DELIVERING INJECTABLES:

FORMULATIONS, AUTO-INJECTORS AND NEEDLE-FREE

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"Delivering injectables: formulations, auto-injectors and needle-free"

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During 2008 we will be covering the following topics:

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Front cover image "Hydrated liquid crystal depots in water, FluidCrystal®" reproduced with kind permission from Camurus AB.

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INTRODUCTION

Welcome to ONdrugDelivery's first issue of 2008, and our third publication focusing on the topic "delivering injectables". Inside, I am pleased to present a selection of articles tackling issues from across the range of injectable drug delivery. At the "small" end of the spectrum, we discover advanced nanoparticles which self assemble *in vivo* to form drug carriers. Zooming-out to look at the bigger picture, we explore market trends in the area of advanced injection devices.

From the patient's perspective, needle-based injection is seldom the most attractive route of administration, but it is often the only viable option. There was a period of hopeful optimism during the last decade when scores of non-invasive alternatives were promised; some even seemed to hint at the end of the needle and syringe altogether. In reality, of course, drug delivery has not succeeded in banishing the hypodermic needle to the history books, but it would not be at all fair to suggest that the quest to do so has achieved nothing. Important lessons have been learnt along the way.

Although there is not a needleless alternative for every currently injected product, considerable progress has been made. Numerous technologies offering non-invasive alternatives to injection have been developed and many products using these systems have reached the market.

The nasal route of administration is one which has proven successful at bearing viable alternatives to injections. Although not without its own challenges and problems, nasal delivery has several attributes, including rapid onset of action which is crucial in the context of replacing an injection. Systemic nasal products such as nicotine, sumatriptan, nafarelin and calcitonin, as well as nasal vaccines such as the live influenza vaccine, FluMist, have been launched in recent years, with numerous other products coming through the pipeline.

On page 20 of this issue, Matthias Birkhoff of Pfeiffer (Randolfzell, Germany) comments further on the commercial success that nasal drug delivery has had in offering an alternative to injection. He draws particular attention to lifestyle drugs – a $23 billion global market enjoying double digit annual growth – as an important growth area for nasal products.

An interesting point that Pfeiffer makes is that its devices are Drug Master File supported and all materials used are known and approved by the US FDA. In terms of regulatory scrutiny of material contact, this brings their nasal spray products into the same league as injectable products.

A NEW TAKE ON NEEDLE-FREE

If the example of nasal drug delivery can be linked with realistic product opportunities for alternatives to injection, many people might hold up needle-free injection as an example of a sector that, while chasing attractive dreams, has yet to achieve market success. Personally I have always believed that the needle-free sector has much to offer and that commercial success – although hampered by misfortune and bad press – would eventually arrive.

And then along came a man with an elegant new approach to needle-free injection that decisively changed the question hanging over the commercial success of needle-free injector from an "if" into a "when" and then into a "how soon". His name is Charles Potter, founder and chief executive of Glide Pharma (Abingdon, UK).

I am particularly pleased to present in this issue an article from Glide Pharma. It describes the company's Glide SDI technology which, instead of accelerating a liquid jet across the skin like other needle-free injectors (NFIs), uses a solid dose. With innovative ideas such as this progressing through development, perhaps the needle-free sector will blossom a little sooner than we previously imagined.

NEEDLES ARE STILL NEEDED

We have learnt how better to identify the instances where it really is possible to substitute the needle for a non-invasive delivery system and, as described above, technology is moving on apace. However, crucially, the industry has also learnt to spot those instances where it is not yet possible to avoid injection. This latter point is significant because being realistic about the limits of non-invasive delivery allows proper attention to be given to developing the best possible needle-based injectable delivery systems.

The injectables market continues to expand, particularly with advances in subcutaneous self-injection technology moving injections from the professional clinical setting into the home, and thus edging into the market that non-invasive delivery systems have not been able to fill.

Those involved in developing improved injection delivery systems will be looking in detail at all aspects of the device or the formulation, with the aim of optimising:

- Needle safety
- Comfort
- Cost-effectiveness
- Ease of use
- Manufacturability
- Stability
- Storage
- Frequency of injection
- Applicability across different types of compound
- Applicability across therapeutic categories
- Product differentiation
- IP position

In his article on page 15, Ian Thompson, Head of Business Development at Ypsomed (Burgdorf, Switzerland), gives an excellent overview of factors influencing the injection device market, and the criteria for selecting different types of device, or combinations of device characteristics – pen or auto-injector; standard prefilled syringe or safety-enhanced syringe; dual chamber or single chamber; mono-dose disposable or multi-dose reusable. He describes some of the recent technology developments, such as the emergence of the mono-dose disposable dual chamber injector for lyophilised products.

Turning from devices to injectable formulation technology, Camurus (Lund, Sweden), is developing self assembling lipid liquid crystal and nanoparticle systems which overcome some of the limitations commonly encountered by formulation approaches such as liposomes, emulsions and micro-emulsions. A summary of the advantages of self assembling lipid liquid crystal formulations – in terms of patient benefits, pharmaceutical benefits and technical/commercial benefits – can be found in the boxed text on page nine.

One fascinating characteristic of the systems Camurus is developing stems from the fact that they self assemble *in vivo* on contact with aqueous fluid inside the body. This means that the single formulation can exist in effect in two different conformations – pre-delivery and post-delivery. Thus the formulation can be designed optimally to fulfil the requirements on it before delivery (storage, high drug payload, no need to re-constitute, low viscosity etc). Then, once inside the body the pre-delivery requirements no longer apply, so the formulation can change its structure and related functional properties for the optimal timed and/or targeted *in vivo* drug release profile.

From needle-based injection devices and formulations to needle-free and nasal alternatives, I hope that this publication provides you with an interesting and informative insight into the world of injectable drug delivery.

Our next injectables-related publication is out in April 2008 and focuses in on the topic of prefilled syringes.

Guy Furness
Publisher

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LIPID SELF-ASSEMBLY IN DRUG DELIVERY:

PRETTY STRUCTURES AND A SERIOUSLY HANDSOME COMMERCIAL PROPOSITION

Here, Fredrik Joabsson, PhD, Director, Drug Delivery Systems, Technical Business Development, and Fredrik Tiberg, PhD, President and CEO, both of Camurus AB, describe a novel type of self assembling lipid structures – liquid crystal gels and their corresponding nanoparticles – which overcome the problems associated with previously used lipid-based, self-assembling structures such as micro-emulsions and liposomes.

Camurus was founded in 1991 by scientists pioneering the discovery and characterisation of self-assembling lipid structures. The potential such structures had in drug delivery was clear and had been demonstrated by several products which, using such systems, had achieved market success. Examples include Novartis's Sandimmun Neoral® (a micro-emulsion); AstraZeneca's Diprivan® (an emulsion); and J&J's Doxil® (which uses Alza's STEALTH® liposome technology).

However, it was also apparent that many formulation technologies based on simple lipid self-assembly structures, such as the commonly used micelle, micro-emulsion, emulsion and liposome systems, had limited applicability for numerous reasons.

Use of micellar and emulsion systems is basically limited to the handling of solubility issues of sparingly water-soluble substances, and they are sometimes associated with limitations in local and systemic tolerability. Liposomes are used to load and encapsulate water-soluble compounds. However, high encapsulation efficiencies typically require active loading by use of, for example, pH gradients, limiting their applicability to charged water-soluble compounds. Moreover, the preparation, scale-up, manufacturing, and storage is in many cases hampered by an inherent physical instability.

High manufacturing and excipient costs are also potential hindrances for the use of liposomal drug delivery systems, as is their limited ability to slow down and control the release of active agents in sustained-release applications. The latter fact is due to the single bilayer barrier of more physically stable unilamellar liposomes (compared with multilamellar liposomes).

In light of these drawbacks, Camurus began developing a number of novel structures – lipid-based, self-assembling liquid crystal gels of interconnected non-lamellar cubic, hexagonal, sponge (denoted L_3), and discrete micellar cubic phases and their corresponding nanoparticles.

LIPID LIQUID CRYSTALS

Lipid liquid crystals are well-defined three-dimensional structures comprised of coexisting lipophilic and hydrophilic nanodomains that can be either interconnected or isolated depending on the phase structure.

As shown in figure 1, lipid liquid crystals self assemble to form complex and very beautiful natural structures. Yet what these structures can actually do represents something far more interesting and attractive than their mere appearance.

Lipid liquid crystals offer a unique means of solubilising, encapsulating, and transporting active pharmaceutical ingredients (APIs), including small molecules, peptides and proteins. Importantly these structures also offer a means to control their release in the body and to protect sensitive molecules from degradation *in vivo*.

Most pharmaceuticals have a therapeutic window, below which they are essentially not effective and above which they may be toxic. By using transport facilitating and/or controlled release drug-delivery systems it is possible to develop new therapies that otherwise would be ineffective or potentially toxic to the patient.

Examples of current drug delivery chal-

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lenges and opportunities addressed by lipid liquid crystals are:

- Continuous delivery of peptide and protein therapeutics by use of biocompatible eroding depots
- Delivery to and targeting of cancer cells with e.g. cytotoxic agents
- Lipid-mediated cellular delivery of RNA therapeutics
- High drug load requirements of sparingly soluble or amphiphilic drugs
- Stability enhancement – enabling of new therapeutic products

Aside from facilitating development of new therapeutic products, many existing products have suboptimal properties which can be improved by exploiting the inherent delivery properties of lipid-based systems. Such improvements include increasing patient convenience and compliance, reducing side-effects, and improving efficacy.

The broad solubilisation and encapsulation spectrum together with high drug payloads, as well as the ability to protect sensitive substances like peptides and proteins, and facilitate absorption, make lipid liquid crystals all the more interesting and attractive alternatives to simple lipid carriers.

Similar to micro-emulsions, emulsions and liposomes, they can be designed to self-disperse into colloidal particles. This property is essential in many applications where the delivery system should have a carrier function and where water-free liquid or powder pre-concentrates are the desired dosage forms.

Camurus' liquid crystal-based technologies are applicable in oral, topical and parenteral drug delivery. The lipid liquid crystal gel technology is known as FluidCrystal® and the nanoparticle systems are known as FluidCrystal® NP, featuring Cubosome®, Hexosome®, and Flexosome® nanoparticle carriers.

Within the injectables field, there are two principle uses, one for each of the two systems:

1. FluidCrystal® is applied in the formulation of depot injection products for subcutaneous, intramuscular and intracavital administration.
2. FluidCrystal® NP is applied in the formulation of intravenous (IV) products

FLUIDCRYSTAL® FOR DEPOT INJECTIONS

One key feature differentiating FluidCrystal® from other formulation systems such as microspheres and liposome foam structures is that the structure of the lipid liquid crystal drug carrier matrix self assembles *in vivo*.

Be it in a prefilled syringe or vial, the product is presented as a simple non-aqueous

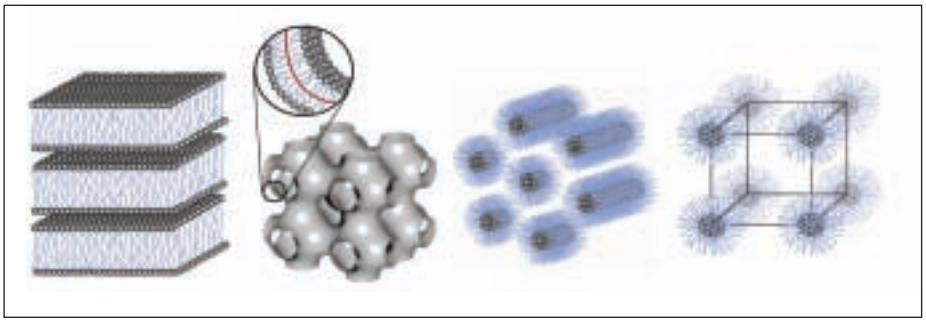

Figure 1: Schematic representation of nanostructured lipid liquid crystals formed in water or aqueous body fluids. From left to right: lamellar phase Lα; bicontinuous cubic phase Q_{II}; reversed hexagonal phase H_{II}; reversed cubic micellar phase I_2.

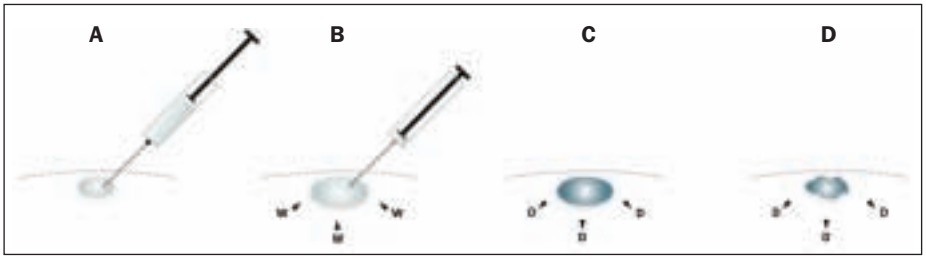

Figure 2. Schematic illustration of the evolution of the FluidCrystal depot illustrating the A) injection, B) hydration and aqueous self assembly, C) release, and D) biodegradation phases.

liquid pre-concentrate. Only after injection, *in situ* on contact with minute quantities of aqueous fluid, does the inactive precursor transform into the active delivery system – a controlled release liquid crystal matrix (see figure 2). FluidCrystal® products are thus precursors to the to the *in vivo* active liquid crystal delivery systems.

So, pre-injection, the formulation has a different structure to that which it has after it has been administered. This brings several unique advantages because, clearly, before injection a formulation actually needs to fulfil very different functions to those it must fulfil after injection.

FluidCrystal® in effect allows one single formulation to inhabit two structural identities each suited to the different functional requirements pre and post administration.

PRE INJECTION:

Manufacturing of products based on Camurus depot technology involves just a few standard pharmaceutical processing steps. Poor drug stability and complex processing requirements are avoided because encapsulation of the drug in the nanopores of the liquid crystal phase structure does not take place until after injection.

Products are ready to inject, without the need for complicating reconstitution and mixing steps, thus making them ideal for prefilled syringes. The low viscosity of our injectable formulations permits the use of thin needles – 23-25 gauge is standard – so there is less pain on injection compared with most conventional microparticle depots typically requiring 19-21 gauge needles. Moreover, the high solubilisation capacity of FluidCrystal® with drug payloads of

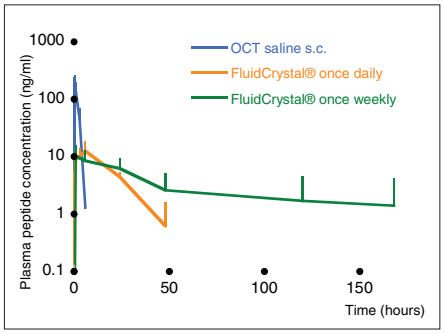

Figure 3: Pharmacokinetic profiles demonstrating 24 hours and 1 week release duration of octreotide (OCT) from subcutaneous FluidCrystal® injections in rats.

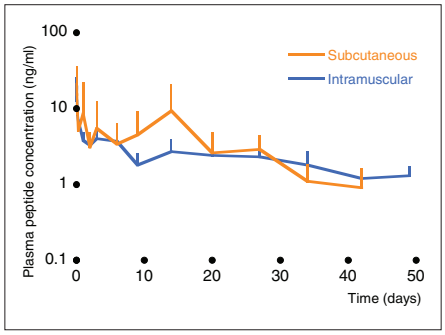

Figure 4: Long-acting release of octreotide from subcutaneous and intramuscular FluidCrystal® injections in dogs.

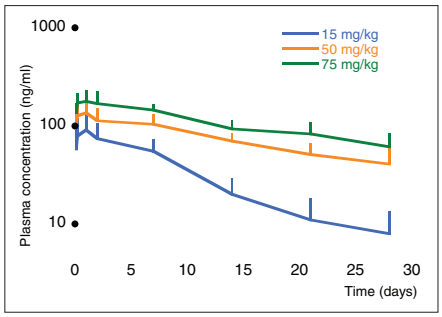

Figure 5: Long-acting release of buprenorphine from subcutaneous FluidCrystal® injections in rats.

up to 30% allows smaller injection volumes.

Combined with excellent stability with many active agents, the FluidCrystal® delivery system represents an integrated solution to classical formulation challenges encountered in the development of new injectable drug products.

POST INJECTION:

Once inside the body, the nanoscale matrices spontaneously form to create protective "cages" around delicate therapeutic molecules with coexisting hydrophilic and hydrophobic domains. Proteins and peptides are stabilised in the nanostructured lipid membrane environment and are protected from degradation by endogenous enzymes, thus providing improved bioavailability and prolonged "effective" half-lives.

Rapid structure formation means that FluidCrystal® avoids the common side effects associated with high initial plasma levels from rapid drug release on injection (drug burst).

Thanks to the interior nanostructure, comprising both hydrophilic and lipophilic domains forming discrete (mono-) or bi-continuous networks, the liquid crystal depot system is capable of providing in vivo sustained release of a wide range of therapeutic agents over controlled periods of time, as exemplified in figures 3, 4 and 5.

Importantly the connectivity of the aqueous domains can be changed, for example, from

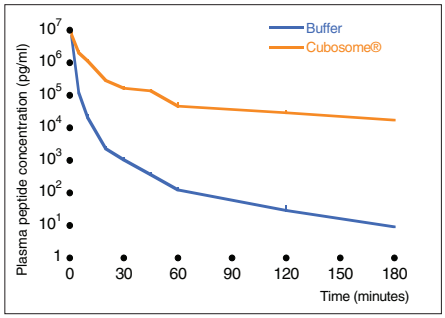

Figure 7: Plasma profiles following IV bolus injections of a GLP-1 buffer solution and a GLP-1 Cubosome® formulation showing extended in vivo circulation.

the interconnected network of aqueous and oily domains in the bicontinuous to the discrete water domains of the reverse cubic phase schematically depicted in figure 1. Thus, this offers one way of controlling release properties. Further fine tuning of *in vitro* and *in vivo* release rates is achieved by including lipid components that facilitate fragmentation (faster erosion) and degradation of the depot or that specifically interact with the active agent.

The main mechanism of drug release from the depot is the continuous biodegradation of the depot locally at the site of injection. Extensive toxicological, local tolerance, and biodegradation data in different animal species is available to support the safe use of FluidCrystal® depot and its individual lipid components.

PRODUCTS UNDER DEVELOPMENT

FluidCrystal® is by no means just a technology concept. On the contrary, one product – a dental gel using FluidCrystal® – is on the market for the treatment of periodontitis, and pharmaceutical projects are under development both in-house and in collaboration with partners. Non-limiting examples of active agents where desired sustained-release properties of the FluidCrystal® delivery system has been proven include: small molecules, such as testosterone derivatives and opiates; multiple peptide agents including, octreotide, leuprolide, somatostatin, salmon calcitonin, GLP-1 and analogues; and several therapeutic proteins.

Two injectable products are currently in clinical development, including CAM2032, a long-acting LHRH agonist for the treatment of prostate cancer. In May 2007, it entered a Phase I/II single-dose, dose-escalating, open-label, multicentre, cohort trial in 24 male patients with advanced/metastatic prostate cancer, to determine the leuprolide drug serum profile and the serum testosterone suppressing effects after a single subcutaneous administration of three different doses. Assessment of safety was a further key objective.

Another clinical-stage product is CAM2029, a long-acting formulation of octreotide, for the treatment of acromegaly, carcinoid syndrome and vasoactive intestinal peptide (VIP)-producing tumours

In a recent double-blind, randomized, parallel-group, placebo-controlled Phase I trial for the assessment of safety, pharmacokinetics and pharmacodynamics, 32 healthy volunteers received single-dose injections of three subcutaneous doses and one intramuscular dose of CAM2029 and the corresponding placebo FluidCrystal® formulations.

The local tolerability at the injection sites was very good. Systemic safety was also good with adverse events being limited to transient gastrointestinal side-effects related to octreotide itself.

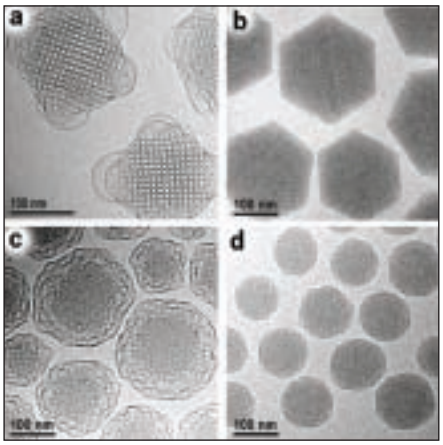

Figure 6: High-resolution cryo-transmission microscopy images of FluidCrystal® NP: a) Cubosome®, b) Hexosome®, c) Flexosome®, and d) Cubosome® (I_2).

CAM2029 was furthermore found to provide long-acting release of octreotide resulting in a statistically significant suppression of the clinical biomarker insulin-like growth factor 1 (IGF-1) over the target one-month therapeutic period.

Crucially, FluidCrystal® has enhanced the formulation characteristics so that it has a number of key advantages over microparticle depot products:

1 It can be administered subcutaneously, as well as intramuscularly, with similar pharmacokinetic profiles (see figure 4)
2 It provides immediate onset of release without the lag phase typically observed for the microparticle systems
3 It is presented as a ready-to-use formulation without the need for premixing or reconstitution and is compatible with prefilled syringes
4 The high drug loads and liquid nature of the FluidCrystal® products allows for small-volume injections using thin needles
5 Product manufacturing is simplified, involving only standard pharmaceutical processes

FLUIDCRYSTAL NP® FOR IV INJECTIONS

Micelles and oil-in-water (o/w) emulsions have traditionally been used extensively in parenteral formulations, using relatively mild surfactants or lipids, such as polysorbates, cremophors, egg lecithin, and soybean oil. Examples of drugs intended for IV administration, utilising micelles and o/w emulsions as solubilisation aids, include Taxol® (paclitaxel, Bristol-Myers Squibb), which takes advantage of Cremophore micelles, and Diprivan® (propofol, AstraZeneca), which is an o/w emulsion stabilised by lecithin.

Conventional o/w emulsions are best adapted for strongly lipophilic drugs that require an oil

medium for optimal solubilisation. In contrast, amphiphilic drugs – and in particular peptides and proteins – are often less compatible with emulsion systems.

More recently, liquid crystalline nanoparticles of cubic, hexagonal and "sponge" phases, denoted Cubosome®, Hexosome®, and Flexosome®, respectively, have emerged as potential new functional carriers for future drug products (see figure 6). Camurus has a robust intellectual property estate surrounding these particles and their use as drug delivery carriers. Cubosome® and Flexosome® nanoparticles of the cubic and "sponge" phases, respectively, are being used in different development products intended for injectable applications, in particular for IV products.

Especially noteworthy is the nanostructured interior of the particles, featuring both hydrophilic (aqueous) and lipophilic (lipid) domains. In contrast to liposomes, which consist mostly of water even for relatively small liposome radii, the lipid content of typical liquid crystal nanoparticles is high (normally in the range of 50-80 wt%). Because of coexisting hydrophilic and lipophilic domains and an enormous surface area of several hundred square metres per gram, the FluidCrystal® NP carriers have a broad spectrum of applicability, comprising lipophilic and amphiphilic bioactive agents, and peptide and protein drugs.

The key functionalities are:

1 Encapsulation vehicle for aqueous soluble compounds, including peptides and proteins, offering protection against degradation
2 Exceptional solubilising and carrying capacity of sparingly soluble and amphiphilic drug compounds
3 Controlled release facilitating reduced exposure to toxic compounds, potentially eliminating the need for slow infusion administration
4 Extended circulation and optionally active targeting by surface functionalisation

Proteins and peptides may be encapsulated in the nanostructured interior of the particles and thereby protected from rapid in vivo degradation, by endogenous enzymes for example. This feature is exemplified in figure 7, where glucagon-like peptide-1 is administered intravenously formulated in a Cubosome® nanoparticle solution. The peptide is effectively stabilised by the Cubosome® nanoparticles.

The high solubilising and carrying capacity is another attractive feature of the FluidCrystal® NP system (see figure 8). The favourable safety profile compared with, for example Cremophore and Polysorbate micellar systems, further emphasises its potential applications as a carrier for sparingly soluble compounds in injectable applications.

WORKING WITH CAMURUS

With the unique FluidCrystal® controlled release system and FluidCrystal® NP carrier, Camurus offers documented solutions to many of the key development and market issues facing the biotech and pharmaceutical industry today; be it the need to revitalise marketed products by improving patient convenience or compliance, or finding an effective means of alleviating technical and biological hurdles encountered in the development of a new small molecule, peptide or protein.

Each new collaboration project starts with a thorough desk evaluation based on our discussions with our partner's development team. The evaluation comprises a detailed examination of the problem, the desired outcome, and the project timing.

The next step following establishment of a collaboration agreement is often a feasibility study in which the formulation product concept is assessed in relation to a target product profile. The endpoint of the study is typically a preclinical proof-of-principle study, for example a pharmacokinetic or pharmacodynamic investigation, which could be performed by Camurus, its partner, or a CRO of its choice. The study duration from agreement to final report generally ranges between two and six months.

At this stage the transition to full development and preparation for clinical trial occurs. Camurus will at this point take different roles depending on the partner preference and resources: performing straightforward tech-transfer or continuing actively to support development up to and beyond initial clinical trials.

A collaboration may start under a simple feasibility study agreement or a formalised option license agreement depending on study objectives and mutual preferences. With more than ten ongoing collaborations Camurus has extensive experience of managing and driving collaborations from both a business and project development perspective.

EXPANDING PIPELINE OF IN-HOUSE PRODUCTS

Camurus has a growing in-house product pipeline. It investigates the use of its proprietary drug delivery systems in the development of value-added formulations of selected generic drugs and products nearing patent expiry.

After successful proof-of-concept, which is usually a Phase I pharmacokinetic study, these products are available for licensing to companies with clinical R&D capability and strong sales and marketing operations globally or in relevant market segments.

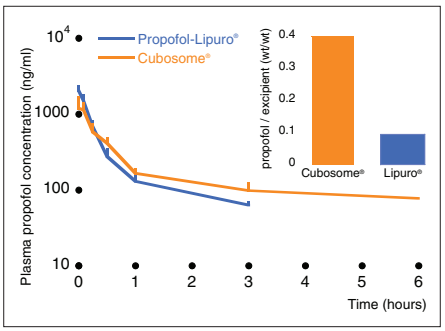

Figure 8: Plasma concentration after IV bolus injection of Propofol-Lipuro and a propofol Cubosome® formulation to rats. The insert shows the difference in drug load between the two systems.

SUMMARY

In summary, Camurus presents an attractive business proposition with:

- An advancing clinical drug product pipeline
- Innovative nanoscale drug delivery systems
- Strong strategic partnerships in place:
  - >10 projects
  - Feasibility studies & co-developments
  - Five with top-ten pharma companies
- Near-term clinical milestones
- Growing revenue stream
- Great teams

BENEFITS OF LIPID LIQUID CRYSTALS: A SUMMARY

Patient/clinical value

- Increased convenience and compliance
- Improved efficacy
- Decreased side effects
- Decreased health care costs due to simplified handling and less frequent administration
- Decreased risks of drug misuse and misdirection

Pharmaceutical value

- Means of solubilising, encapsulating, and transporting APIs
- Broadly applicable (to small molecules, nucleotides, peptides and proteins)
- High drug loading
- Allows true controlled release
- Stability enhancement (improved shelf-life and/or in vivo stability)
- Allows targeting (e.g. of cancer drugs)

Technical/commercial value

- Already proven safe and effective in the clinic
- Extends patent-life
- Attractive ROI
- Enabling technology for the development of NCEs/NBEs
- Scaleable and transferable process

Easy, solid dose injection of therapeutics and vaccines

Glide SDI™ - the Solid Dose Injector

- Very simple to use
- Small, handheld, spring-powered device
- Solid, stable dosage form
- Needle-free
- Preferred to a needle and syringe
- Cost-effective
- Patent protected

Applications include:

Vaccines:
Industrialized countries, developing nations and emergency use

Biologicals:
Proteins and peptides for self-administration

Small molecules:
Needle-free alternative for injectable generics and originator products

Glide Pharma

Delivering Solid Solutions™

www.glidepharma.com

SOLID DOSE INJECTION OF THERAPEUTICS AND VACCINES:

EFFECTIVE, CONVENIENT AND COST-EFFECTIVE ALTERNATIVE TO NEEDLES

The majority of injection devices available – both needle-based and needle-free – deliver the formulation in a liquid form. Needles penetrate the skin creating a hollow channel through which the liquid passes, and needle-free systems force a jet of liquid or powder through the skin. Both of these systems have their own sets of drawbacks. Here, Dr Simon Bennett, Business Development Director at Glide Pharma, and the company's Chief Executive Officer, Dr Charles Potter, present something different – Glide SDI™, a unique needle-free system that delivers a solid dose through the skin.

Why the continued interest in needle-free injection delivery? Most obviously, patients do not like needles. However, a number of therapeutics and vaccines cannot be delivered orally, and neither nasal nor transdermal delivery are not viable options for many applications. Injection is the only suitable delivery route. Combine this with the introduction of stricter regulations – particularly in the USA – to avoid needle-stick injuries, and the need for safe, reliable yet cost-effective alternatives to the traditional needle and syringe becomes self-evident.

Even though the first needle-free injection technology was presented over 150 years ago it has only been in the past two decades that significant technology advances have appeared. Major investment in research and development led to a first wave of liquid jet and powder delivery technologies, which stimulated interest but failed to convince the industry for a variety of reasons. Having learned these lessons, Glide Pharma is now leading the next wave with its new approach.

GLIDE SDI™ – PUSHING SOLID DOSES

What makes the Glide SDI™ so different is that Glide Pharma has solved the problem of how to inject a solid dose accurately. It has done so by making the dose itself the delivery vehicle. Thus, a solid dosage in the form of a tiny rod with a pointed end is pushed into the skin using a spring-loaded, handheld actuator which resembles a pen (see figure 1). With minimal sensation, the dosage pierces and penetrates the skin in a fraction of a second and the simple click tells the patient that the drug

Figure 1: Glide SDI™ - the Solid Dose Injector. Using the Glide SDI™ system, the solid dosage form penetrates the skin using a simple, spring-powered, handheld actuator

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Application	Key Benefits of the Glide SDI™ system	Examples
Vaccines	• Enhanced stability (no cold chain requirement) • Potential for prime and boost in one injection • Better compliance (preferred to needle and syringe) • Easy to use delivery system	Seasonal and pandemic flu, hepatitis B, HPV, malaria, anthrax, small pox, West Nile virus, Ebola etc.
Biologics	• Easy self injection • Needle-free administration • Enhanced stability • Better compliance	Interferon alpha & beta, FSH, insulin, PTH, glucagon, hGH, EPO, GLP-1 etc.
Small molecules and peptides	• Easy self injection • Needle-free administration • Product differentiation • Bioequivalence development strategy	Sumatriptan, octreotide, fentanyl, epinephrine etc.

Figure 2: Market opportunities. The Glide SDI™ system offers a wide range of market opportunities in small molecules and peptides, biologics and vaccines.

has been delivered. The dosage subsequently dissolves or degrades releasing the drug or vaccine at the desired rate.

provide immediate and/or sustained release of the drug to achieve the desired release kinetics in the systemic circulation or, in the case of vaccines, to stimulate immune response.

"GLIDE PHARMA HAS SOLVED THE PROBLEM OF HOW TO INJECT A SOLID DOSE ACCURATELY … BY MAKING THE DOSE ITSELF THE DELIVERY VEHICLE."

The Glide dosage comprises the active drug (or vaccine) mixed with excipients. The formulation may contain one or more active drug components and the excipients are selected to

The Glide SDI™ is primed by pushing the end of the drug cassette against the skin. This action compresses the main driving spring of the actuator and, when the preset spring force is achieved, the Glide SDI™ automatically actuates and pushes the drug from the drug cassette into the skin. The pushing action is important because it means that the drug is delivered in a controlled manner to the same depth in the skin every time, regardless of the skin type or area of injection.

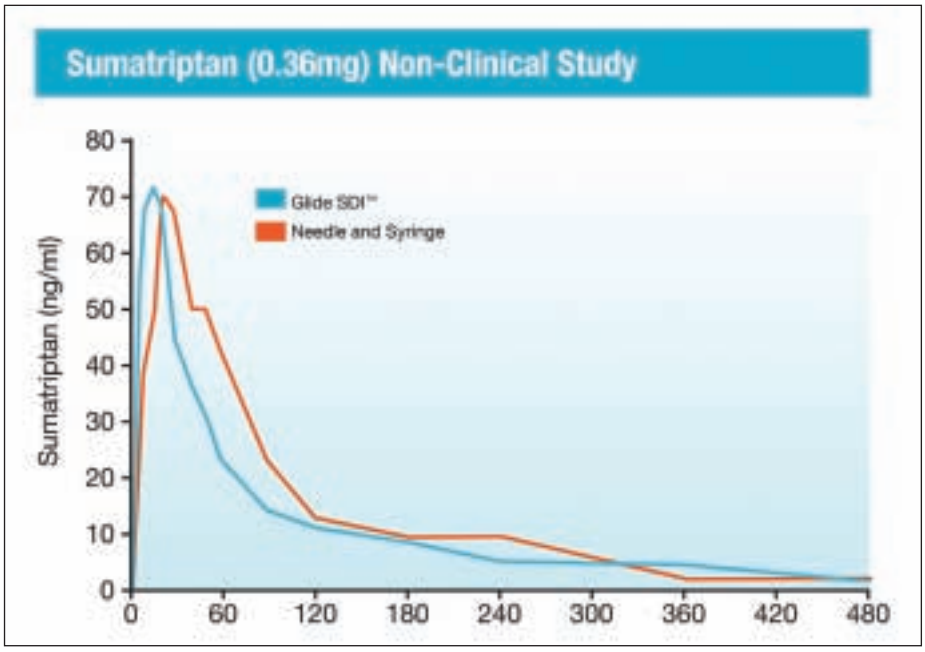


Figure 3: Non-Clinical study showing bioequivalence of Sumatriptan (0.36mg) delivered subcutaneously by the Glide SDI™ system compared with the market product Imigran®/Imitrex® delivered with a needle and syringe.

The Glide SDI™ can be reused hundreds of times, and is light and easy to transport. Alternatively for single-use applications, such as emergency-only products, the simple design and economics of large scale production means the Glide SDI™ could be fully disposable. The disposable drug cassette component does not contain any sharps, so it can be safely thrown away with normal household waste following use.

PUTTING PATIENTS FIRST

One of the key drivers for needle-free injection is that people simply do not like needles. As many as 10% of the population actually admit to being frightened of needles, whilst most of the remainder would adopt an alternative option if available. In addition, needle-stick injuries are painful and, importantly, increase the risk of spreading blood-borne infections. Safe disposal of used needles is also burdensome and expensive.

In a clinical study in healthy volunteers, 88% said they would choose injection with the Glide SDI™ over a needle and syringe. In addition, all volunteers thought that the Glide SDI™ would be easy for self-administered injection and, moreover, would be happy to use it.

Owing to the dislike of needles, patient compliance (and therefore therapeutic effectiveness) is a particular concern for treatments where self-administration is necessary. As well as the cost of failing treatment, healthcare providers are becoming increasingly concerned about the cost of "wasted" drug therapy. Despite needle-free injection options being available, the traditional needle and syringe has been a hard habit to break as it is at least dependable and cheap. Now with the Glide SDI™, a convenient, easy-to-use and inexpensive system is available which has the potential significantly to increase compliance.

As well as patient acceptance and compliance issues, there are other solid reasons for delivering solid doses with the Glide SDI™ system. First, the therapeutic or vaccine will typically be more stable and may not require cold chain storage - offering significant benefits in terms of overall cost, ease-of-use and reliability. Also, the Glide SDI™ can overcome the need for re-

constitution of proteins and peptides, a process that can be extremely time-consuming and complicated, especially in emergency situations.

In addition, for vaccine delivery, a solid formulation presents the opportunity to combine both fast-acting and delayed-release formulations, meaning that both the 'prime' and 'boost' can be given together in a single administration.

A SIMPLE, SAFE PUSH 'N' CLICK™

Glide SDI™ is suitable for use by a healthcare professional and also for self-administration by a patient. Requiring minimal training, individuals can be shown how to use the device very quickly – a simple push until you hear the click.

"FOR VACCINE DELIVERY BOTH THE 'PRIME' AND 'BOOST' CAN BE GIVEN TOGETHER IN A SINGLE ADMINISTRATION."

This would mean fewer trips to see the healthcare professional, saving money and making the process more convenient for the patient. Furthermore, many people fail to return for their boost jabs and therefore remain unprotected, so a single administration would improve the effectiveness of vaccination programmes.

FROM SMALL MOLECULES TO VACCINES

Glide SDI™ has a wide range of potential applications in proteins, peptides, small molecules and vaccines (see figure 2). As a specialty pharma company, Glide Pharma is building its own pipeline of products based on the re-formulation of off-patent drugs such as: (GP01) sumatriptan for migraine; (GP02) octreotide for acromegaly; and (GP03) fentanyl for breakthrough pain.

When taken as a pill, sumatriptan, for instance, does not work sufficiently fast enough for approximately 10% of migraine sufferers who therefore inject the drug instead. Non-clinical studies have shown bioequivalence for sumatriptan using the Glide SDI™ compared with conventional subcutaneous delivery with a needle and syringe (see figure 3).

Glide Pharma has also initiated an in-house biologic programme and the company is collaborating with a government organization to demonstrate the use of the Glide SDI™ for the effective delivery of vaccines.

Unlike many therapies, particularly biologics, which often require complicated reconstitution steps before delivery, the ready-to-use drug cassette with pre-loaded drug, is simply removed from the sterile packaging and attached to the actuator. This makes it particularly easy for treatments requiring regular administration at home and, for example, in scenarios such as a pandemic outbreak of influenza, mass vaccination in the third world, biodefence applications or even for vaccinating large numbers of animals.

Furthermore, Glide SDI™ eliminates the risk of needle-stick injury and there are no biohazardous sharps to dispose of. The used, detachable, drug cassette is thrown away in the household waste and the "pen" actuator kept for reuse.

PRESSING ALL THE RIGHT BUTTONS

The effective, convenient and easy-to-use Glide SDI™ system will not only ensure user compliance and trust, but also provide cost-effective solutions for safe, reliable and controlled needle-free injection of therapeutics and vaccines for a wide range of applications.

Glide Pharma is now actively seeking to expand its list of co-development partners particularly for the delivery of proteins, peptides and vaccines, as well as for generic injectables.

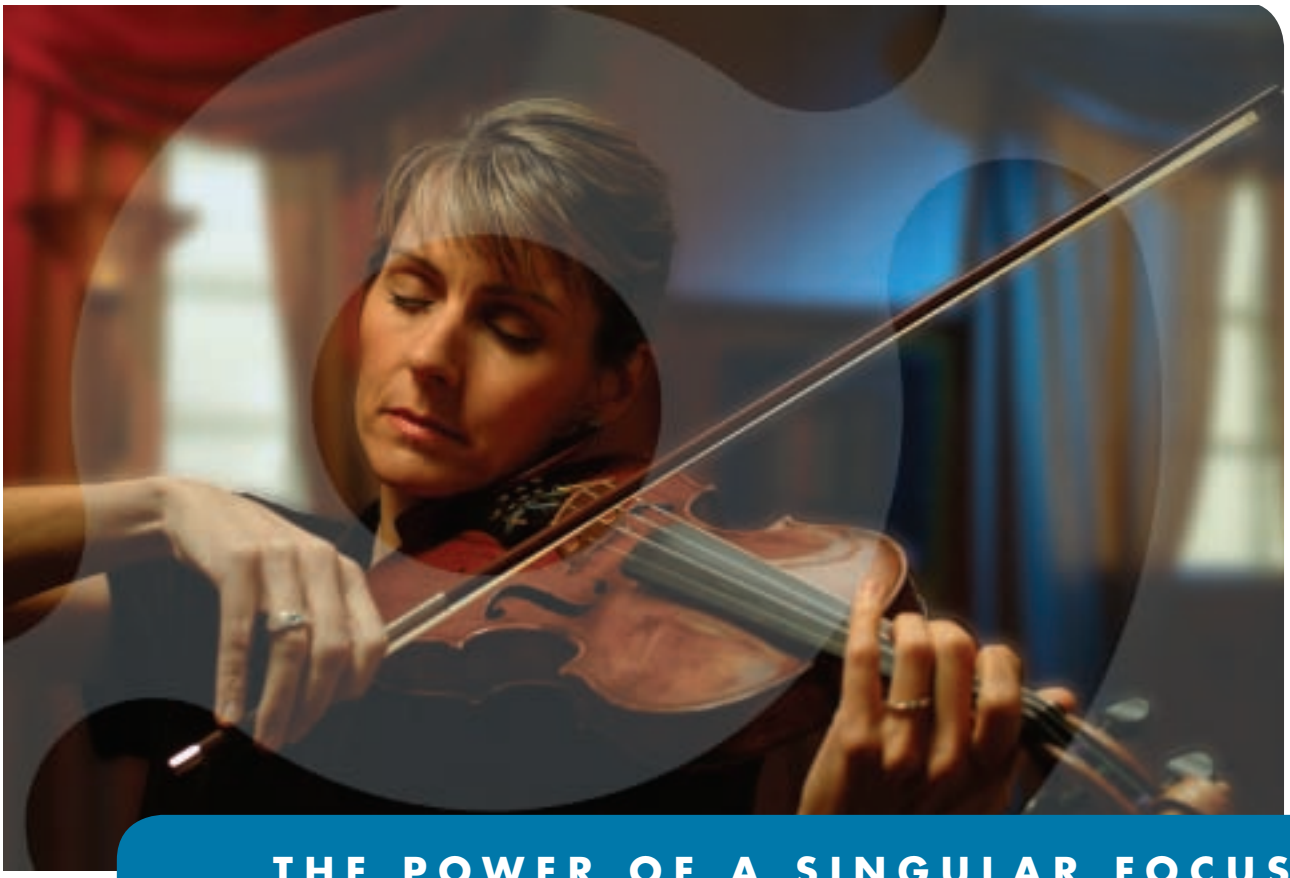
The Glide SDI™ system offers a competitive edge in terms of product differentiation and patent extension for life cycle management, and/or so-called "supergeneric" products, as well as for original, new products that need to be injected.

Using its extensive in-house expertise and supply chain Glide Pharma is conducting feasibility and technology evaluation studies to provide ready-to-use products for non-clinical studies. Having an established chain of key suppliers means that Glide Pharma is able to take a drug candidate from dry powder through the entire manufacturing process, to supply product for clinical evaluation and commercial sale. The first product through this process is likely to be a Glide Pharma own-branded product. By advancing its own products, Glide Pharma is able to demonstrate the commercial viability of the Glide SDI™ system which in turn is helping to mitigate any perceived risks for its partners.

ABOUT GLIDE PHARMA

Glide Pharma is a leading speciality pharma company focusing on solid dose injection of biologicals, small molecules and vaccines. Through licence partnerships and its own drug pipeline, Glide Pharma leverages its revolutionary Glide SDI™ (Solid Dose Injector) drug delivery system by improving convenience, safety and ease of use for the healthcare professional and/or patient. Offering pharmaceutical, generic and biotech companies a significant competitive edge, Glide SDI™ represents the next generation of needle-free delivery technologies. Comprising a pen-like actuator and cassette containing the medicine in the form of a tiny, rod-shaped solid dosage form, Glide SDI™ literally pushes the drug into the skin in a smooth, one-click action. This avoids a range of drawbacks – such as accurate dosing in different skin types – associated with other needle-free injection approaches, and, furthermore, is preferred over an injection with a needle and syringe. Glide Pharma has commercial relationships with a growing list of both big and small pharma as well as biotech companies.

the power of CONCENTRATION



THE POWER OF A SINGULAR FOCUS

We focus on one thing – and that's the development of self-injection devices.

We have one vision – and that's to be specialists in our field. It is our purpose to use our expertise, dedicated resources, and experience to provide our customers the ultimate device solutions.

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MARKET TRENDS:
DISPOSABLE MONO-DOSE AUTO-INJECTORS AND PEN-INJECTORS

In previous articles in this series Ypsomed has discussed the scale of convenience for prefilled syringes and auto-injectors, and market trends for self-injection devices. In this article, Ian Thompson, Head of Business Development at Ypsomed, focuses on disposable pens and auto-injectors for mono-dose formulations, which are influenced by the primary drug container and the user/patient population.

The market for self-injection devices – pens and auto-injectors – continues to show above-average growth due to the continued development of injectable drugs. The market for pen injectors (see Box 1) continues to evolve and grow for frequent cartridge-based injections such as insulin, GLP-1, hGH, FSH and PTH. In addition, the demand for new drugs with less frequent injections is growing rapidly requiring devices for mono-dose formulations such as auto-injectors (see Box 2) and manual pen injectors.

The relevant indication areas include: long-acting formulations of traditionally frequently injected drugs; drugs for the treatment of auto-immune diseases such as, for example, TNF-inhibitors; and emergency injections. The prefilled syringe is the primary container of choice for liquid-stable drugs while the dual-chamber cartridge is most convenient for lyophilised formulations (see figure 1).

Mono-dose formulations are single doses where the dose is fixed and fully injected or can be varied and therefore partially injected. In either case only a single dose is given and the syringe / injection device is disposed of after the injection:

1. Ideally the drug is liquid-stable and the full dose is injected from a prefilled syringe. The need to inject a partial dose using a prefilled syringe is not very common. If different doses are needed then providing different drug volumes / concentrations and thus different SKUs (stock-keeping units) is often preferred, e.g. Amgen's Aranesp (erythropoietin (EPO)).

2. If the drug is lyophilised the preference is to use a dual-chamber cartridge and inject the full dose after reconstitution. Manufacturing various concentrations of freeze-dried drugs is costly and there are examples of devices on the market today where a partial dose is injected from a dual-chamber cartridge, e.g. Schering-Plough's Pegintron/α-IFN (see figure 2).

Figure 1: Prefilled syringe (above) and dual-chamber cartridge (below)

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Figure 2: Three marketed mono-dose injectors: Amgen's Enbrel/Sureclick (top); Abbott's Humira-Pen (middle); and Schering-Plough's Pegintron/-IFN (bottom)

DEVICES FOR PREFILLED SYRINGES AND DUAL-CHAMBER CARTRIDGES

For the **prefilled syringe** the device may simply be the standard syringe without any additional injection aid. More typically a safety syringe or fully disposable auto-injector is offered. The choice of device depends on factors such as:

1. Proportion of patients self-injecting
2. Frequency of administration, duration of therapy
3. Need for needle safety to prevent needle-stick injury
4. Necessary level of convenience (i.e. patients with motor disabilities)
5. Competitive situation

WHAT IS AN AUTO-INJECTOR?

Auto-injectors, as their name implies, automatically insert the needle and perform the injection - typically spring driven - and are usually designed for use with fillable or prefilled syringes. *Auto-injectors* have been on the market as long as pen injectors but, until the 1990s, their use was restricted to emergency situations such as epinephrine for treating anaphylactic shock and sumatriptan for treating migraine. Re-usable auto-injectors have been used since the 1990s for syringe-based hormone replacement therapies, and for newer waves of biotech molecules as for example, β-interferon for treating multiple sclerosis (MS). The first disposable auto-injector for a therapeutic protein was launched in late 2005 by Amgen for its EPO, Aranesp.

For example, heparins were traditionally provided in prefilled syringes and are now supplied in safety syringes to protect hospital staff from needle-stick injuries as most of the injections are performed in the clinical setting. Another example is the TNF-inhibitors which are predominantly self-injected at home by rheumatoid arthritis (RA) patients with potential motor disabilities and are increasingly offered in a disposable auto-injector presentation, e.g. Amgen's Enbrel/Sureclick and Abbott's Humira-Pen (Figure 2).

A **dual-chamber cartridge** must be used with a luer or pen type needle and requires some form of easy-to-use device to allow the injection to be carried out. The simplest version is Vetter's Lyoject, which is often used in the clinical setting with a luer connection. For home use, patients require more convenience in the form of pen type systems. The dual-chamber cartridge puts special demands on the pen system in terms of intuitive reconstitution and priming. With ease of use being paramount it is essential that these steps are easy to learn.

DISPOSABLE AUTO-INJECTOR DEVELOPMENTS

Disposable auto-injectors (an example is shown in figure 3) have come a long way over the last few years. In order to provide the maximum amount of convenience they have a certain level of internal complexity to provide the following key features and handling benefits:

1. Large viewing window for clear visualisation of the syringe and drug before injection
2. Safety mechanism to prevent inadvertent activation
3. Two-stage injection mechanism to ensure the skin is fully penetrated before the injection starts
4. Audible and tactile injection feedback
5. Full needle hiding to reduce fear of needles plus full needle safety after injection to prevent needle stick injury

Depending on the auto-injector these technical features may be achieved in slightly different ways. They have an impact on the size and handling of the device and must be evaluated depending on the patient population, for example:

1. The geometry / location of the injection spring may have an impact on the size of the auto-injector. For some patient groups (e.g. late-stage RA patients) a larger device may be preferable whereas for other patients the device should be small and discreet (e.g. for emergency injections).
2. Different devices have distinct safety mechanisms which allow the injection to be activated in different ways. The preferred configuration for a particular therapy is best confirmed using patient handling studies.
3. Needle safety can be achieved using a locking needle shield sliding over the needle or the needle retracting into the device housing. Either way the complete volume must be injected before the needle shield is activated. Patients must receive positive feedback from the device at end of injection and the safety mechanism must work every time.

WHAT IS A PEN INJECTOR?

Pen injectors are essentially sophisticated cartridge-based syringes. Pen therapies require frequent, often daily, manual injection with weight-based dosing or dose titration and injections are repeated until the cartridge is empty - usually after one to two weeks. The first pens were introduced for insulin in 1984 and were developed for the reliable and accurate self-administration of the first wave of biotech molecules, mainly 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) and osteoporosis (PTH). During the 1990s the insulin pen market became segmented with the introduction of disposable pens and reusable pens incorporating improved handling functions and electronics.

Figure 3: Disposable auto-injector (Silberhorn)

Figure 4: Dual-chamber injectors (Lynx/Trio)

DUAL-CHAMBER BASED INJECTOR DEVELOPMENTS

Dual-chamber based devices (figure 4) have been on the market for nearly 20 years in the form of multi-dose pens for therapies such as Pfizer's Genotropin/hGH. More recently disposable mono-dose pen devices have been developed which are essentially the equivalent of the disposable auto-injector for dual-chamber cartridges. Key technical features to look out for in these devices are:

The method of reconstitution and priming. Manual preparation is easy to visualise and easy to perform for patients with good motor control, special designs are needed for patients with motor disabilities. Automating these steps may help patients with motor disabilities but this adds complexity and cost to the device.

Dual-chamber devices must be designed so that the handling steps - which are more numerous and more complex than for disposable auto-injectors – are always performed in the correct order. Ergonomic designs ensure that the device is held in the correct position during reconstitution to prevent incomplete mixing or inadvertent expelling of the drug.

Automating the injection step is similar to the disposable auto-injector – the main difference being the higher friction forces of the dual-plunger configuration.

A pen type needle always needs to be attached to the device. But needle safety can be incorporated into the device or a safety pen needle can be used.

CONCLUSION

In summary, the market for mono-dose injectors is growing, based on patent-protected technical designs customised to patient and pharma companies' specific needs. Novel technical features to provide safe and reliable use have by no means been exhausted, and the choice of the correct device requires careful selection and close collaboration between the patient, the primary packaging company, the device company and the drug manufacturer.

| Pfeiffer |

NASAL DELIVERY AS AN ALTERNATIVE TO INJECTION: SCIENCE AND TECHNOLOGY MEET MARKET DEMAND

Nasal drug application represents a huge pharmaceutical growth area all over the world. Dispensing medication via this route ensures that it enters the blood quickly and effectively, due to the large surface area, porous endothelial membrane, high total blood flow and the avoidance of first-pass metabolism (see figure 1). Extremely high patient convenience levels, which cannot be offered by intravenous vaccination alternatives, complete this positive picture. Here, Matthias Birkhoff, Director of Business Development of the Pfeiffer Pharma Division, shows how technology has enabled the company to rise to the challenge of providing nasal dispensing systems to meet accelerating demand, without compromising safety or performance.
Pfeiffer is equipped for the rapidly growing trend towards nasal applications with its Unitdose and Bidose systems

THE PRESENT AND FUTURE OF NASAL APPLICATION

Nasal application for medication is becoming increasingly popular in all markets, for users of all ages. Supporting the strong anatomical arguments that prove this method's unrivalled effectiveness are numerous user benefits. A nasal spray is far easier for a patient to use without help than an injection, thus enabling welcome speed and independence. In a social context, with resources for caring for invalid and elderly patients being severely stretched, any safe possibility for the patient to self-administer medication presents a major benefit.

Furthermore, as a huge number of individuals turn to lifestyle drugs to impede symptoms of ageing, research indicates that the nasal route for many of these products represents massive future growth. And with the current lifestyle drugs market being valued at US$23 billion and showing double-digit annual growth (Source: Global Business Insights report, London, UK) this is certainly not a fact to be overlooked.

UNITDOSE AND BIDOSE EQUIPPED FOR EXPANSION

Pfeiffer has more than two decades of experience in developing and manufacturing unitdose systems and has a very strong patent portfolio related to this technology. The Pfeiffer Unitdose and Bidose nasal spray devices have become market leaders for applications as diverse as anti-migraine and anti-osteoporosis products. The Unitdose is designed to administer one accurate dose of a drug formulation via the nasal route. Its counterpart, the Bidose, administers two doses and is ideal for the situation when more medication is required than can be applied via one nostril.

The current, ultra-modern systems are completely closed and able to deliver metered doses with a volume of 100 µl each. The fact that the medication does not come into contact with air before dispensing responds precisely to the vital user demand for uncontaminated medication. Its uniquely consistent spray performance fulfils the need for optimal dispensing efficiency, with maximum convenience coming from the integrated pressure point actuation mechanism with no need for initial priming (see figure 2).

100% PROTECTION OF MEDICATION

Extensive research and development work, spanning several years, partnered by in-house German engineering, has enabled Pfeiffer to produce a nasal spray that is unique in that it

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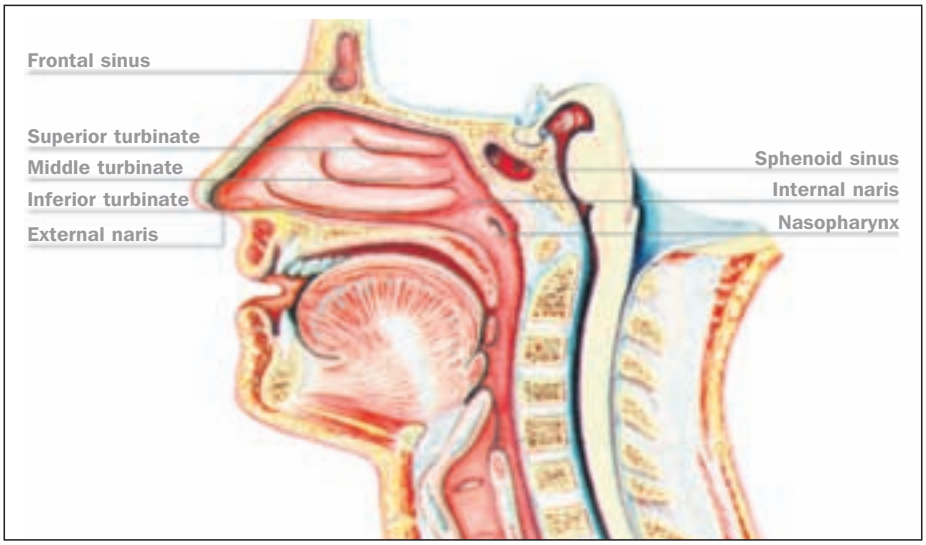

Figure 1: Anatomy of the nose

protects the contents 100% until they exit the system after actuation.

The functionality is based on a pressure point mechanism, the vial holder is connected to a plastic disc through three perforation bridges (see figure 3). After applying a pre-determined force to the bottom of the vial holder, the adjustable perforation breaks. Subsequently, the vial holder moves upwards, allowing the needle to penetrate the stopper. As the actuation continues, the integrated spray insert pushes the stopper down to the bottom of the vial. The liquid product then escapes through the needle up into the actuator where the integrated insert mechanically generates a perfect spray profile.

The sudden and fast breaking of the perforation prevents the patient's actuation motion from influencing the consistent spray performance. In particular, the increasingly used substances – peptides, insulin and other common vaccines – require an application that is more appealing and practical than injection, with infallible protection from environmental influences including light.

With the Pfeiffer Unitdose and Bidose solutions, these substances have found their ideal environment and dispensing method.

QUALITY TESTING

The testing of this protective characteristic and the quality of the glass used was assigned to an independent external laboratory* and carried out in accordance with ISO 17025. This process was geared specifically towards the US FDA Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics**, which stipulates that "A container closure system should provide the dosage form with adequate protection from microbial contamination."

The test (see figure 4) involved filling Pfeiffer Unitdose and Bidose devices with a solution and submersing them in a bacterial suspension to produce a severe microbial challenge. A total of 20 filled Pfeiffer units were pre-incubated at 30ºC for 14 days, then submersed at 20ºC (±2ºC) for a period of 10 hours under different conditions of stress and pressure. Following this

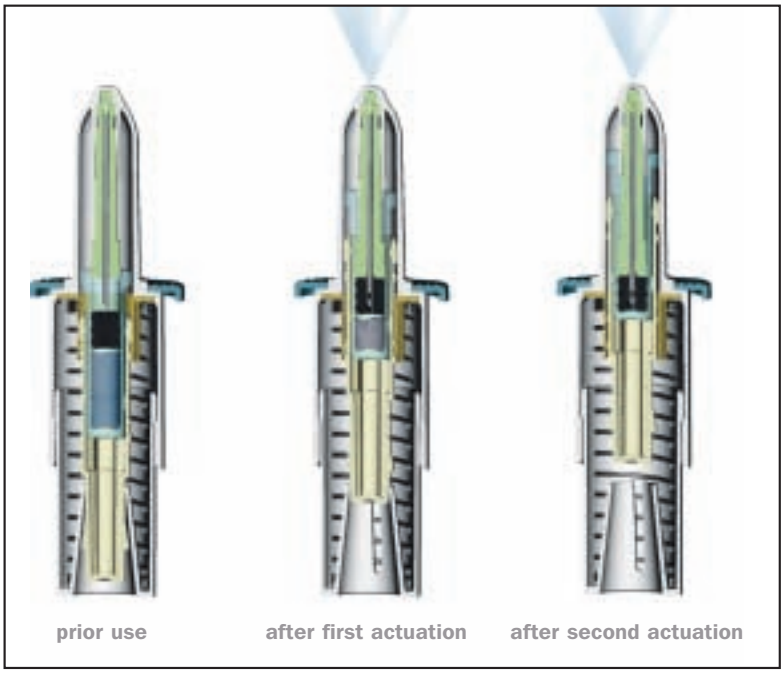

Figure 2: Primary packaging in relation to the drug product

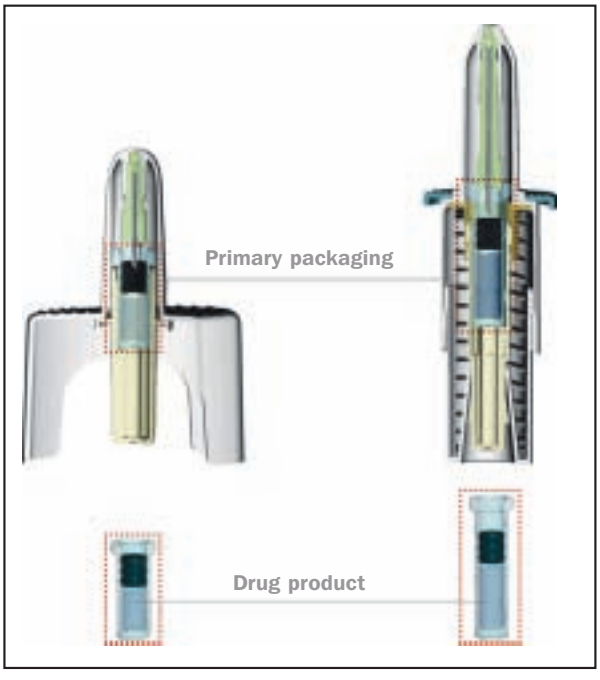

Figure 3: Functioning of the Bidose Spray System

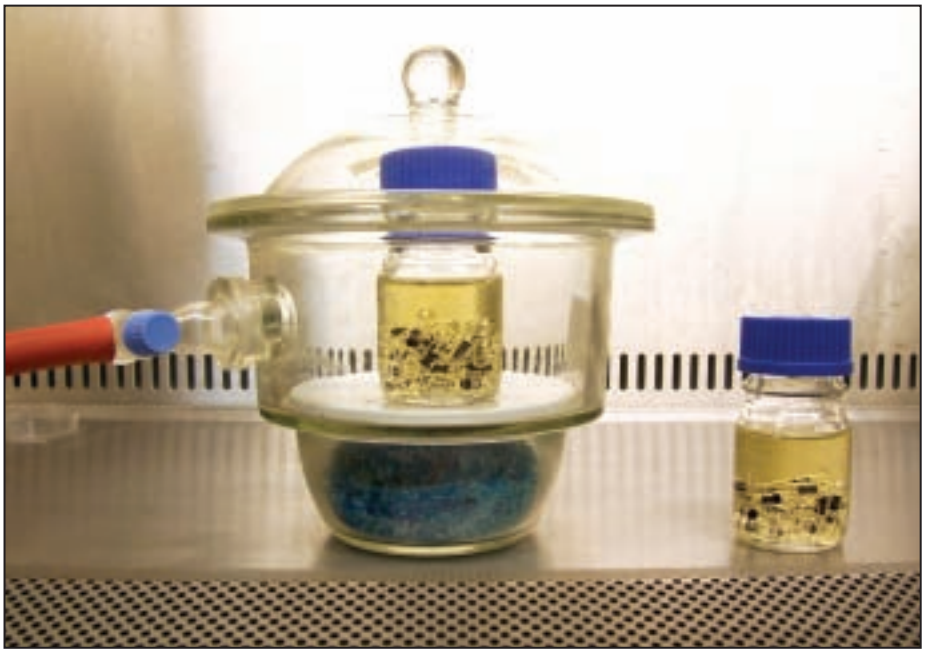

Figure 4: Integrity testing of the Pfeiffer Unitdose and Bidose systems at Qualis Laboratories (Constance, Germany)

was incubation at 30ºC for 14 days.

All of the samples passed the severe tests demonstrating no traces of microbial growth and therefore proving the system's ability to act as a sterile barrier. The fact that the drug product only comes into contact with two substances (glass and rubber) further confirms the nasal spray system's suitability as a viable alternative to injection in terms of patient convenience.

ACCELERATED TIME TO MARKET

In a rapidly expanding pharmaceutical market, the clock is ticking fast – and for manufacturers this of course translates into huge time pressure when introducing new products into the market. At Pfeiffer, extremely close cooperation between research and development and marketing has made unrivalled progress in shortening the time to market for its products to give customers an extremely valuable competitive edge.

The Pfeiffer Unitdose and Bidose systems are Drug Master File supported. Pfeiffer has expansive, traceable experience in supporting FDA submissions and all materials used in these systems are known and therefore already FDA approved.

Figure 5: Clean-room production at Pfeiffer

This differentiates the system from many other spray systems of competing manufacturers and puts the Unitdose and Bidose in a league with injection systems in terms of material contact. For the customer this means accelerated time to market with very welcome minimal administrative time and expense. The success of the nasal systems has in the meantime triggered the development of sublingual unitdose devices and these have also been perceived very well by the industry.

THE REAL VALUE OF AN A-Z SERVICE PACKAGE

In response to the tough demands placed by the market, Pfeiffer has redefined the concept of service in the context of the Unitdose and Bidose systems, drawing on decades of technical and business experience. The key to this success has been a deep understanding of customers' development, manufacturing, filling and logistical challenges.

The resultant A-Z service package extends from the very first pilot filling trials, which can be carried out on dedicated Pfeiffer filling lines (see figure 5) with assured confidentiality, right through to the possibility of local production, for example in the US. Pfeiffer of America as the Princeton, New Jersey based Sales Office of Pfeiffer GmbH offers a complete support process for the development of Unitdose and Bidose projects requiring FDA approval. The sales, technical, regulatory, engineering and customer services of Pfeiffer of America are complemented by more than 50 years of German engineering and production experience (see figure 6).

Business relationships are also in place for contract manufacturing, offering the opportunity for a complete service package custom fit to the Pfeiffer systems.

Such supply chain management provides a huge success factor. Customers value these long-standing relationships highly. Pfeiffer gives them access to contract fillers and manufacturers around the world. In many cases this can be the decisive factor in the selection of Pfeiffer products above others. It enables levels of efficiency, competitiveness and flexibility that would otherwise be out of reach.

A further proven advantage of the service package is the Pfeiffer network of local competence centres. These integrate full technical assistance from the early to final stages of production, ensuring fast-reacting, hands-on support that is tailor-made to specific local customers' requirements. Other complementary elements of the service spectrum are 100% tailor-made Drug Master File support for the Unitdose and Bidose products and the continual harmonisation of test methods.

CONCLUSION

Considerable effort is being devoted to discovering and developing superior drugs for all types of indication, for example, in pain management and sexual dysfunction. Two main approaches are being followed and in both cases partnership between the pharmaceutical producer and the device manufacturer plays a key role.

The first approach involves the exploration of newly discovered targets for such drugs. The second approach is to improve the clinical utility of existing and new molecules by the use of new formulations and delivery techniques. The Pfeiffer Unitdose and Bidose systems make a significant contribution to the process of maximizing drugs' efficacy and minimising their side effects.

Figure 6: The Pfeiffer facilities in Eigeltingen, Germany

PFEIFFER AT A GLANCE

The company Ing Erich Pfeiffer GmbH was founded in 1947. Today it is one of the world's leading pharmaceutical and cosmetic pump manufacturers and has 660 employees. The company headquarters are in Radolfzell in Southern Germany with the main production facilities in nearby Eigeltingen. Pfeiffer also is represented across all five continents via an extensive network of sales offices. The Pfeiffer product portfolio encompasses a wide range of dispensing systems for the pharmaceutical sector and a culture of continual innovation ensures a targeted response to future market needs.

* *Qualis www.qualis-laboratorium.com*

** *FDA Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics www.fda.gov/cder/guidance/index.htm*

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