The aim of all pharmaceutical treatments is to offer the patient optimum control of their condition with minimal side effects. Delivery devices need to facilitate optimum compliance and ease of administration and dosing via a route that is without pain or inconvenience for the patient. Ideally they should offer minimal administration at widely spaced time periods, and safety and reliability are essential. Devices also need to evolve to meet emerging market driven and regulatory requirements – many first-generation devices are not suitable for these emerging requirements.

**MARKET DRIVERS OF DEVICE DEVELOPMENT**

**Biologics**
Around two thirds of drugs in development are biologics and the optimum delivery route for many is subcutaneous or intramuscular injection with a target delivery volume of 1 ml or less. Delivery of high volumes by infusion is less than ideal as it is costly and clinical attendance by the patients inconvenient. Many formulations are highly viscous due to a high protein concentration in a small volume, and/or lyophilised. Biologics are driving a need for auto-injectors that can deliver high-viscosity and lyophilised formulations.

**Improvement of existing drugs**
Drug levels in the body of many first-generation injectable drugs rapidly decline due to rapid absorption or excretion. For chronic conditions, injections may be required several times a day, possibly for the lifetime of the patient leading to poor compliance, which itself leads to increased complications of the disease.

An emerging trend for existing therapeutics is the development of improvements that alter their physical and chemical characteristics to enhance efficacy, reduce frequency of administration and therefore increase patient compliance. This trend to make existing drugs better is being driven on the one hand by the success of some biologics and the opportunity to improve these therapies (known as “biobetters), and on the other hand by a general lack of productivity in the development of new therapies. The perception of a failure to develop new drugs is reinforced by big pharma’s recent actions such as: cost cutting; the closure or often low-profile relocation of research facilities to lower-cost countries or those with more favourable tax domiciles; a focus on outsourcing drug development and in-licensing; and the creation of pharma’s own venture funds.

**Sustained release & increased drug half-life**
The trend to improve existing drugs is being enabled by new technologies that increase drug half-life and reduce dosing frequency. Strategies include the use of microspheres, suspensions, liposomes, gels, lipophilic solutions, nano-particles and other biodegradable polymeric drug delivery systems. PEG and related technologies for increasing the circulating half-life of proteins are also available. Modified-release parenteral drug products that in general terms alter therapeutic release, absorption or metabolic breakdown are now available. As for biologics, these
technologies create highly viscous and/or lyophilised formulations that, as mentioned, are ideally delivered sc or im in 1 ml volumes or less.

Whilst the effects on the pharmaceutical products of such delivery systems are beyond the scope of this article (the next issue of OndrugDelivery will focus on formulation aspects of injectable drug delivery), in general terms drug designers need to make sure that such carriers allow a linear release profile, although in cases where intermittently raised concentrations are required, a pulsed profile might be preferred. Similarly the pharmaceuticals need to avoid the burst-release phenomenon whereby immediately after injection an excess amount of drug is made available and causes a peak in plasma concentrations. Similarly, drug carriers need to be stable, biodegradable, biocompatible and meet all safety requirements required by the patients and regulators.

EROSION OF ESTABLISHED INJECTABLE MARKETS

While the above factors are creating new opportunities for injectable drug delivery, certain market opportunities are diminishing with the development of new non-injectable routes of administration.

Oral formulations to replace injectable delivery

Oral administrations are now available with coatings and nanotechnologies that offer enhanced gastric and intestinal protection, whilst allowing enhanced release via an enteral route.

Inhaled delivery as an alternative to injection

Metered-dose inhalers similarly can provide administration of many pharmaceuticals via the respiratory epithelium, although there have been problems in recent history with the failure to administer proteins and small peptides successfully via this large membranous area due to the immune and physical rejection of the applied proteins.

Mucosal and transdermal technologies as an injection alternative

In mucosal and transdermal drug delivery, where systemic bioavailability of a drug is limited by its own permeability across the barrier, we have seen the evolution of simple drug patches that elute their drug across the membrane and microneedle arrays which offer micropenetration and may overcome the barrier problems seen with penetration of the stratum corneum by drugs formulated in simple patches.

Microneedle arrays are further developing with the use of pressure pumps (for example generated by the pressure of boiling liquids activated by body temperature), iontophoresis and phonophoresis pumps, and other similar devices that use the electrochemical characteristics of the pharmaceuticals or carriers to help penetrate the epidermis.

Implantation as an injection alternative

New implants are similarly in design and development and offer the possibility of micro-reservoirs or micro-electromechanical pump. In the case of diabetes, for example the ability to offer a synthetic pancreas would be the gold standard treatment for the patients, especially if one could combine an automated glucose monitoring system within the pump to offer a failsafe control of insulin release. Maintaining glucose levels within the normal range would have a dramatic effect on the complications of diabetes seen by most patients.

REDUCING DEVICE DEVELOPMENT COST AND RISK

Injection remains a low-cost and low-risk development route

Parenteral drug delivery by intravenous, sc or im injection offers a route of easy access to the systemic circulation without the first-pass metabolism that affects oral therapeutics. In addition, use of conventional syringes and needles for drug administration is low risk compared with the development of new delivery technologies such as needle-free injectors, micro-infusion pumps or reformulation for solid implantable dosage forms.

Whilst continuous intravenous infusion is used in many clinical situations, it ties the patient to a healthcare environment, is expensive and absorbs huge healthcare resources. An emerging trend is parenteral drug reformulation for injection via the sc or im routes to minimise the frequency, cost and inconvenience of injections.

Prefilled syringes

For the vast majority of parenteral injections, the market is rapidly changing towards prefilled syringes (PFS) as the benefits of increased safety, security, accurate dosing and anti-tampering and counterfeit protection provided by such devices have become widely recognised. An exponential rise in the use of PFS has been witnessed with a doubling of units sold every three to four years. Inevitably as PFSs become the accepted route, auto-injectors that can incorporate PFSs are a natural market evolution.

Reducing device development risk and cost

A low-cost and faster route to market for a new device is to work with the existing drug packaging — that is, the PFS. Needle-free jet injectors and other non-needle dependent technologies may be a viable alternative for some drug categories but they require formulation of the pharmaceutical product at early stage to meet the delivery requirements. Why take this technology development risk when an auto-injector that incorporates existing needles and syringes and can deliver high viscosity and lyophilised formulations will meet your needs?

REGULATORY DRIVERS OF INJECTABLE DEVICE DEVELOPMENT

Needle safety

All devices now need to be needle safe, and emerging requirements are likely to stipulate that the needles need to be inside the main device at the start and end of the injection cycle. This regulation, which will make non-needle-safe devices obsolete, is driven by the approximately one million needle-stick injuries per year in the US and Europe.

COST DRIVERS OF INJECTABLE DEVICE DEVELOPMENT

Growth of auto-injectors incorporating PFS

Auto-injectors have been shown to reduce primary healthcare costs by as much as 95% as being able to send patients home to self-medicate offers huge clinical cost savings to healthcare providers. Patients, the regulators and healthcare providers are now demanding needle-safe auto-injectors. These proprietary auto-injectors also offer pharma companies a way of extending their product lifecycle where ease of delivery is a key market differentiator.

Given that the PFS has become an accepted format and because of the high cost of developing new non-standard needles and syringes it is inevitable that auto-injectors that can work with the existing PFS formats will dominate the market.

EMERGING TECHNICAL CHALLENGES

High viscosity injectable delivery

Many emerging new drugs products are viscous liquids and many show non-Newtonian characteristics during delivery – that is, under pressure, their viscosity increases further and they may even form gels, making them even more difficult to deliver. Patients want painless injections that administer drug as efficiently and painlessly as possible. As discussed, this means that formulations need to be concentrated to minimise the volume required, and delivered by high-quality, fine-gauge needles of a minimum of 25G and preferably 27G or 29G.

However, such physical requirements present challenges for delivery device manufacturers. Concentrating these drugs makes them viscous, and the application of sustained-release technology or PE Gylation to these molecules increases the viscosity of the product still further.
Many existing devices will fail to deliver such highly viscous products safely and may result in failure of the primary container. Devices, such as Future Injection Technologies’ SafeClick™ Visco, are therefore evolving to offer increased force of delivery while utilising existing PFS, allowing higher drug concentrations, lower volumes and a smaller diameter of needle.

DEVELOPMENT STAGE OF PRIMARY PACK SELECTION

Earlier selection of PFS/auto-injector combination

For new biologics drugs, it is becoming clear that the interactions between pharmaceutical products, components of the prefilled syringe and the needle are far more complex than those seen with simple aqueous drugs. The US FDA now holds databases of any interactions and there have been a few notable disasters, where change of, for example, the glue holding the needle to the syringe, or forming techniques in the manufacturing of the needle, have led to failures of batches of pharmaceuticals and regulatory involvement. This is leading to an earlier selection of the drug primary-pack in the development process. Identification at an early stage of a PFS/auto-injector pairing that is compatible with painless high viscosity delivery is important as having to change the PFS at a late stage in the development process can cause high-cost clinical delays and slow development to market.

LYOPHILISED FORMULATIONS

Other parenteral formulations are available, such as lyophilised preparations which require reconstitution with a solvent before injection. Dual-chamber cartridge systems are increasingly being used. Other methods of drug reconstitution involve multi-chamber transference techniques or simple injection of the solvent into the solute, but these is increasingly frowned upon in healthcare due to the risks of needle-stick injury, misdosing, contamination and incomplete or unsuccessful process. Devices are now evolving to allow reconstitution and injection from dual-chamber cartridges to avoid these problems.

CONSOLIDATION – THE DEVICE/FILL FINISH/PHARMA TRIUMVIRATE

Currently the trend is for fill-finish companies gradually to bring all processes under one roof to minimise the risks of a fault in production, such that the drugs will be entirely packaged within one line in a continual process rather than moving from plant to plant. Such logic has led some fill-finish companies to buy in their own drug delivery devices with the added advantage of offering pharma clients an entire solution to their development and fill-finish requirements from early stage drug development to production.

We now see a triangle forming between the pharmaceutical companies in one corner, the fill-finish and packaging companies in another and the drug delivery device organisations in the third. These parties and those associated with them need to work together from an early stage of drug delivery to minimise the risk of disaster at a later stage, which could result in the expense and loss of time of patent protection resulting from alterations required a late stage in any of the processes required to get the product to market. Early-stage co-operation between all parties will allow the drug delivery device companies to optimise the physical requirements of their devices to meet the requirements of the pharmaceutical product and optimise selection of the needle and syringe solution.

THE FUTURE – A REQUIREMENT FOR INCREASED VERSATILITY OF AUTO-INJECTOR PLATFORMS

As the pressures to reduce cost in the industry build, the days of a new auto-injector for every indication are over. Device design has moved to “platform design” and the platform for delivering injections needs to be scalable to incorporate any primary pack as well as requiring many features to meet the emerging demands of the market, regulators and patients.

These platforms that will incorporate existing needles and prefilled syringes will require the following technical features:

- Scalable to accept any “primary pack” (i.e. any needle and any syringe)
- Ability for im and sc administration
- Ability to deliver high-viscosity drugs using existing syringes and via fine-gauge needles
- Option to work with non-siliconised syringes
- Excellent protection of the glass syringes from high “breakout” forces
- Full and automatic needle protection inside the device – no needle shields
- Fully automatic needle insertion and retraction
- Drug delivery only at the correct needle depth
- Lyophilised delivery using dual chamber cartridges
- Needle hidden from sight of user at all times
- Secondary safeties inherent in design – option but not necessary for a button
- Plunge activation option for musculoskelatal impaired e.g. rheumatoid patients
- A viewing window or visual indicator of administration

- Audible “clicks” on initiation and completion
- Low cost – i.e. only 6/7 plastic components, single split moulding
- Amenable for automated assembly

ABOUT THE AUTHORS

Both authors are employed by Future Injection Technologies Limited and are responsible for the development of FIT’s SafeClick auto-injector platform developed for delivery of high viscosity, lyophilised and standard injectable formulations using existing pre-filled syringes.

Bob Sharp is the Medical Director of Future Injection Technologies. A Consultant Orthopaedic Surgeon at the Nuffield Hospital, Oxford, UK, he leads their departmental research team and has a special interest in rheumatological diseases. He has been widely published and his current roles include advising the UK National Institute for Health & Clinical Excellence (NICE) on modern technologies in his field, as well as being Medical Director of the UK Professional Jockeys’ Association. Mr Sharp undertook his medical training at Cambridge University followed by Oxford University. He then completed his orthopaedic training on the Oxford Rotation before completing a Fellowship in Australia. He was awarded the Gold Medal by The Royal College of Surgeons of England for The Most Outstanding Achievement in the FRCS Trauma and Orthopaedics exam in 2000, and was awarded The President’s Travelling Scholarship in 2001.

Paul Whyte is Chief Executive Officer of Future Injection Technologies. He has experience in commercial leadership roles spanning the pharmaceutical, academic and emerging technology environments, from partnering late-stage pharmaceutical products to exploiting innovative emerging products and technologies. Paul was responsible for leading the commercial development and partnering of therapeutic medicines at Evolutese PLC as Director of Business Development and prior to this for partnering the cancer and inflammatory therapies and therapeutic discovery platform at Avidex Ltd (now Medigene). He also spent several years at Cancer Research Technology (CRT) in a commercial role, and was instrumental in forming a joint venture company - Cancer Therapeutics Limited - with Antisoma PLC to develop a late-stage cancer therapy. He has an honours degree from Warwick University, a PhD in Immunology and an MBA.