pen technologies can be modified to accommodate a dual-chamber cartridge allowing simple reconstitution prior to use.

Today however, the dual-chamber cartridge is more often used for monodose therapies where it is difficult to develop a liquid-stable drug formulation. This requires disposable monodose pen devices which are essentially the equivalent of the disposable auto-injector for dual-chamber cartridges. Monodose dual-chamber-based injectors may include needle safety or, even better, the needle safety is provided by a dedicated safety pen needle.

**HELPING THE PATIENT TO RECONSTITUTE AND INJECT**

Manual twist-motion reconstitution of a dual-chamber cartridge and priming is easy to visualise and easy to perform for patients. Automating these steps may help patients with motor disabilities but this adds complexity and cost to the device. Whether manually or automatically operated, the device must ensure that all the steps are performed in the correct order. Regardless, the device must always be held in the correct position during reconstitution to prevent incomplete mixing or inadvertent expelling of the drug. Injection may be performed manually or automatically depending on the needs of the patient.

Ypsomed Delivery Systems’ LyoTwist family of devices (see Figure 4) all include intuitive and proven manual reconstitution and priming and also provide excellent visualisation of the dual-chamber cartridge. The handling steps can only be performed in a certain order. Needle safety is provided in combination with Clickfine AutoProtect safety pen needles.

**CONCLUSION**

Pen and auto-injector technology is maturing in a market which continues to grow at above average rates. Pharma partners are experiencing increasing cost pressure and are looking for standardised device platforms that can be leveraged across different therapies.

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Ypsomed Delivery Systems offers a complete range of self-injection systems based on proven and patent-protected designs customisable to pharma partner needs. The possibilities of developing new technical solutions to provide safe and reliable injections have not been exhausted, while the correct choice of device relies upon careful selection and close collaboration between the drug manufacturer and the device company.
Go for simplicity.

The 2-step autoinjector

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