

# INJECTABLE DRUG DELIVERY 2012: DEVICES FOCUS



ONdrugDelivery  
**ISSUE No 33**  
**JUNE/JULY 2012**  
ISSN 2049-145X



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## “Injectable Drug Delivery 2012: Devices Focus”

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### PRODUCTION/DESIGN:

Mark Frost  
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ONdrugDelivery is published by  
Frederick Furness Publishing.  
(ISSN 2049-145X print / ISSN 2049-1468 pdf)

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## ADVANCEMENTS IN PREFILLED SYRINGE TECHNOLOGY:

# IMPROVING COMPATIBILITY WITH BIOLOGICS WITH A NOVEL CROSS-LINKED SILICONE COATING

Silicone oil is commonly used as a lubricant coating in prefilled syringes (PFS) and is becoming one of the most highly discussed topics in the PFS market, particularly for developers of highly sensitive biotech drugs. In specific biological drug cases, unexpected drug-container interactions have been reported that were attributed to or associated with sub-visible particles generated from the lubricating silicone layer. Here, Sebastien Jouffray, Core Team Leader, R&D Advanced Product Development, BD Medical – Pharmaceutical Systems, describes an innovative immobilised silicone coating: cross-linked silicone, XSi™. It significantly reduces sub-visible particles while retaining lubrication performance. XSi™ does not introduce any new materials, enabling rapid implementation in PFS for both legacy as well as pipeline drugs.

### INTRODUCTION

The worldwide prefilled syringe market is estimated at approximately 2.7 billion units, with annual growth of around 4-6%.<sup>1</sup>

Prefilled syringes provide numerous benefits that explain their steady market growth:

- minimisation of cross-contamination
- less waste of valuable drug product resulting from over-filling of traditional syringes
- elimination of container preparation (vial washing, depyrogenation, preparation of stoppers and crimp caps)
- filling line efficiency
- reduction in medication errors due to fixed dosing
- streamlined preparation of drug before administration and thus reduced sources for error
- improved patient compliance
- added convenience through combination with an auto-injector.

The increasing dominance of parenteral drugs, particularly biologics, is another factor

in the growth of prefillable syringes. In 2000 just two of the top-20 pharmaceutical products sold in the US were biologics. By 2016, 10 of the 20 leading US drugs by sales, and seven of the top eight, will be biologics whose annual sales will top about US\$50 billion (£32 billion).

The trend towards self-administration for chronic diseases like multiple sclerosis and rheumatoid arthritis has fuelled growth of more convenient delivery devices such as auto-injectors, pens and others that rely on prefilling. Patients prefer the convenience and time savings of prefilled devices,<sup>2</sup> a factor known to improve adherence to self-administered treatment regimens.

Since biologics are sensitive molecules, developers need to assess various attributes of the syringe before launch to ensure that the molecule will not interact in an unexpected way with its primary container. The most common syringe characteristics considered are tungsten, rubber, adhesive, silicone, and sub-visible particles (SbVPs).



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## SUB-VISIBLE PARTICLES

Visible and sub-visible particle levels are critical to quality attributes of liquid injectables packaged in prefilled containers.<sup>3</sup>

The US FDA's container closure Guidance presents a framework for minimising SbVPs as well as absorption, adsorption, or degradation of active pharmaceutical ingredient, degradation of the container by drug product, and assuring patient safety.<sup>4</sup> A later FDA document addresses SbVPs, particularly their analysis, in greater detail.<sup>5</sup>

Detection of SbVPs, defined as particles that cannot be reliably detected by visual inspection with unaided human eye, is continuously improved by emerging analytical techniques. In particular, the extension of the SbVP size detection limit below 10 µm, potentially into the sub-micron range, and the ability to differentiate the nature of those particles will greatly enhance the potential to monitor and report this critical attribute. Such analytical techniques can be used to understand better the contribution of silicone oil, traditionally used as lubricant in prefilled syringes, to the overall pool of detected SbVPs. This knowledge will be critical to monitor, control and, if a specific need arises, reduce this contribution.<sup>6</sup>

The three significant populations of silicone-induced SbVPs present in a prefilled syringe format are illustrated in Figure 1.

Silicone-induced SbVPs in a PFS originate from the silicone lubricant applied to the inner syringe surface; three groups are distinct in their formation and potential impact. The first class of silicone droplet (A) is released (or emulsified) into solution soon after filling and is therefore in contact with the drug solution throughout the entire product shelf-life and could be considered for its ability to form silicone-protein complexes. The second type of silicone particle (B) is part of the silicone surface that remains in contact with the drug solution throughout the product shelf life, but may at some point during storage move into solution. The third type (C) is created from the bulk silicone layer sloughed off the wall during injection only. Type C particles are in contact with the drug product for a much shorter time than the other particles types. However, they represent a significant portion of the measured particles with current compendial methods.<sup>6</sup>

Several years ago, to address SbVP challenges, BD embarked on a development project to reduce silicone-related SbVPs to their lowest possible levels while retaining "syringeability" and auto-injector functionality,<sup>7</sup> as well as managing change control risks. Among the

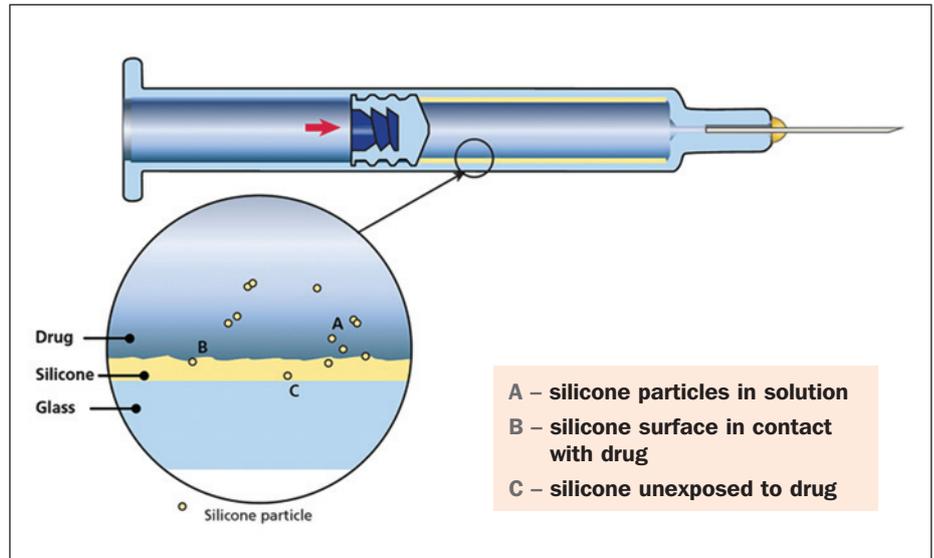


Figure 1: Mechanisms of silicone SbVPs formation.

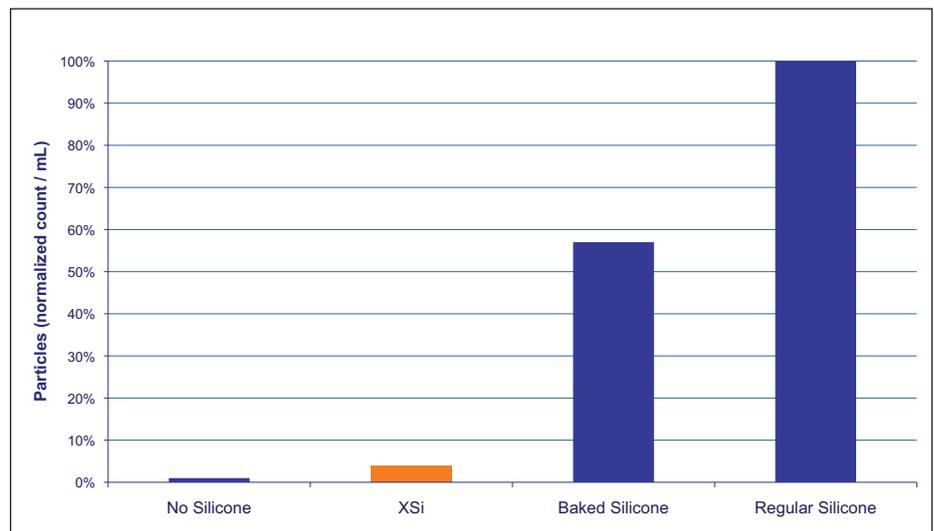


Figure 2: Comparison of unsilicised, XSi™, baked silicone and conventionally-lubricated BD syringes. (Normalised particle counting 1-100 µm by MFI™. All containers were filled under the same conditions: identical buffer solution & stopper).

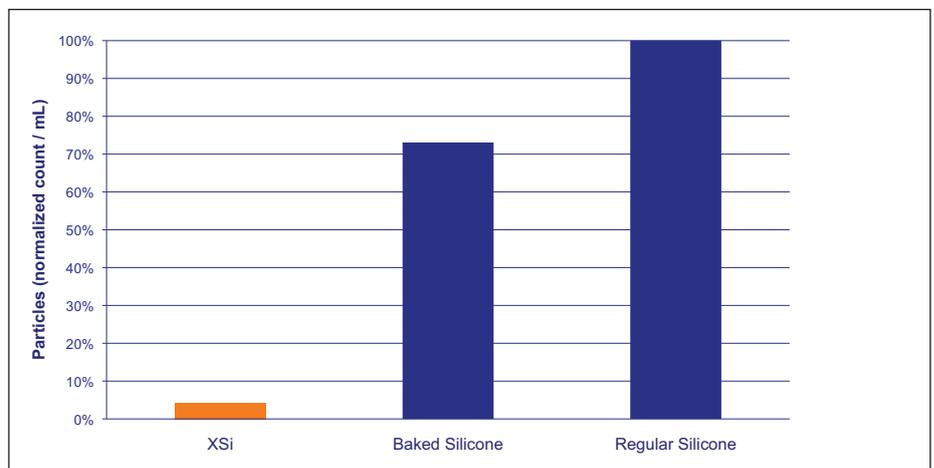
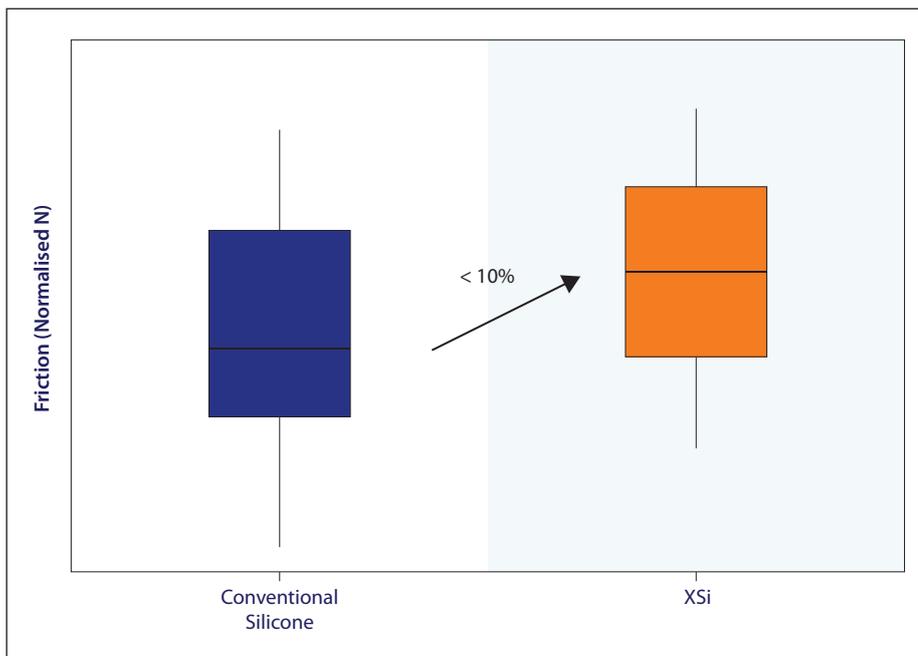


Figure 3: Sub-micron range particles counts of XSi™, baked silicone and conventionally-lubricated BD syringes. (Particle counting, 200 nm-1 µm by Nanosight Ltd. All containers were filled under same conditions: identical buffer solution & stopper).



**Figure 4: Empty friction forces at 380 mm/min for conventionally siliconised syringes versus XSi™ syringes. (Identical stoppers were used for both configurations).**

evaluated technologies were coatings based on new materials such as fluoro-polymers and parylene, a baked silicone process aimed at reducing mechanically active silicone, and an entirely new silicone-based cross-linked coating, BD XSi™.

## XSI PERFORMANCE

Overall syringe performance depends on several key attributes such as rubber stopper gliding and container inertness with respect to SbVPs. Through internal product design and collaboration with pharmaceutical industry partners, BD has demonstrated that XSi™ technology containers achieve superior coating resistance over time compared with previous generations of prefilled syringe products, while fulfilling the requirements of an all-new prefilled syringe.

The benefits of this new technology include:

- significantly reduced SbVPs
- compatibility with auto-injectors
- no new materials in the fluid path
- comparable extractable / leachable profile to conventional prefilled syringes
- improved stability with respect to lubricant surface and drug

These advantages relative to conventional spray silicone-based lubrication are covered in the remainder of this section.

### Particle Reduction

The industrial batch-to-batch analysis of particle-counts measured by HIAC (Hach Company, Loveland, CO, US) relative to commercially available prefilled glass syringes indicates a minimal reduction (in the worst case) of 90%, when baked silicone syringes result in slight SbVP reduction.

The trends in observations are even more obvious under stress or shipping conditions.

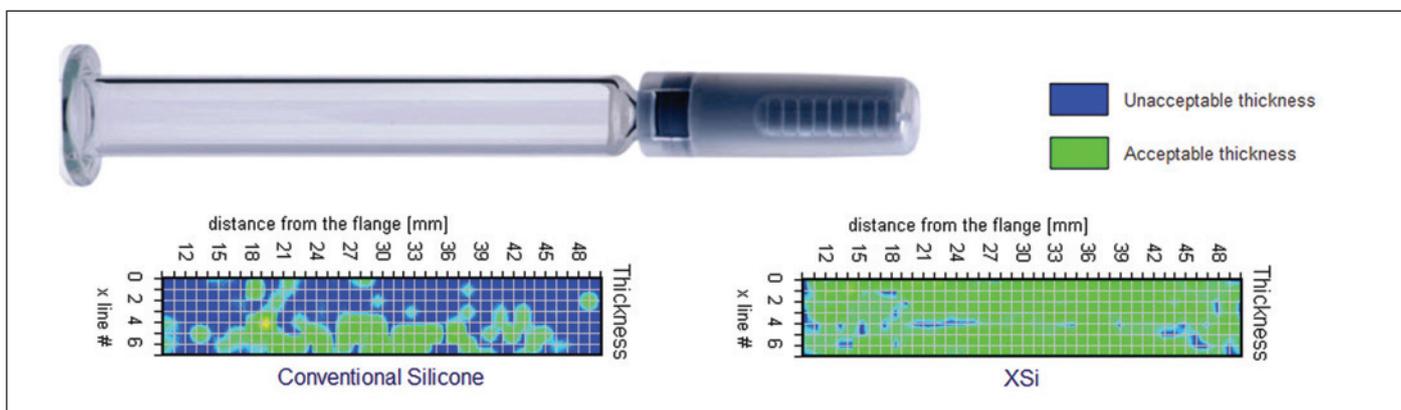
XSi™ syringe is characterised by dramatic reduction of sub-visible particles as shown in Figure 2, which compares regularly siliconised prefillable syringe surface, baked silicone surface, non-siliconised reference surface, and XSi™. The BD proprietary XSi™ coating does not impede high syringe quality and performance, but minimises SbVPs. Indeed, superior reductions were observed using an orthogonal particle characterisation technique with MFI™. Note that in this experiment high surface tension buffer was removed by pipette and analysed without activating the plunger.

Even more striking was the effect of XSi™ on sub-micron particle sizes, as shown in Figure 3. In this study, various techniques based on nano-particle size tracking analysis (NanoSight Ltd, Amesbury, Wiltshire, UK) indicated particles in XSi™ syringes were reduced more than tenfold compared with baked silicone and conventional sprayed-silicone prefilled syringes. Three additional particle-counting methods provided comparable results. This experiment demonstrates that XSi™ provides a true reduction in particles in both micron and sub-micron ranges and not just a shift in counts from one size range to another.

### Auto-Injector & Attached Needle: Syringe Suitability – Syringeability

XSi™ treatment significantly reduces drug and container interaction without introducing new surface materials to the fluid path. It also provides the usual lubricious behaviour with a similar level of functional gliding performance as conventional diving nozzle siliconised syringes. This feature, manifested by the time and force required for injection, is known as “syringeability” and is known to affect patient compliance with autoinjected drug regimens.<sup>7</sup>

Figure 4 shows that the maximum increase in pure frictional forces measured on empty syringes is approximately 5-10% for XSi™ syringes compared with conventionally silicon-



**Figure 5: Syringe coating layer integrity after drug contact (48 hrs agitation), characterised by coating layer thickness by reflectometry. Green colour indicates initial coating coverage range. Both layers had the same thickness before drug filling and storage.**

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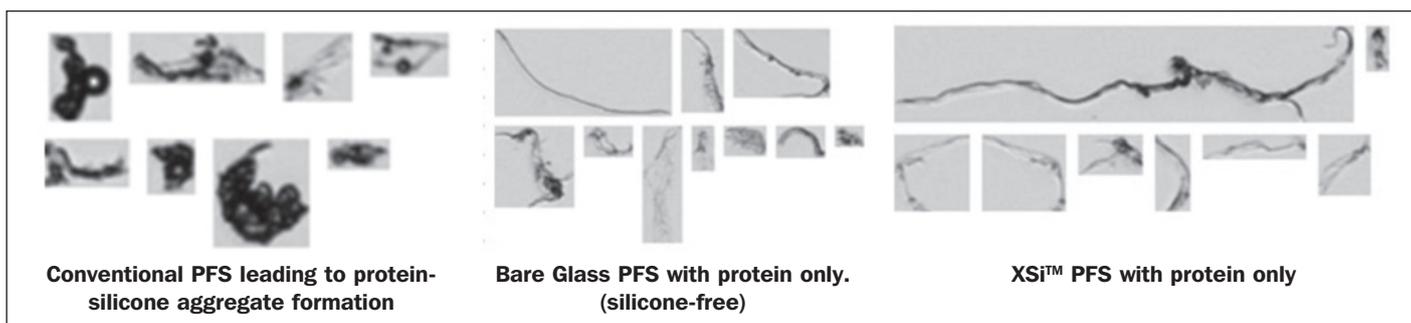
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**Figure 6: Drug-container interference examples after storage in a conventional glass PFS, bare glass syringe (vial like), and XSi™ glass syringe. (Particles pictures >25 µm by MFI™. All containers were filled under same conditions: identical buffer solution & stopper, 1 month storage).**

ised glass PFS. The effect on gliding performance will be even lower in a filled syringe due to the contribution of the force required to expel the liquid through the needle.

The absolute injection times when using an auto-injector such as BD Physioject™ for water for injection and for a more viscous solution (for example, >10 centipoise) were well under 10 seconds for XSi™ syringes. This represents an acceptable injection time for self-administration for many parenteral drugs.

#### Layer integrity after drug contact

Another way to evaluate container performance over time is to monitor its integrity during product shelf-life testing. To mimic realistic but extremely stringent conditions, this approach was experimentally applied to placebo-filled PFS. Resulting data demonstrate that XSi™ coating possesses exceptional stability over time, retaining its critical quality attributes of density, chemical composition, and dimension even after storage with drug contact. Figure 5 compares standard silicisation and BD XSi™ coating layers after prolonged contact with a high-surface-tension solution. The figure indicates that the XSi™ barrel in contact with the drug retains acceptable thickness, while under the same conditions the sprayed silicone coating thickness was not maintained.

#### Sensitive Drugs: Interactions & Compatibility Risks

Pharmaceutical companies routinely conduct stability tests on the drug product using dynamic light scattering or other particle characterisation methods. BD has demonstrated (in specific cases) that some sensitive proteins in contact with XSi™ surfaces exhibit improved stability during storage compared with conventional silicone coating. Combined with BD Neopak™ glass prefillable syringes, interaction with biological drugs could be similar to that from silicone-free containers (see Figure 6). Thus, some drugs that currently may not be suitable for launch in a PFS format due to stability issues could be packaged in a glass syringe with XSi™ coating.

pH shifts and leachables / extractables during storage are two factors that adversely affect drug stability within a prefillable container. During validation pH stability over time in XSi™ prefillable syringes was comparable with standard silicised and non-silicised glass containers. For extractables XSi™ performed nearly identically to uncoated barrels, and showed remarkable stability with respect to leachables over time at multiple temperature conditions studied. BD has subjected XSi™ technology to exhaustive physico-chemical characterisation, leachable / extractable studies, and additional testing to assess the biocompatibility of this innovative coating. XSi™ was comparable, and for some data points superior, to other glass prefillable containers evaluated.

#### PRESENT AND FUTURE

Prefillable injection devices have evolved from mere market differentiators for biological drugs and vaccines to critical components for driving manufacturer and patient value. Particularly for self-administered biologicals, prefillable syringes have become state of the art.

Designing delivery systems for today's complex biologics requires that drug formulation and packaging strategies converge early in development: developers of self-administered biological drugs do well to evaluate delivery options from the ground up, particularly with respect to product stability. Reducing SbVPs to the lowest extent possible through BD's XSi™ technology is a very effective way to reduce the risk of undesired drug-container interactions. As XSi™ does not introduce any new materials, it retains the benefits of prefillable, self-administered biologicals, without the need for extensive and costly evaluations.

The goal of BD's XSi™ research program was to develop a BD prefillable syringe system, comprised of barrels and marketed stoppers, that is fully compatible with auto-injector performance and provides the lowest possible sub-visible and visible particle levels.

BD XSi™ technology combines container and lubricant layer inertness, resistance to deg-

radation by drug product, biological drug stability, silicone-like friction performance, and the low silicone-derived SbVPs characteristic of untreated glass vials. BD XSi™ technology is ready for adoption with no alteration to existing prefillable syringe manufacturing or filling processes. In addition to its strategic benefits, XSi™ exhibits overall container performance that is equal or superior to conventional delivery systems.

Designed for glass+needle syringes and used with conventional stoppers, BD XSi™ proprietary coating employs an advanced, well-characterised and unique silicone based technology that minimises the risks and facilitates adoption.

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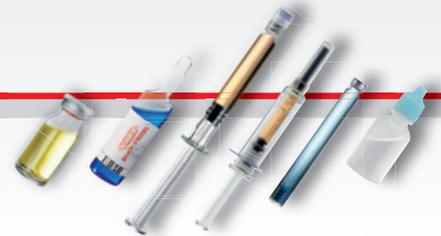
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## NEW VIAL ADAPTER ELIMINATES INJURY & RE-USE, IMPROVES FUNCTION, & DIFFERENTIATES PRODUCTS

In this piece, Simon Williams, Business Development, Duoject Medical Systems, describes the evolution of a new safe vial adapter design. The safety feature, in addition to eliminating the risk of injury from the adapter and preventing its re-use, allowed the re-introduction of a stainless-steel needle, thus also improving the functionality of the device.

Vial adapters are now in regular use to enhance and improve the safety of reconstituting a wide variety of lyophilised drugs with diluent supplied in a luer lock prefilled syringe. One year ago, Duoject established a project looking to make improvements to the variety of common adapters available on the market today. The key objectives were to improve user safety while enhancing the user experience.

**“A VERY THIN AND VERY SHARP PLASTIC SPIKE POSES A SIGNIFICANT RISK OF INJURY”**

The devices on the market today use plastic spikes to penetrate the vial stopper. Although a plastic spike seems safer than a stainless steel needle, for the device to work effectively and the attachment force to be kept to a minimum, the spike needs to be as thin and sharp as possible.

A very thin and very sharp plastic spike poses a significant risk of injury. As a result, Duoject felt that a protection disc should be added to the device to prevent any possibility for the user of coming into contact with the spike, thereby eradicating all possibilities of a stick injury. The safety disc is securely locked into place prior to activation and is only unlocked when the aluminum seal from the vial is inserted into the adapter.

By adding the safety disc, we also reduce the opportunity for contamination. As the user cannot touch the spike they in turn cannot contaminate the fluid path before the vial adapter is attached to the vial.

When trying to optimise the plastic design to minimise attachment force and ease of stopper penetration, we realised that, having added spike protection and eliminated any possibilities of a stick injury, we could now use a transfer stainless steel needle to penetrate the stopper. With a needle we now have the optimum “spike” design. Needles can of course be much thinner and sharper than a plastic spike so stopper penetration is optimised.

In addition, a needle offers the following benefits:

- Reduces the attachment force (especially with the popular coated or laminated stoppers), giving the adapter a smoother operation
- Minimises particulate generation
- Provides excellent penetration even without silicone
- Allows us to optimise needle length easily to minimise drug hold up
- Enables us to optimise needle diameter to suit the viscosity and/or other properties of the reconstituted medication.

Having realised the benefits of using a needle over a plastic spike, we knew that we had



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**Figure 1: Cut-away view of device showing the safety disc.**

to ensure the continued protection of the needle in the unlikely event of a patient removing the adapter from the drug vial. We found a way to ensure that in the event the adapter is removed from the vial, the safety disc immediately clicks back into place, shielding the needle.

As we enhanced the re-protection feature, with a very simple modification we could offer a version of the device that was able to prevent accidental re-use. If ever the device is removed from a drug vial, the disc returns to its original protective position and locks into place, preventing the now used, non sterile, adapter from being attached to a new drug vial.

Through innovative design, Duoject has incorporated these features with the addition of one small plastic part, ensuring a competitive solution to the adapters in use today.

The adapter device is called EZ-link. Figure 1 shows a cut-away image of EZ-link with the safety disc visible.

In Figure 2, EZ-link is shown with a luer-lock prefilled syringe, with a lyophilised drug vial, and in its packaging.

We are confident that this improved vial adapter offers real benefits to both the pharmaceutical manufacturer and end user alike. The device has patents pending and is available in both 13 mm and 20 mm finish sizes.

## ABOUT DUOJECT

For more than 25 years, Duoject has been at the cutting edge of medical device design, developing devices for many of the world's leading pharmaceutical companies. Duoject



**Figure 2: EZ Link device with a luer-lock prefilled syringe and lyophilised drug vial.**

**“DUOJECT HAS ENTERED A NEW PHASE IN ITS EVOLUTION AND HAS MOVED FROM A DESIGN AND DEVELOPMENT COMPANY TO BECOME A FULLY-FLEDGED DEVICE MANUFACTURER IN ITS OWN RIGHT”**

specialises in the areas of drug reconstitution and delivery and now holds over 60 patents in these fields.

Originally, the company exclusively licensed this technology. This allowed its pharmaceutical customers to differentiate and enhance their products in the market place and use its device IP to support their drug sales, even after expiration of their drug patent.

In an exciting new development driven by its customers, the push towards home medication and the expectations placed on the markets by the needlestick legislations in the US and Europe, Duoject has entered a new phase in its evolution and has moved from a design and development company to

become a fully-fledged device manufacturer in its own right.

Duoject has identified a range of core products, which includes the new EZ-Link reconstitution device. These core products utilise the company's IP but are not proprietary to a specific customer or applicable to a unique drug or even a specific class of drugs. These core devices have been put into production in Duoject's US FDA-approved manufacturing facility and are available for incorporation into your drug package, to enhance and improve the safe reconstitution and delivery of your drug products.

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# EZLink

The unique vial adapter with integrated safety disc

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## GROWTH IN AT-HOME ADMINISTRATION SPARKS NEED FOR INTEGRATED DELIVERY SOLUTIONS

In this article, which emphasises the increasing importance of human factors in drug delivery device design, Graham Reynolds, Vice-President, Marketing & Innovation, Pharmaceutical Delivery Systems, West Pharmaceutical Services, describes recent trends for more home use of injection devices and self administration and how the use of novel materials and technologies, in combination with product design that includes human factors testing, encourages patient adherence to medication as well as fostering brand loyalty.

Growth in injectable therapies has resulted in an increasing number of new biologic drug products. Treatment regimens for these products can be complex, and often fall directly to the patient or a caregiver rather than a trained clinician. Many new and desirable treatments may require larger doses, which would require multiple injections by the patient. Biologic drug products are often of a higher viscosity and may require a high-volume dose that cannot be easily delivered using traditional methods. Delivery devices such as pens, auto-injectors and patch injectors are often the best choice for self-administration.

In addition, many products may require some degree of preparation prior to injection. Systems that enable the patient or caregiver to carry out reconstitution of lyophilised or powdered drugs, such as the MixJect® (Figure 1) and Mix2Vial® reconstitution systems from Medimop Medical Projects Ltd, have been used to help patients prepare medications such as Factor VIII used to treat haemophilia and Betaseron® for multiple sclerosis.

Recent trends in auto-injectors include the increasing use of electronics for re-usable systems, continuing growth in disposable devices and ergonomic enhancements designed to improve an impaired patient's ability to deliver

an effective injection. However, current systems based on glass primary containers have had problems with issues such as breakage, incomplete injection and variability of functional performance. Many are also limited with regard to dose size, which can detract from the patient experience by either requiring more frequent injections or intravenous administration due to the high volume of drug needed.

With the increasing trend toward self-injection and home administration of drugs, there is a growing need for drug delivery devices that can deliver higher volumes of drugs subcutaneously. Innovations in this area include novel devices that are either attached to the body, such as a patch injector, or delivery systems that meet the requirements of biologics.

As these trends grow, pharmaceutical manufacturers must address the relationship between the delivery system design and the end-user earlier in the drug development process. This relationship is perhaps the most important factor in a drug product's success. Since a drug is not effective if it's not administered properly, or the patient does not adhere to the appropriate regimen, consideration of the delivery system early in the product development process is vital. Systems that support or improve patient compliance can provide a competitive advantage to



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their companion drug products, particularly in a crowded market.

Through the use of novel materials, effective early partnerships with packaging manufacturers and human factors considerations, pharmaceutical manufacturers may help reduce the risks associated with delivery systems or devices and enhance the rewards, including patient adherence to treatment regimens and long-term brand loyalty.

### MITIGATING RISK: NOVEL MATERIALS OFFER DELIVERY SYSTEM SOLUTIONS

For any drug product – new or old – the risk of a market recall is ever present. The US FDA has become increasingly aware of glass-related quality issues, including breakage, cracks, delamination, contamination and particulates (often formed over time due to interaction between the glass and the drug). The number of recalls related to glass issues has increased in recent years. Also, any automated injection process runs the risk that the system may not function effectively. Risks include failure of the device and failure of the device-container combination. In either case, the system would not be able to deliver the drug to the patient.

High-profile recalls have been initiated for drugs that have experienced problems between the container closure system and the device. For example, if a glass prefilled syringe is used in an auto-injector, there is a possibility of breakage caused by the force used to activate the system. Further, glass syringes within an auto-injector may fracture or break if subjected to a sudden force, and this may not be visually detectable. Other issues, such as uneven siliconisation, may result in incomplete injections, and there have been recalls for potential loss of sterility caused by cracked glass syringes.

Understanding how the device and drug container integrate is a critical part of ensuring the effective operation of the drug delivery system for the end user. Recent developments around the use of polymeric materials for drug containment have allowed delivery system companies to work closely with drug manufacturers to develop novel systems designed specifically to meet patient needs. The design and manufacturing flexibility of a polymeric drug container, combined with the ability to create patient-friendly devices designed with human factors engineering, enables the development of more innovative overall delivery systems that may aid in patient compliance through ease of use and enhanced technology. Cyclic olefin polymers, such as the Daikyo Crystal Zenith® polymer, provide a transparent, break-resistant alternative to glass.



**Figure 1: The MixJect® reconstitution system from Medimop enables a patient or caregiver to carry out reconstitution of lyophilised or powdered drugs.**

### INTEGRATED SYSTEM DESIGN CONSIDERS HUMAN FACTORS

Criteria for selecting a successful integrated system must include not only how the drug product interacts with its primary containment system, but also the needs of the end-user and how the patient interacts with the delivery system. A drug product must provide treatment in an appropriate form that enables effective delivery with an optimum delivery rate and frequency. Additionally, the drug must be held in a container that maintains safety and optimum quality over a period of time. Finally, the drug should be compatible with the containment system and be designed to enhance the drug delivery experience for the patient or caregiver.

As patients take an even greater role in decisions regarding their treatment, easy to use delivery systems will be essential. Increasingly, the market is evolving toward the use of sophisticated, patient-friendly delivery systems with increased capabilities for use in the home environment that deliver more than 1 mL in a single injection, including electronic patch injection systems. These technologies deliver biologics and other high-viscosity drugs at larger volume doses over a longer period of time with minimal patient discomfort or inconvenience.

There is a strong correlation between drug product administration and patient adherence, so manufacturers must shift from a product-centric focus to a patient-centric focus when designing an effective drug delivery system. To build an effective delivery system, manufactur-



**Figure 2: The ConfiDose® auto-injector system platform.**



**Figure 3: SmartDose® electronic patch injector system platform.**

ers must focus on the relationship between the delivery system design and the patient, and develop a deeper understanding of the emotional and physical needs of the intended user.

Human factors testing allows manufacturers to support delivery system development from a range of critical perspectives. From a regulatory standpoint, such testing accounts for important human factors inputs that the FDA expects to see as part of the development process for any delivery system. These same inputs also ensure that risks from user-based errors are identified early in the development process and provide critical user information for the development team to initiate risk mitigation measures throughout the development cycle.

The process by which a testing team engages users should also yield valuable information regarding a user's physical and emotional needs, desires and the lifestyle challenges faced in managing the disease. Understanding how to analyse and effectively utilise this information serves as a strong foundation for guiding the design process

to develop delivery systems that are not only intuitive and easy to use, but also encourage experiences that enable positive emotional connections between the user and delivery system.

Addressing all of these factors is the cornerstone to enabling a delivery system to achieve the goals of encouraging adherence and fostering brand loyalty between patient and pharmaceutical manufacturer while mitigating both product and development risks. Drug manufacturers should seek partners who can apply proprietary technologies, manufacturing excellence, and market and patient understanding to ensure that a partnership works seamlessly to help mitigate risk, encourage patient adherence and enhance the value of a product.

### FUTURE TRENDS

With the increase in combination products – and drug/device combinations in particular – many pharmaceutical companies are becoming involved in drug delivery device technologies

and the accompanying containment materials much earlier in the drug development process. Pharmaceutical and biotech companies are working closely with drug delivery system manufacturers to ensure that there is efficient development of an overall system to enable cost-effective drug delivery. Cost factors may include the ability to move the product to market as quickly and effectively as possible; reducing in-process rejects due to breakage or lack of function; and the overall cost of quality, which has to be built into a system from the start.

West is uniquely placed with a well-established expertise in primary containers, including polymeric systems, and has combined this expertise with innovative delivery system technology platforms such as the ConfiDose® auto-injector system platform\* (shown in Figure 2), the SmartDose® electronic patch injector system platform\* (shown in Figure 3) and many proprietary technologies for mixing and reconstitution. These technology platforms offer a range of options for dose volume, injection time and electronic control/feedback, and are designed to meet the challenges of today's innovative drug products.

As the industry continues to grow through more sophisticated drug delivery systems, there will be an increase in self-administration of therapies. For novel devices, continued trends toward safety and a strong focus on the needs of the patient will drive the market, while reimbursement, environmental factors and regulatory pathways will continue to influence drug delivery system development. In addition, understanding the importance of the drug container as it relates to the integration into the overall drug delivery system will continue to be a key factor. Early partnerships can aid both pharmaceutical and delivery system manufacturers as the industry moves forward.

*\*For investigational use only by our pharmaceutical and biotechnology development partners. West markets SmartDose® and ConfiDose® as integrated systems with drug filling and final assembly completed by the pharmaceutical company.*

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**ConfiDose<sup>®</sup>** Auto-Injector System  
 Platform Technology\*



**SmartDose<sup>®</sup>** Electronic Patch Injector System  
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*For investigational use only*

For your home-administered injectable drugs, you want a safe, easy-to-use delivery system. With a West system, you can deliver a positive end-user experience.

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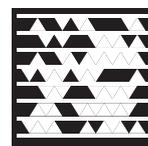
The ConfiDose system technology is designed for a 1mL dose; the SmartDose system technology is designed for larger doses.

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\*West markets these products as multi-component systems only. Final assembly of the prefilled component is completed by the pharmaceutical company.

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# USING NOVEL RECOMBINANT HUMAN SERUM ALBUMINS FOR OPTIMAL DRUG SAFETY AND STABILITY

In this piece, Mark Perkins, PhD, Customer Solution Specialist, Novozymes Biopharma, reviews the key drug formulation challenges and issues associated with conventional excipients. Dr Perkins also compares the physicochemical properties of a range of commercially available albumins, and presents application examples to demonstrate the unique properties of rAlbumins.

Pharmaceutical manufacturers rely heavily on the correct choice of excipients for the success of their formulation programmes. However, conventional excipients have been proven to suffer from performance inefficiencies, particularly when it comes to the stabilisation of complex small molecules, proteins and peptides. In addition, excipients from different vendors and sources may exhibit significant variability in their functional and physical properties. Recently developed, multifunction-

## DRUG FORMULATION CHALLENGES

An acceptable drug formulation must be safe to administer, must be physically, chemically and biologically stable, and must have low immunogenicity and an appropriate shelf-life. However, developing new or redesigning existing therapeutics with these attributes is a time- and resource-consuming procedure, the success of which cannot be guaranteed.

Increasing pressure is thus placed on drug manufacturers to implement improved drug formulation processes.

Excipients play a vital role in the manufacture, delivery and performance of safe and stable pharmaceutical products, therefore choosing an appropriate excipient early in the development process is crucial.

During preformulation stages, the physical and functional characteristics of excipients must be evaluated in order to determine their desirable properties. Excipient characterisation also enables drug manufacturers to predict potential interactions between the drug and the excipient that may impact the safety and efficacy of the final product.<sup>1</sup> However, excipients obtained from multiple vendors may exhibit different properties, depending on the

**“TO DEMONSTRATE THE PHYSIOCHEMICAL VARIABILITY OF ALBUMIN BETWEEN DIFFERENT VENDORS, A SELECTION OF ANALYTICAL TESTS WERE PERFORMED ON TWO rALBUMINS & A RANGE OF COMMERCIALY AVAILABLE ALBUMINS.”**

al recombinant human serum albumins (rAlbumins) offer superior functional and physicochemical properties, stability, pharmacokinetic attributes and regulatory compliance. As a result, more rapid development of safe and stable formulations of even the most difficult drug candidates can be achieved.



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quality standards, reliability of supply, and regulatory and technical support of each vendor. Additionally, excipient characterisation can be time consuming and costly, delaying the registration process and prolonging time-to-market.

## ISSUES WITH CONVENTIONAL EXCIPIENTS

Formulation of challenging drug candidates from the classes of complex small molecules, difficult-to-stabilise antibodies, proteins, and poorly soluble or surface-binding peptides may not be achieved with conventional stabilising excipients such as sugars, amino acids and detergents (SADs). In response, human serum albumin (HSA) has emerged as an efficient alternative. HSA is the most abundant protein in human plasma and has a long history of pharmaceutical use. In addition, albumin is a multifunctional excipient contributing to a reduction in aggregation, oxidation and adsorption losses. Together these benefits make albumin an ideal excipient.

Traditionally, HSA has been sourced from human serum, however due to increasing regulatory concerns in relation to the use of animal-derived material in the manufacture of human therapeutics and the quality and variability issues arising from the use of a pooled plasma product, there is a growing need for a safer and more consistent albumin product.

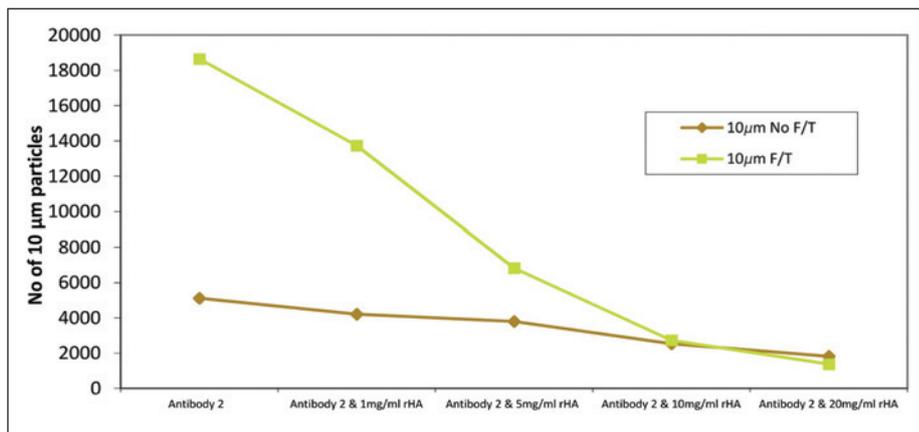
## THE ADVENT OF RECOMBINANT HUMAN SERUM ALBUMINS

A new generation of recombinant human serum albumins (rAlbumins) have been developed, which are manufactured through an animal-free process to the highest quality standards, while also delivering safe, consistent, stable and high-performance pharmaceutical products. Additionally, by using rAlbumins, development timelines can be considerably reduced, accelerating time-to-market.

The new rAlbumins also have unprecedented technical and regulatory support. They are manufactured according to cGMP quality standards in large-scale facilities, are USP-NF compliant, and supported by a strongly documented safety package and drug master file. As a consequence, rAlbumins reduce registration and regulatory issues.

## QUALITY CHARACTERISTICS OF RALBUMINS

To demonstrate the physicochemical variability of albumin between different vendors, a selection of analytical tests were performed on two rAlbumins (Novozymes' Recombumin®



**Figure 1: Measurement of sub-visible particles below 10 µm detected for a monoclonal antibody formulated both with and without rAlbumin. Data were recorded before and after freeze-thawing.**

and AlbuCult®) and a range of commercially available albumins.

### Visual Inspection

Visual inspection examines the colour and clarity of the excipient under investigation, providing drug manufacturers with first impressions of product quality and purity, which may influence their decision as to which product they will move forward with. A selection of albumins from various vendors were tested, derived from both serum extraction and recombinant sources. All albumins demonstrated good clarity, however significant colour variability was observed, with rAlbumins being the least pigmented, an indication of high purity.

### Excipient Purity

Size exclusion chromatography (SE-HPLC), SDS-PAGE and electro-spray mass spectrometry (ES-MS) were used to examine excipient purity. Experimental results indicated rAlbumins as the most homogeneous products. SE-HPLC showed that rAlbumins had more than 97% monomer,

for unwanted aggregation to occur, negatively impacting product recovery, delivery and immunogenicity. In order to enhance operational flexibility while maintaining product stability, protein drug substances may be exposed to bulk freeze-thaw stress. This means that proteins may be exposed to low temperature, altered concentration of solutes and pH changes, all of which can alter the conformation of the protein molecule, leading to the formation of aggregates and visible and sub-visible-particles.<sup>2</sup>

rAlbumins can serve as effective stabilisers against protein aggregation during the freeze-thaw process. A malarial antigen protein, merozoite surface protein 2 (MSP-2) (4.0 mg/ml), subjected to freeze-thaw cycles in the presence of varying concentrations of an rAlbumin (Recombumin®, Novozymes), was shown to be protected from degradation, as a result reducing aggregation.

A fully humanised IgG4 antibody (1 mg/ml) with varying rAlbumin concentrations was subjected to five controlled freeze-thaw cycles (-40 °C to + 20 °C). Subvisible particles at 10 µm were analysed using a HIAC 8012 liquid particle

## “IT IS NECESSARY TO CHARACTERISE THE PHYSICAL AND CHEMICAL PROPERTIES OF EACH EXCIPIENT ACCURATELY DURING PREFORMULATION STAGES”

compared with the most heterogeneous sample tested, which had only 80% monomer. The homogeneity and purity of rAlbumins compared with other commercially available albumins were also confirmed by SDS-PAGE and ES-MS.

## APPLICATION EXAMPLES

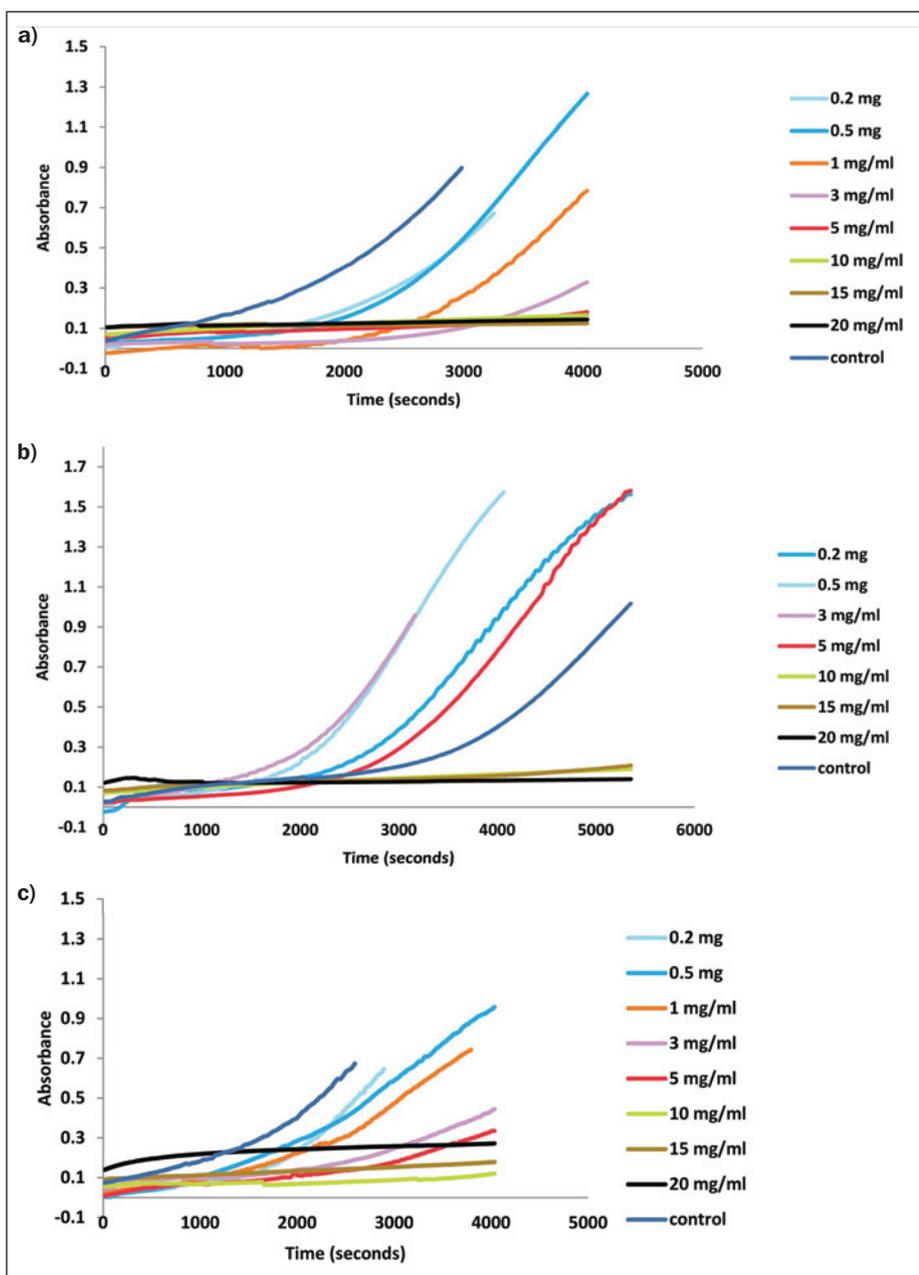
### Protection against Aggregation during Freeze-Thaw

During manufacture and storage of therapeutic proteins and vaccine products, it is common

counting system. Using rAlbumin at 10 mg/ml was sufficient to eliminate 10-µm particle formation in a concentration-dependent manner (Figure 1).

### Protection Against Aggregation During Transport and Storage

Following final formulation, fill and finish, the final drug product can be subjected to additional stresses during transport and storage. Liquid formulations in particular are exposed to temperature variation and agitation, which can cause protein aggregation and increase particle



**Figure 2: Testing the colloidal stability of rAlbumin and a range of formulation excipients in three separate IgGs in the presence of different rAlbumin concentrations.**

formation. rAlbumins were used to assess colloidal stability. Turbidity changes in solution after exposure to elevated temperature were measured for three separate IgGs in the presence of different rAlbumin concentrations (Figures 2a, 2b and 2c). The lag time increased in a concentration-dependent manner compared with the control formulation, suggesting that rAlbumin offered protection against aggregation.

A fully humanised antibody (Ab3) at 50 mg/ml was then subjected to vigorous shaking (600 rpm) in the presence of various rAlbumin concentrations and the level of particle formation was analysed. The rAlbumin contained a small amount of polysorbate 80, so a control sample containing 0.002% polysorbate 80 and no rAlbumin was included in the experiment.

Results showed that vigorous agitation caused a greater than four-fold increase in the number of 10  $\mu\text{m}$  particles in the formulation containing Ab3 plus 0.002% polysorbate 80 compared with unshaken control. rAlbumin protected against 10  $\mu\text{m}$  particle formation during agitation in a concentration-dependent manner. It also provided comparable protection in this formulation to the 0.01% polysorbate 80 that is typically used in antibody formulations.

#### Protection against Oxidation

Excipients and active drug products are vulnerable to oxidation, especially excipients containing reactive aldehyde, alcohol and phenolic groups. The methionine and cysteine residues on protein surfaces can also be par-

ticularly susceptible to oxidation. Induced by normal process operations, such as air and light exposure and heavy metal ions, modification of proteins by oxidation can lead to inactivation or unwanted activation of the drug, altered binding affinities, increased susceptibility to aggregation, proteolysis, and altered immunogenicity.

Current US FDA legislation requires oxidation to be controlled in the product formulation of therapeutic proteins.<sup>3</sup> However, this is a challenging task as oxidative degradation reactions can be complex. Free radical formation through normal process operations interacts further with oxygen to form peroxy radicals. These radicals can then interact with the oxidisable drug substance and break down to produce more free radicals, which can then be involved in additional reactions. Detergents such as Triton and polysorbate 80, which are widely used in biochemical formulations, are susceptible to oxidative degradation during storage with the formation of unwanted peroxides.<sup>4</sup> New rAlbumins act as potent anti-oxidants, primarily due to the free-thiol at position Cys 34 and its surface methionine residues, with HSA-SH serving as a potential scavenger for reactive oxygen species (ROS).

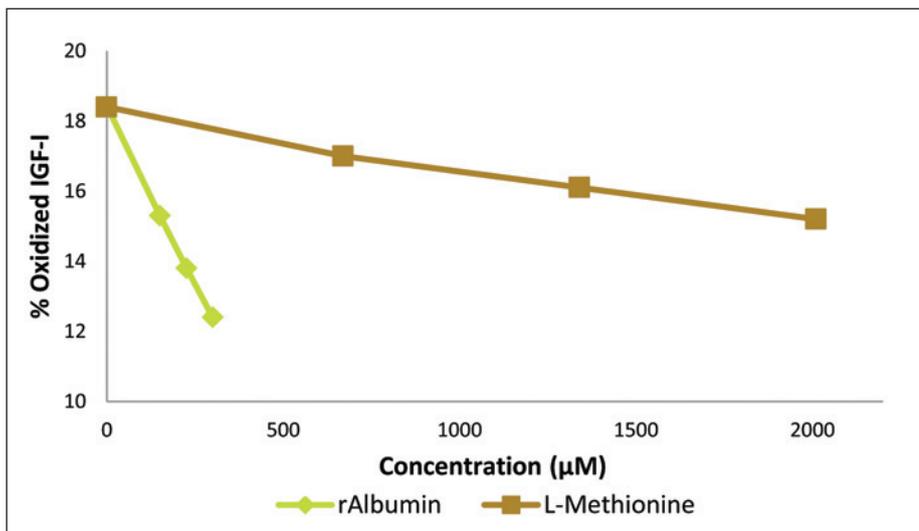
Pharmaceutically relevant concentrations of insulin-like growth factor-I (IGF-I), known to be susceptible to oxidation during storage, and two malarial antigen protein MSP-2 allelic variants, were exposed to trace amounts of the oxidising agent hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) in the presence of different rAlbumin concentrations. rAlbumins were shown to reduce protein oxidation effectively, thereby enhancing protein stability.

To demonstrate further the ability of rAlbumin to serve as an efficient antioxidant following exposure to  $\text{H}_2\text{O}_2$ , a comparison was drawn with the commonly used antioxidant L-methionine. rAlbumin was found to provide almost complete protection against the formation of oxidised species at the top concentration and proved effective at molar concentrations approximately 13 times lower than that of L-methionine (see Figure 3).

#### Reduced Non-Specific Binding to Surfaces

Non-specific adsorption to surfaces can cause significant instability of pharmaceutical products since it alters the concentration of the drug in the administered dose, potentially changing its pharmacokinetics and efficacy. Additionally, protein binding to surfaces can result in conformational changes, leading to aggregation and loss of product.<sup>5</sup>

The most common method employed to minimise non-specific adsorption of protein drug products is to use blocking agents in for-



**Figure 3:** H<sub>2</sub>O<sub>2</sub>-induced oxidation of IGF-I (20 µg/ml) in the presence of increasing concentrations of Recombumin or L-methionine.

mulation. Owing to its high interfacial activity that enables it to bind to both hydrophobic and hydrophilic surfaces, rAlbumin acts as an effective blocking agent preventing protein adsorption.<sup>6</sup> This was proven in a study, whereby the recovery of TGF-β3, an active ingredient used in scarless wound healing, or the malarial antigen protein (MSP-2), was measured after exposure to glass containers in the presence of rAlbumin. Results confirmed that rAlbumin can significantly reduce product loss to manufacturing and storage surfaces (Figure 4).

## CONCLUSION

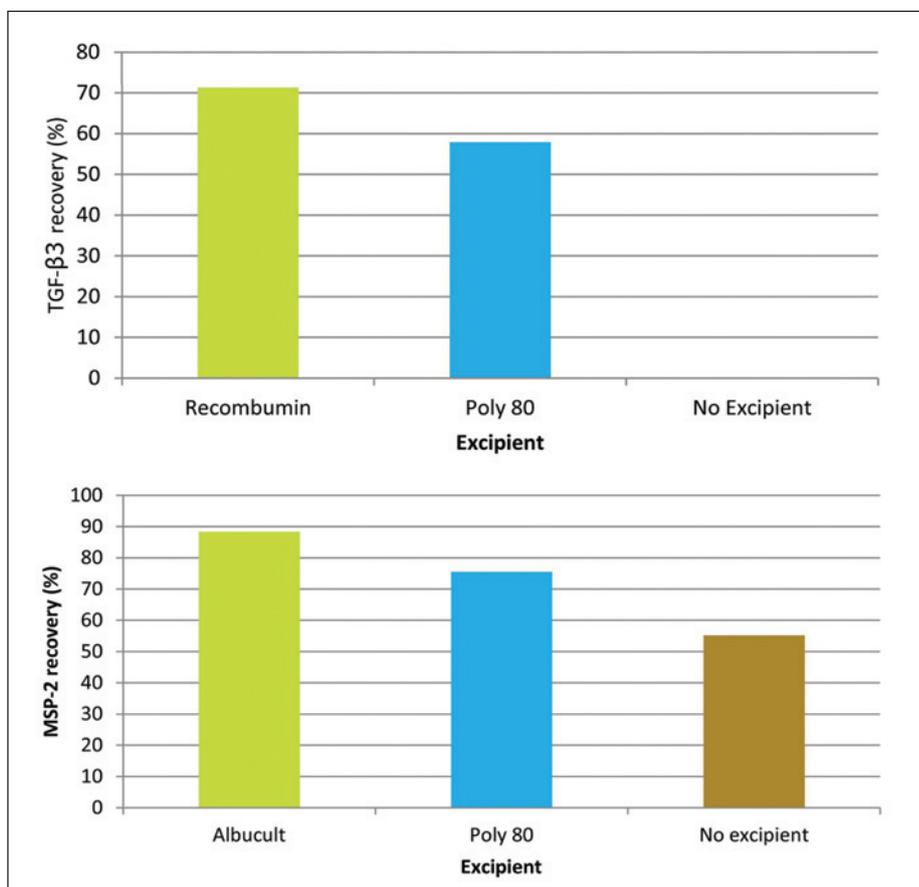
Excipients play a vital role in drug formulation programmes, ensuring stability and performance of pharmaceutical products. However, physical and chemical interactions between the drug and excipient as well as excipient impurities can lead to loss of efficacy and safety. To address these issues, it is necessary to characterise the physical and chemical properties of each excipient accurately during preformulation stages and make sure that they are all manufactured to the highest quality standards.<sup>7,8</sup> Experimental data demonstrates the vast variability between vendors and sources of albumin as a commercial excipient. rAlbumins offer a powerful formulation solution that facilitates the development of safe and stable drug products by reducing aggregation, oxidation and surface adsorption.

Particularly valuable for liquid formulations, rAlbumins can significantly decrease the attrition rate in formulation development and provide increased freedom to choose the best candidate for further development.

To learn more about Novozymes' rAlbumins, please visit: [www.biopharma.novozymes.com](http://www.biopharma.novozymes.com).

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**Figure 4:** Measurement of protein recovery in the presence of excipient.

NOVOZYMES

# STABILITY

BIOPHARMA

## IS OUR MIDDLE NAME

### Stabilizing your drug formulation is simpler with rAlbumin

Our high quality animal-free recombinant albumins (rAlbumin) have been developed and optimized for your drug delivery and formulation needs. Manufactured to cGMP quality standards in large-scale facilities, Novozymes Biopharma's rAlbumins are USP-NF\* compliant and are supported by a strongly documented safety package and drug master file.

Ideal for stabilizing drug formulations, they can help you to:

- Achieve liquid formulations of protein therapeutics
- Limit protein loss due to non-specific adsorption
- Prevent functional or structural changes caused by oxidation
- Reduce aggregation/sub-visible particle formation and therefore potential immunogenicity concerns

Find out more about stabilizing your drug formulation with rAlbumins, and the additional benefits that these products offer you, by visiting our website or emailing [biopharma@novozymes.com](mailto:biopharma@novozymes.com)

\*Meets National Formulary (NF) standards as published by United States Pharmacopeia (USP)

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novozymes®   
Rethink Tomorrow

## COMPANY PROFILE – HASELMEIER



Haselmeier is dedicated to meeting the self-injection needs of pharmaceutical manufacturers and patients.

In 1920, Wilhelm Haselmeier established a medical device company in Stuttgart, Germany. Since that time, Haselmeier has continued to develop and create injection devices designed for patient comfort and ease-of-use.

Today, Haselmeier is one of the leading designers and manufacturers of pen and auto-injector systems. Many of these systems feature Haselmeier's patented hidden needle system, which is designed to help patients overcome the fear of self-injection, provide a more comfortable injection and help increase compliance of the patient's medication.

### PRODUCT DESIGN

Our capabilities include design and development from concept to finished device using Haselmeier's strong IP portfolio or tailoring of existing Haselmeier designs to meet customer and therapeutic needs.

All designs undergo comprehensive testing, in addition to risk management, risk analysis and FMEA design review. Three-

dimensional CAD designs are utilised for creation of customer-specific concepts or customisation of existing designs.

### MANUFACTURING AND QUALITY

As a specialist in the manufacture of complex system assembly, product integrity is assured by Haselmeier's manufacturing processes. All new device concepts are cre-

13485:2003 and Annex II, Section 3 of the European Directive 93/42/EEC on medical devices. CE certification is certified by TÜV SÜD Product Service (Munich, Germany).

### PLATFORM & PRODUCTS

**Axis Pen System: variable-dose injection device**

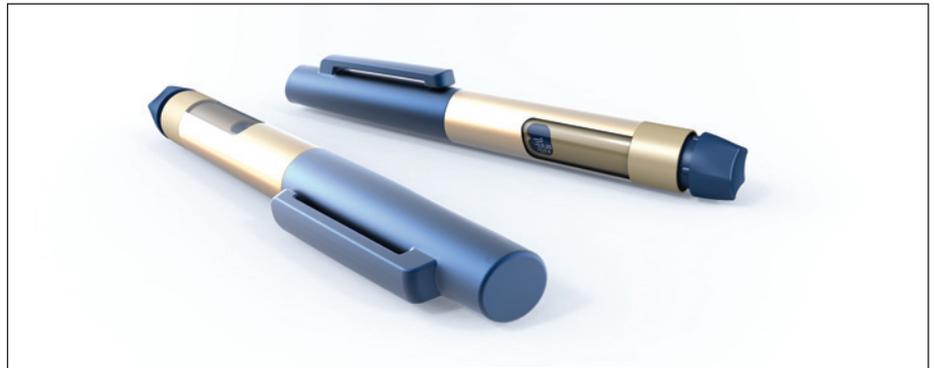


Figure 1: Axis Pen System – variable-dose injection device.

ated with an "Integrated Design Approach" which focuses on both, the device and the efficiency of manufacture and assembly.

All manufacturing is within compliance with applied standards EN ISO

The Axis Pen System is a variable-dose injection device for manual injection. It is available in a disposable or re-usable presentation. The Axis-D and Axis-R Pen Systems (Figure 1) provide a new, unique technical function.



Figure 2: i-pen: re-usable – variable dose injection device.



Figure 3: i-pen?: re-usable – variable dose all-plastic injector device.

The Axis pens feature:

- No or minimal priming
- Accurate dose reading with sliding window
- No rotating outer components
- Protected dose scale

#### **i-pen: re-usable, variable dose injection device**

The Haselmeier i-pen is a re-usable, variable-dose injection device for use with a standard 3 ml cartridge. The i-pen (see Figure 2) features an elegant non-medical design which is the result of extensive research and patient testing.

The i-pen is available as a standard Haselmeier design or can be customised to your specific requirements. It features:

- Dose adjustment from 0.01-0.6 ml per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All metal outer body

#### **i-pen<sup>2</sup>: re-usable, variable dose all-plastic injector device**

The i-pen<sup>2</sup> (Figure 3) is a reusable, variable dose injection device for use with a standard 3ml cartridge. The i-pen<sup>2</sup> was specifically created to provide a high-quality pen at economic cost.

The i-pen<sup>2</sup> is available as a standard Haselmeier design or can be customised to your specific requirements. It features:

- Dose adjustment from 0.01-0.6 ml per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All plastic components

#### **Softpen – reusable injection device**

The Softpen (Figure 4) is a fully automatic, re-usable injection device featuring Haselmeier's patented hidden-needle design. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue followed by delivery of the solution. The Softpen features:

- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection
- Multiple injections from single 3 ml cartridge



**Figure 4: Softpen – a fully automatic, re-usable injection device featuring Haselmeier's patented hidden-needle design.**



**Figure 5: The disposable Penlet is a fully automatic, fixed-dose injection device designed for use with a standard 3 ml cartridge.**

#### **Penlet – disposable, fixed-dose injection device**

The Haselmeier disposable Penlet is a fully automatic, fixed dose injection device designed for use with a standard 3ml cartridge. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue which is followed by delivery of the solution. The Penlet features:

- Ready for use by the patient and no dose adjustment required
- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection

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# Technomics



## THE NEW *i-pen*<sup>2</sup>

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# THE IMPORTANCE OF USABILITY STUDIES IN THE DESIGN OF A SECOND-GENERATION INJECTION DEVICE FOR PARKINSON'S DISEASE

Here, Adele Graham-King, Business Development, Smallfry, describes the crucial role of usability studies in the development of a second-generation subcutaneous infusion device for use in the treatment Parkinson's disease symptoms.

Human beings are complex and their behaviours are unpredictable – we don't do what we're told, we do what we want. Even those who are educated to understand the consequences of non-compliance of self-medication will resist and fall short in their regimens if they don't like what they have to do, or if the limitations of treatment interfere with their daily lives or become attention focusing from others. Only by considering how people feel and react, manage and want will the design community be successful in fulfilling the enjoyable patient journey, making medical treatments or devices part of overall quality-of-life improvement.

Long-term, progressive diseases are life altering and anything that can assist in the management of these conditions is important in the prognosis, and quality of life for patients. Recent decades have seen an exponential shift in the number of patients with progressive degenerative medical conditions self-medicating outside the hospital environment within their own home. Aside from the financial relief on healthcare costs (for example, on NHS spending in the UK) this can have a substantial impact on the quality of life and care to the patient and their family.

The design community widely accepts that end-user conformity is fundamental to the potential commercial success of a medical device. However, only the patient or medical/care professional can confirm how socially and clinically acceptable it is to use on a regular basis.

Parkinson's disease is a good example of this. It is a neurodegenerative condition that manifests itself in varying degrees of severity yet generally results in diminished fine motor function, slowness of movement, altered gait and a recognisable tremor. Later stages can include cognitive impairment, behavioural changes and dementia. As there is no cure for the condition, treatment is based around symptomatic improvement, maintaining quality of life and managing symptoms.

Due to the effects of the disease and the fact that they are not only physical, but cognitive

and mental, a wide variety of considerations need to be taken into account when designing and developing potential therapies and mechanisms of drug delivery. Specifically in Parkinsonism there is a characteristic of 'punding' whereby individuals may develop habits of obsessively performing tasks repetitively, adding another dimension to consider in the design process.

The patient is the new consumer – patients are able to choose what they use in treatments to an extent and they reserve the right to say 'no'. It has become wise business to examine the outcomes of our design processes with this in mind and embed the findings in marketed products.

The Apo-Pod, from STADA Arzneimittel subsidiary Britannia Pharmaceuticals Ltd (Newbury, Berkshire, UK), is a continuous subcutaneous infusion device used by late-stage Parkinson's disease sufferers delivering apomorphine via a pump mechanism. Historically, the infusion set was housed in a material pouch to carry the device which consisted of a subcutaneous syringe and a pump (see Figure 1).

Due to the complexity of the drug assembly process and number of returns the manufacturer received, they took the initiative and embarked up a design innovation project in partnership with Smallfry to make the pump system more portable and user friendly in terms of assembly, disassembly and usability.

The outcome of the design process resulted in the second generation of Apo-Pod (Generation II), presented in a splash- and impact-resistant case, with improved usability and aesthetic appearance (Figure 2).

During the innovation process, Smallfry assessed the usability of the device. The original system required various tasks to be completed in order to assemble the drug dosing unit; retrieving the parts from the bag, assembling the pump, inserting the vial, assembling the line and a Luer connection and then infusing the active ingredients via a pump driven process through a subcutaneous infusion line.

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Many of these tasks require a reasonable amount of dexterity and fine motor control in a patient cohort that is often compromised in these areas. Indeed, many patients were unable to complete these tasks so they fell to carers, both professional and personal. Ultimately if the process was to be successful these steps needed to be reduced and simplified.

The casing was redesigned to facilitate improved usability so the pump no longer needed to be removed from the unit, which also prevented patients from potentially interfering with the pump. The primary packaging was more fully integrated and designed so that it could be attached to a belt or trousers, hiding the actual device and also the fact that there is a medication process taking place while in situ. This was one of the primary aims of the alteration in design.

A flange has been introduced to the pump to act as an adapter to the drug vial – this makes it easier to insert the vial which is held in place through compression and seals against leakage, providing immersion resistance with a series of ‘O’-rings. The outcome of the process resulted in a new package with patent protected design features, giving the same device enhanced usability, fewer assembly steps, and providing overall a better user experience.

But.... it is a common pitfall to assume that a design process will automatically improve the usability of a medical device within specific patient populations. Since each group of people have their own individual needs and issues it is necessary to be able to assess how a device will be received by the relevant cohort. In order to assess and verify the effectiveness of the design alterations a formative usability test was carried out by an independent consultancy to assess various parameters of the Apo-Pod. The groups, which comprised both patients and carers, included:

- a) Currently injecting Parkinson’s disease patients
- b) Non-injecting Parkinson’s disease patients
- c) Non-professionally qualified carers and care nurses for Parkinson’s disease patients
- d) Professionally qualified Parkinson’s disease nurses

In a controlled environment led by an independent moderator and an independent observer each group was asked to perform the following tests:

- a) Assembly of the pump and infusion set
- b) Installation of the drug system and infusion set



**Figure 1: The first-generation Apo-Pod infusion device as it used to be presented.**

- c) Discharge of the drug such that it could be infused in an appropriate manner
- d) Disassembly of the pump and infusion set

The patients were placed in a simulated setting that was similar to the home environment. Independent observations and records were maintained along with verbal and written feedback from the participants.

The outcomes of the usability study resulted in the following observations:

- a) All tasks (100%) pertaining to the Primary Operating Functions (set up, preparation and execution of the drug delivery) were successfully performed across all user groups.
- b) 69% of the Primary Usability Goals (20 out of 29 tasks) were completed by 100% of the participant cohort.
- c) Out of the nine remaining usability goals there was an average of 88.8% completion across all groups.
- d) The device received an overall usability score of 91% across all tasks.
- e) Within all the user groups the new design was well received both on an aesthetic and

usability basis. The fact that it no longer “looked medical” was important and made a difference.

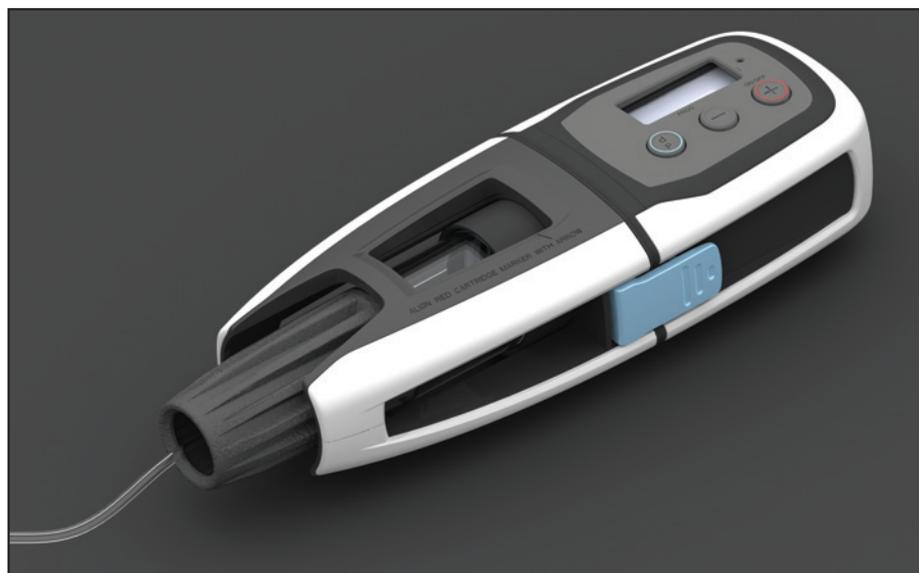
- f) The concealment of the device provided enhanced protection from water and impact damage.

Enhanced usability has been achieved due to the following alterations in design:

- a) A reduction in the number of steps in the set-up of the device.
- b) Introduction of an adapter to facilitate the attachment of the drug vial to the pump.
- c) The avoidance of the medical appearance.

The study has provided valuable insights into how patients and carers receive the device and how they will cope in the home setting. It is this type of insight that assists the manufacturer and developer effectively to achieve a high degree of conformity from the patient.

Ultimately the clinical prognosis and quality of life of sufferers of long-term conditions such as Parkinson’s disease rely on these individuals being able to self-medicate or receive consistent and simple drug regimens.



**Figure 2: The new Apo-Pod (Generation II).**

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September 2012	Drug Delivery in Diabetes	August 20th
October 2012	Prefilled Syringes	September 3rd
November 2012	Pulmonary & Nasal Drug Delivery (OINDP)	October 1st
December 2012	Delivering Biotherapeutics	November 5th
January 2013	Oral Drug Delivery	December 3rd
February 2013	Prefilled Syringes	January 14th
March 2013	Transdermal Delivery, Microneedles & Needle-Free Injection	February 4th
April 2013	Pulmonary & Nasal Drug Delivery	March 4th
May 2013	Injectable Drug Delivery 2013: Formulations Focus	April 2nd
June 2013	Injectable Drug Delivery 2013: Devices Focus	May 6th

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# OVERCOMING THE LIMITATIONS OF TRADITIONAL FOCUS GROUP RESEARCH

In this piece, John Reynard, Chief Executive Officer, Creative Medical Research, highlights the importance of market research in device development, and describes a methodology for combining qualitative and quantitative data from focus groups.

Successful medical device developers understand that as well as being a regulatory necessity, market research is essential for testing the **real market appeal, safety and usability** of their concepts and designs. There are various market research techniques that are appropriate for each phase of new product development (see Figure 1). In this article we will look at qualitative research, in the form of ethnographic research and the use of focus groups.

Ethnographic research is certainly the very best starting point for identifying ill-met and unconscious clinician / patient needs.

Interviews are conducted in hospital or at the patient's home and the clinical procedure is viewed in silence while the interviewer makes notes on what is being observed. After the procedure has been completed the interviewer asks in-depth questions around the detail of product usage, what worked / didn't

## "THE INTEGRATED FOCUS GROUP COMBINES BOTH QUALITATIVE AND QUANTITATIVE METHODOLOGIES"

work, what was found challenging, what they would have liked to have done that they could not, and so on.

Armed with such insight designers can start to sketch out possible solutions and it is at this moment – that is, prior to production of any prototypes at all – that such concepts should be tested with users.

The "Voice of the Customer" MUST be heard at this time before any design decisions are made, otherwise assumptions creep into the design that have a nasty habit of becoming permanent, a costly mistake that can be avoided.

### INTEGRATED FOCUS GROUPS

Focus groups are used to gather user requirements in the early stages of product design and for user evaluation of product features at the concept stage. Typically seven or eight people is an optimum size of group; any more and it becomes difficult to obtain views from everybody. It is often useful to have groups in different parts of the country, region or the world to cover different purchasing habits and cultural differences.

A skilled, medically conversant moderator is crucial, together with a discussion guide. The aim of the guide is to highlight areas that need to be covered, but an experienced and confident moderator will allow the discussion to go where it is needed in order to explore ill-met and un-met customer needs.

Often what a client company may think is important turns out not to be and other more essential considerations emerge.

Focus groups however can have limitations:

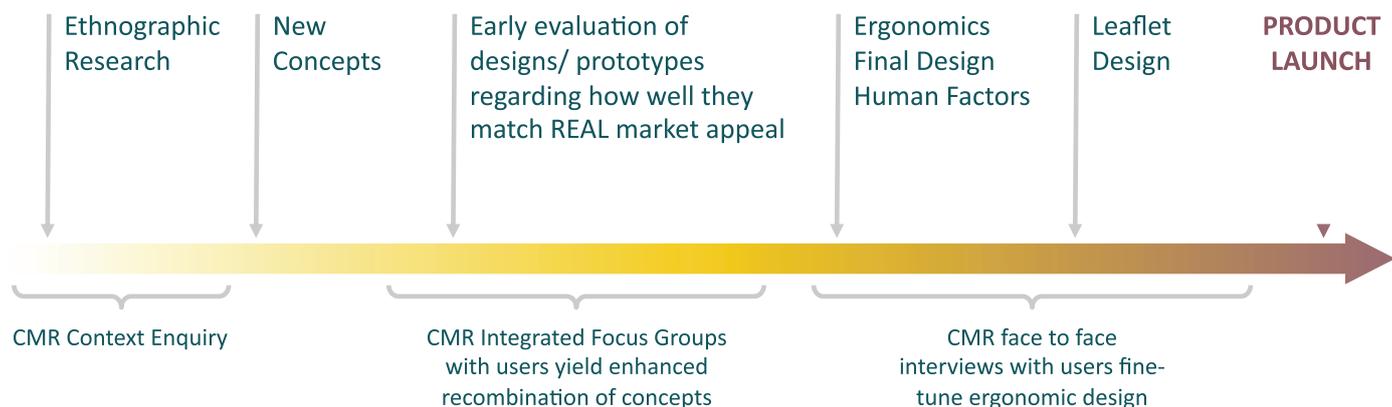
- Even with an experienced moderator, one or two people may dominate the group and sway the opinions of the others
- With sensitive topics, some people may not wish to share their views publicly, and these



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**Figure 1: Different Market Research Techniques Throughout Product Development**

can be important views that need to be included

- It can be difficult to show actionable data from a small number of focus groups where there were widely differing views
- A purely qualitative methodology doesn't satisfy the discerning eyes of stakeholders who want hard facts and figures on which to make key decisions

The alternative is to conduct quantitative studies, conducting individual interviews with a larger number of people by telephone or face-to-face, but these are time consuming, costly, and lack the creative input that comes from the group dynamic.

As a response to this dilemma we have developed the Integrated Focus Group, which combines both qualitative and quantitative methodologies. In this scenario, illustrated in Figure 2, respondents are presented with new designs, prototypes and concepts in one-to-one interviews. They answer a quantitative questionnaire on initial impact, without interacting with anyone else.

The participants are then brought together in a group discussion. The quantitative answers are quickly analysed and the results are presented to the group. In this way the creative session starts from an unbiased starting point of knowing overall the views of everyone and the discussion can be used to dig deeper into the reasons for the

responses and the session guided in such a way that the participants interact and develop the concepts further in line with true end user needs.

One consistent benefit of this type of focus group is that no individual respondent dominates the group because all participants con-

tributed sample is statistically robust and helps underpin decisions.

The qualitative findings from the group give the depth of understanding behind the quantitative data – to understand why people think in the way they do, and because the group starts from an

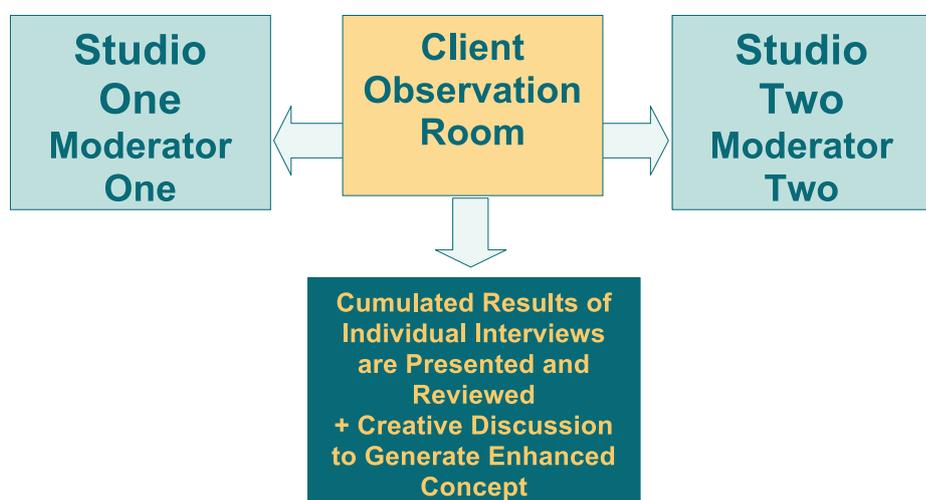
**“ONE CONSISTENT BENEFIT OF THIS TYPE OF FOCUS GROUP IS THAT NO INDIVIDUAL RESPONDENT DOMINATES THE GROUP”**

tribute equally, hence greater value is gained from each respondent, as well as their collective insight. Also, an independent and quantified assessment is made of the concepts on initial impact and, as the exercise is extended over different countries and user groups to give good coverage of the market, the total com-

unbiased and more meaningful place the discussion can go straight to creating the “ideal” concept.

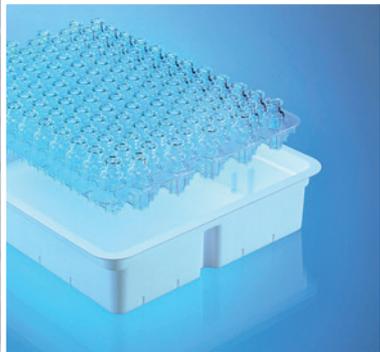
This combined quantitative and qualitative approach ensures a balanced assessment of the concepts and inspired direction as to what else needs to be added or changed to ensure the ultimate success of the new product.

**“THE QUALITATIVE FINDINGS FROM THE GROUP GIVE THE DEPTH OF UNDERSTANDING BEHIND THE QUANTITATIVE DATA”**

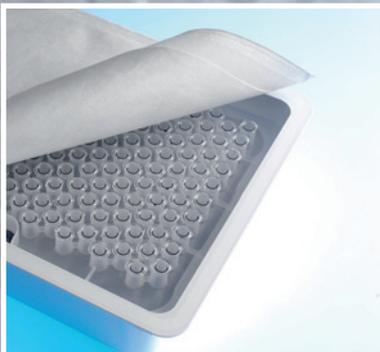


**Figure 2: Integrated Focus Group Structure Combining Qualitative and Quantitative Research.**

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## MATCHING A RANGE OF INJECTORS WITH BOTH PATIENTS' AND PHARMA PARTNERS' NEEDS

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.

In addition, through consolidation and experience, the pharma industry has acquired a high level of knowledge about complex medical devices such as injection devices. There is gen-

**"AS SELF-INJECTION DEVICE TECHNOLOGY HAS MATURED, THE DRIVE TO CUSTOMISE PLATFORM PRODUCTS RATHER THAN DEVELOP COMPLETELY NEW DEVICES HAS INTENSIFIED."**

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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**Figure 1: The Spring-Driven Reusable ServoPen (Left); the Value Reusable Ypsopen Twist (Centre); and the UnoPen (Right).**

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-orientated 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

**“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.”**

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 hor-

mone. Core insulin pen technology can also be applied to therapies that require small or larger multiple fixed doses such as GLP-1 in diabetes, parathyroid hormone in osteoporosis, and niche therapies such as apomorphine in Parkinson’s.

Frequent large doses are today often injected from prefilled syringes. As part of the lifecycle management of these therapies there is also the opportunity to develop preserved formulations that can be injected from pen-based cartridges. An example of this is beta-interferon for treating multiple sclerosis which is available in both prefilled syringes and cartridges.

## 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.



**Figure 2: Ypsomed Delivery Systems' Range of "Push-on-Skin" Disposable Auto-injectors Include YpsoMate (Left) and YpsoJect (Right).**

### AUTO-INJECTOR-COMPATIBLE SYRINGES AND NEEDLES

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. YpsoMate is Ypsomed's latest 2-step push-on-skin autoinjector with a slim and easily customisable design. YpsoJect is highly rated by patients for its patient-controlled needle retraction mechanism (see Figure 2).

### VARIABLE MONODOSE INJECTIONS

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-BASED INJECTORS

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



**Figure 3: DuoPen is Ypsomed Delivery Systems' Cartridge or Syringe-Based Variable Monodose Device for Use in Combination with Needle-Safety Devices.**

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.

*Based on the article which appeared in ONdrugDelivery, Issue 28 (September 2011), pp 48-50.*

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.



**Figure 4: Ypsomed Delivery Systems' LyoTwist Family of Devices with Needle Safety Provided in Combination with Clickfine AutoProtect Safety Pen Needles.**

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# Drug Delivery Partnership Strategies

Case studies in effective licensing, collaboration, and therapeutic differentiation

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