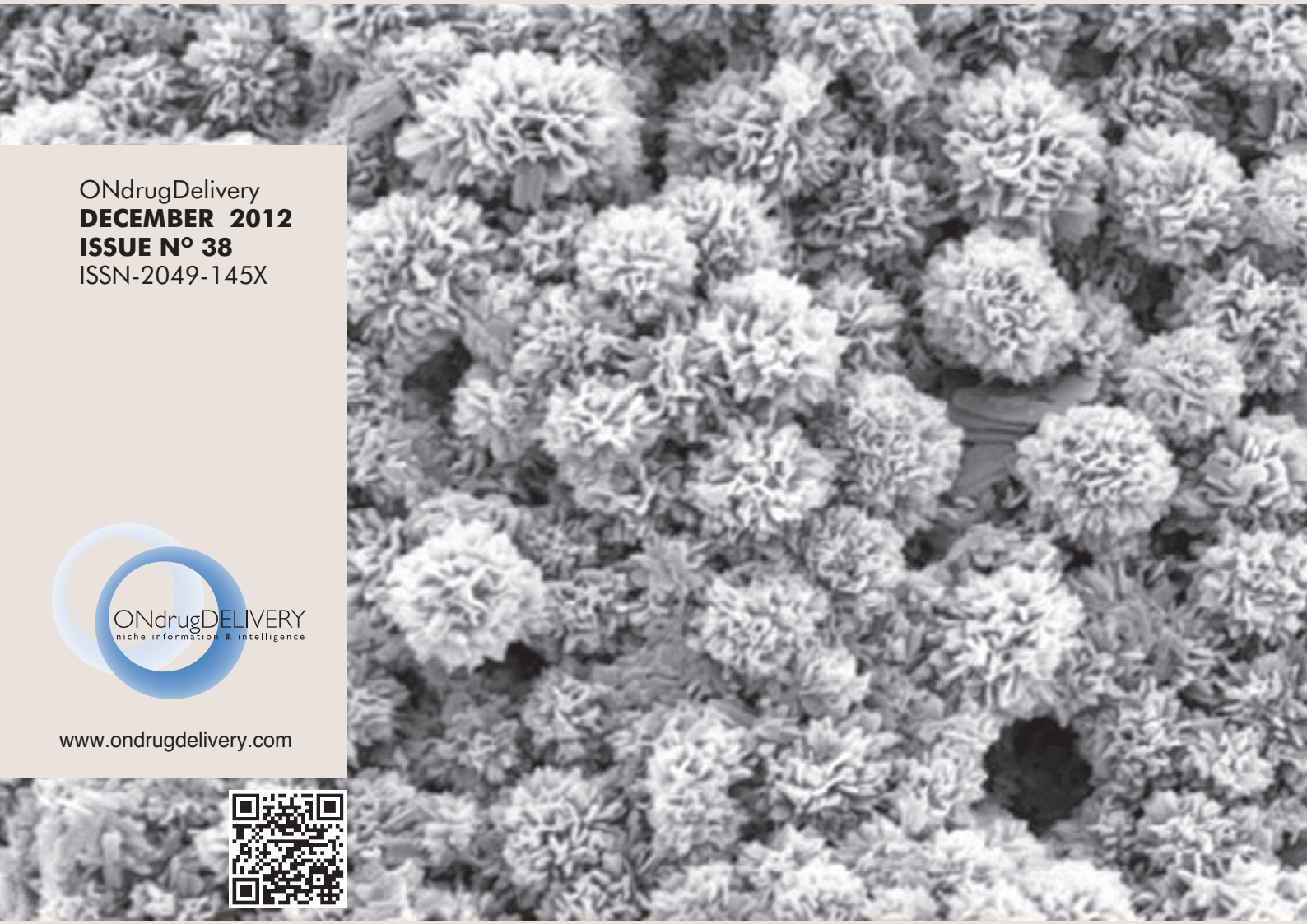
DELIVERING BIOTHERAPEUTICS



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"Delivering Biotherapeutics"

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

EDITORIAL CALENDAR 2013:

Jan	Oral Drug Delivery
Feb	Prefilled Syringes
Mar	Transdermal Delivery, Microneedles & Needle-Free Injection
Apr	Pulmonary & Nasal Drug Delivery
May	Injectable Drug Delivery: Formulations Focus
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Sep	CROs & CMOs Offering Drug Delivery Solutions
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Dec:	Delivering Biotherapeutics

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Front cover image: "XStalBio's glutamine microcrystals coated with a 10% w/w loading of the protein, bovine serum albumin (BSA)", supplied by XstalBio Ltd. Reproduced with kind permission.

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ONdrugDelivery 2013 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
January 2013	Oral Drug Delivery	Open for Last-Minute Submissions
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December 2013	Delivering Biotherapeutics	November 4th

AN INTERVIEW WITH DR MARK PERKINS, CUSTOMER SOLUTIONS MANAGER, NOVOZYMES BIOPHARMA

ONdrugDelivery recently spoke with Mark Perkins, PhD, Customer Solutions Manager at Novozymes Biopharma, to discuss how the company is improving the formulation of many new drugs and allowing manufacturers to modify protein or peptide half-life to suit the requirements of specific medical conditions.

With a rapidly evolving market placing increasing pressure on pharmaceutical companies, the industry is witnessing a significant increase in investment into the development of targeted biological drugs. In addition to formulating more tailored and novel drugs, companies are looking to take these new therapies through clinical trials and to market faster than ever before. However, there is one common challenge delaying the development of new biological drugs, namely that they present short plasma half-lives. As a result, they are subject to reduced bioavailability meaning that once administered they are cleared from the body within a matter of seconds. Therefore patients with chronic conditions require higher dosages, more frequently, which greatly increases the likelihood of experiencing side effects, whilst also driving up the cost of treatment regimes and increasing the possibility of patient incompliance with their medication.

Providing a solution to these issues has received major industry attention over recent years, and there has been real progress in the creation of technologies to modulate the serum half-life of protein-based therapeutics to desired specifications. The most common techniques include increasing hydrophobic volume (PEGylation) and FcRn-mediated recycling (albumin fusions). Yet, although these methods have been successful in extending serum half-life, they still do not offer the possibility of designing protein half-lives to deliver required pharmacokinetics. In response to industry demand, Novozymes Biopharma, a leading manufacturer of recombinant ingredients and technologies, has developed a new half-life extension technology based on the natural, non-immunogenic plasma protein albumin.

Q: Can you please provide our readers with some background on Novozymes Biopharma?

Novozymes Biopharma develops and manufactures high-quality, animal-free, and regulatory compliant recombinant ingredients and technologies. We aim to provide pharmaceutical and medical device manufacturers with solutions that help them address the industry's most common challenges in developing innovative, safe and consistent products. The company has a number of large-scale manufacturing facilities worldwide which are all run to cGMP Q7 quality standards to ensure that customers receive the highest level of product quality and consistency, as well as the security of long-term supply. Across the company we have a customer-integrated approach and combine our scientific know-how and specific needs of customers to deliver improved products and performance.

Q: How is Novozymes working with its customers to develop improved drug products?

Novozymes' primary focus is on developing and producing recombinant products and technologies that offer superior safety and performance to our customers. We do this by providing access to high-quality ingredients, proprietary technologies, and unique know-how, contributing toward the development of improved therapeutic treatments providing real and sustainable benefits to patients.

As a company, we are constantly reviewing industry trends and looking for new opportunities to improve our customers' processes by developing better and safer alternatives to the products that they are currently using. However, we are more than a mere supplier of enabling technologies or products; our relationship with each customer is a partnership. By combining our scientists' unique knowledge of Novozymes' biological solutions with the customers' specific application knowledge, we work with our customers to deliver solutions that solve their most demanding challenges.

Q: Can you explain what Novozymes' half-life extension technology is?

Novozymes' half-life extension technology has been developed to offer our customers improved drug half-life and to significantly reduce the dosing frequency for certain medications. It is the only half-life extension technology to be based on albumin which has a proven safety and regulatory profile, as well as a long history of therapeutic use, making it an ideal choice for drug delivery. We have chosen to base our technology on albumin as it has a naturally long half-life due to its interaction with the neonatal Fc receptor (FcRn), which means it remains in circulation longer than most other proteins. As a result, by attaching drugs to albumin we can increase the length of time that they are effective, reducing the dosing frequency of therapeutics from days to weeks.

Q: How does the half-life extension work?

Albumin along with other proteins is continually sampled by endothelial cells through a process called pinocytosis. The cell membrane internalizes the serum sample to form a vesicle and as the pH decreases in the vesicle, albumin binds to its receptor. Proteins are sorted as the vesicle divides, so those not bound to the receptor are degraded as the vesicle fuses with the cell membrane. Albumin is then recycled back into the circulatory system. We have designed albumin variants with altered binding affinity for the receptor making it possible to modulate its serum half-life. Through either fusion, Novozymes' Albufuse® Flex, or conjugation, Novozymes' Recombumin® Flex to modified albumin, it is possible to modulate the half-life of attached drugs. Novozymes' fusion technology is best suited to non-synthetic peptides and proteins, whereas our conjugation technology is most appropriate for non-natural peptides.

Q: Why has Novozymes chosen to base its new technology on albumin?

We have chosen to base our new technology on albumin as it is a natural, non-immunogenic plasma carrier protein which is extremely stable, highly soluble and large enough to avoid renal clearance. The huge market demand for drugs which work more effectively and have a longer circulatory half-life has led to the formation of many companies that are developing half-life extension technologies. However, our technology is the only technology using natural-functioning, animal-free recombinant albumin. The combination of these unique elements means Novozymes' technology can help our customers to develop and take more advanced drugs to market, cost effectively and more efficiently.

"THE TECHNOLOGY PRODUCES MORE STABLE BLOOD LEVELS IN PATIENTS AND ALSO CONFERS A REDUCED RISK OF SIDE EFFECTS"

Q: How do you see the new technology impacting the industry?

Half-life extension technology can increase a protein's half-life from minutes to hours and hours to days. As a result, it can be used to flexibly control the half-life of the drug in the human body according to the specific medical requirements of what it is being used for. The flexibility of Novozymes' technology to modulate the half-life of proteins allows drug manufacturers to improve treatment regimes and create novel drugs tailored to the specific needs of patients suffering from chronic or acute conditions, such as diabetes, haemophilia and neutropenia.

As there are still only a small number of biologic drugs on the market, companies are looking to adjust and develop those that are available to them. Our technology will allow manufacturers to establish a niche position in the market with more innovative and flexible products. On both a commercial and patient-centric level, the innovation will offer companies a definite competitive advantage due to its ability to improve patients' lives who are suffering from chronic illnesses. In addition, we are able to offer our customers long patents until at least 2030 which will provide manufacturers with a unique competitive edge in current challenging markets.

Q: How does this innovation support Novozymes' goal of creating better lives for patients?

Our scientists work with the goal of the final product in mind, namely to deliver better quality of life to patients. A key clinical advantage of our half-life extension technology is an increase in the *in vivo* half-life of the therapeutic protein. For patients, this means reduced frequency of administration of a drug product and, as a result, a reduced overall dosage. For manufacturers, a less frequent dosage rate also means that the treatment is more cost-effective, something which is becoming crucially important with the growing focus on healthcare costs and accessibility to medicine.

Furthermore, the technology produces more stable blood levels in patients and also confers a reduced risk of side effects because the lower dose rate means that the toxicity level of the protein may not be reached. Instead, the drug dose remains within the therapeutic range, increasing the patient's tolerance to the drug. Since some biopharmaceuticals have to be administered by a nurse at home or at a clinic, the number of visits can also be reduced dramatically, resulting in improved compliance and ease of use.

For further information on Novozymes' half-life extension technology, please visit: www.daystoweeks.com.

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DRUG DELIVERY & PROTEIN STABILISATION

PRECIPITATING IMPROVEMENTS IN THE FORMULATION AND DELIVERY OF THERAPEUTIC BIOMOLECULES AND VACCINES

There are significant formulation and delivery challenges facing the developers of the next generation of therapeutic biologics and vaccines. These include facilitating administration of very high doses of monoclonal antibodies *via* subcutaneous injection, methods for obtaining sustained release of rapidly-cleared peptides and proteins and stabilisation of aggregation-prone proteins to allow for alternative delivery approaches. To meet these challenges it is often necessary to move away from traditional methods of formulating biomolecules and to innovate. In this article, Barry D. Moore, PhD, Research Director, XstalBio Ltd, describes how the company has taken a novel method for preparing dry powders of biomolecules and developed it into a versatile platform for the development of advanced biotherapeutics.

XstalBio's dry powders are prepared by a versatile precipitation process in which biomolecules are transferred isothermally and almost instantly from aqueous solution into the dehydrated state with concomitant immobilisation onto inert water-soluble excipient particles. This results in the capture of near native-state biomolecules in very good yields in the dry state. The high retention of native conformation can be shown by spectroscopy using solid-state circular dichroism[1] and is evidenced more practically by the remarkably high activity of precipitated dry enzymes when used to catalyse chemical reactions in non-aqueous solvents; reaction rates are often 10-100 times higher than those observed with lyophilised enzymes.[1,2]

"ALL OF THE COMPONENTS IN AN AQUEOUS MIXTURE ARE QUANTITATIVELY IMMOBILISED EVEN WHEN THEY HAVE VERY DIFFERENT PH AND PHYSIOCHEMICAL PROPERTIES, ALLOWING MULTI-COMPONENT DELIVERY FROM THE ONE PARTICLE IN THE DESIRED RATIO"

For many applications GRAS excipients such as amino-acids, sugars and salts are used to form an inner microcrystalline core onto which is coated a predefined loading of the dehydrated biomolecule. Because these particles cannot undergo further crystallisation the resultant dry powders are stable to exposure at both high temperature and humidity and can be handled and processed in a similar way to small-molecule drug crystals. Figure 1 shows examples of amino-acid microcrystals coated with a 10 %w/w loading of the protein, bovine serum albumin (BSA).

Depending upon the conditions and excipients used during the precipitation process, the size and morphology of the particles can be

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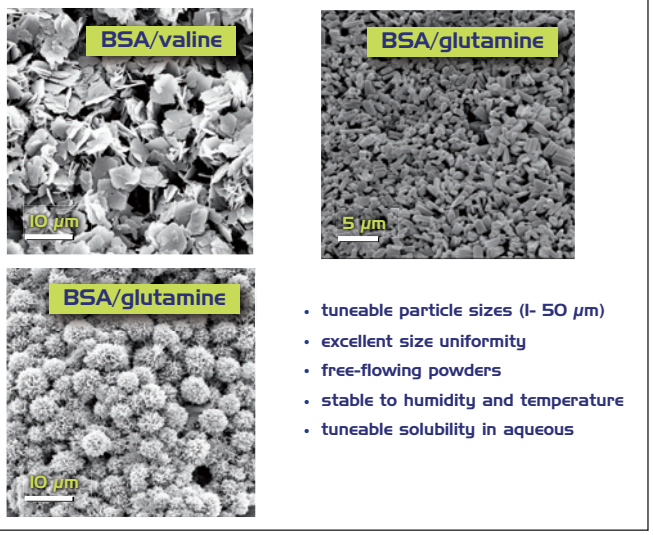

Figure 1: SEM images of three different formulations of BSA-loaded particles (10% w/w). Particle morphology is tuned by appropriate processing conditions.

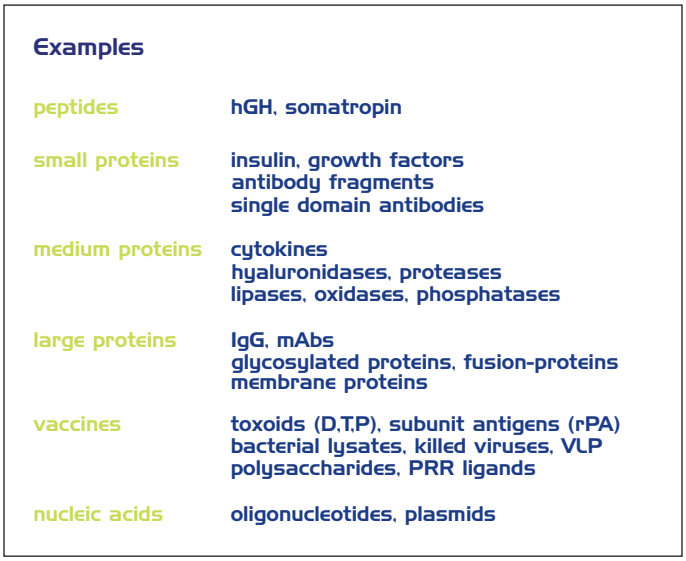

Figure 2: Range of client and in-house biomolecules prepared using XstalBio's precipitation technologies.

altered specifically for different drug delivery applications. The precipitation and dehydration process used to form the particles has been shown to be applicable to a wide range of therapeutic biomolecules (Figure 2). Biomolecules ranging from small peptides through to monoclonal antibodies and to very high-molecular-weight DNA plasmids[3] have been immobilised in high yields (Figure 3) and shown to retain both their integrity and bioactivity.

It is also possible to immobilise mixtures of biomolecules of similar or different types such as proteins, polysaccharides and polynucleotides. Remarkably, all of the components in an aqueous mixture are quantitatively immobilised even when they have very different pH and physiochemical properties, allowing multi-component delivery from the one particle in the desired ratio. This is thought to be because particle formation occurs *via* a mechanism involving initial phase-separation of nanodroplet intermediates, containing biomolecules and excipient, followed by coalescence and crystallisation.

To demonstrate the application of the technology to a small therapeutic protein, Figure 4 shows a comparison of the bioactivity observed for fresh soluble insulin with that for insulin-coated microcrystals which had been stored at room temperature for one year. The vasorelaxation profile as a function of the insulin concentration is shown to be very similar for both formulations, demonstrating that the dry immobilised protein has remained intact without the need for any refrigeration.[4] Achievement of cold-chain free shipping and storage of biomolecules is a major target for those organisations and companies that intend to supply diagnostics, medicines and vaccines in challenging environments and it could also offer considerable cost-savings in other commercial sectors.

For larger aggregation-sensitive proteins, such as monoclonal antibodies, it may be necessary to include additives during the precipitation process which are able to prevent the production of dimers and higher oligomers. These precipitation-stabilising additives are typically zwitterionic with an additional charged side-chain that is able to bind to ionic and polar groups on the biomolecule surface. Charge-charge interactions are stronger in the dry state and so, following precipitation, the outer surface of the immobilised biomolecule becomes decorated with a zwitterionic layer that serves to destabilise intermolecular interactions and prevent the initiation of aggregation.

Figure 5 shows the stability at 40°C of a series of formulations of a monoclonal antibody containing various combinations of zwitterionic additives. Optimally it is possible to reduce the loss of monomer to less

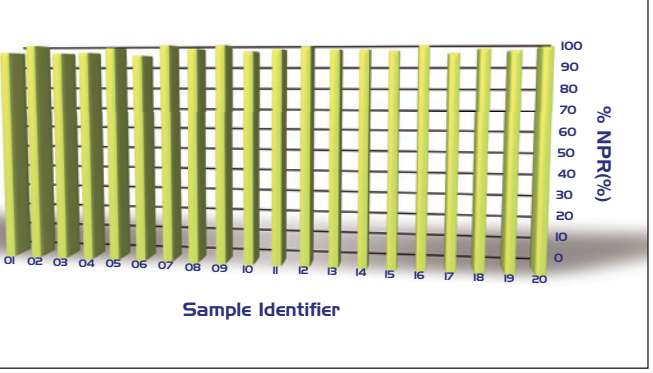

Figure 3: The net protein recovery (NPR) for 20 separately prepared formulations of BSA at a theoretical protein loading (TPR) of 5 % w/w. The formulations were prepared on a small scale by batch precipitation.

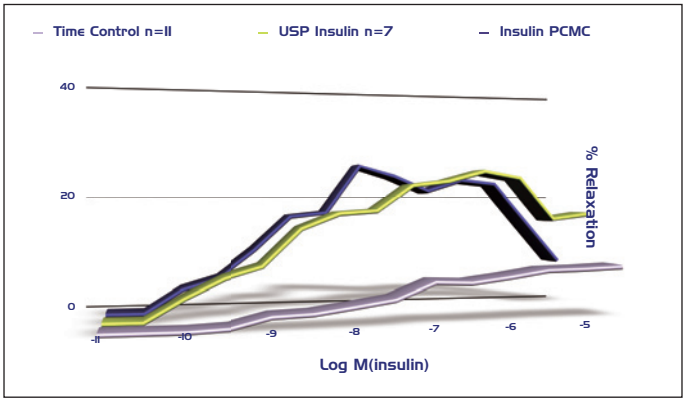

Figure 4: The vasorelaxation of smooth muscle arterial tissue (rat) as a function of insulin concentration. The *ex vivo* perfusion bioassay was determined by wire myography (collaboration, Professor C. Hillier, Glasgow Caledonian University, Glasgow, UK).

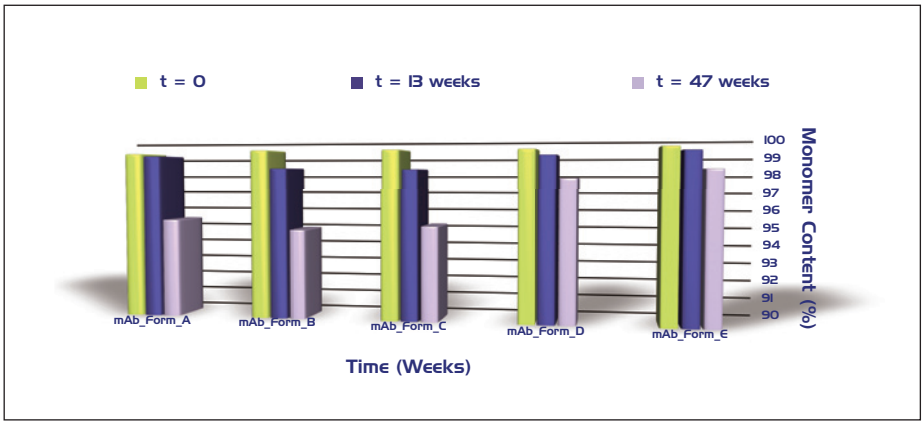

Figure 5: The % retention of monoclonal antibody monomer content (as determined by HPLC) at t= zero, 13 and 47 weeks, at 40°C.

than 1.5 % over a year (mAb Formulation E). This is considerably less than often observed for lyophilised antibodies stored at this temperature which show significantly higher levels of monomer loss. The upshot being that precipitated mAb formulations of this type are expected to exhibit very long shelf-lives under normal storage conditions of 2-8°C.

There has recently been an increasing trend towards the development of formulations of proteins such as mAbs to enable them to be delivered at very high concentration, by subcutaneous injection. The driver for this development is to reduce or eliminate the time spent in the clinic by patients being treated for chronic conditions; currently they may need to receive infusions of protein over several hours and it would be desirable to replace this by a single injection.

Extremely high concentrations are being targeted (>200 mg/ml) meaning that it may be difficult to develop a shelf-stable liquid formulation, and there is interest in preparing dry powders that can be rapidly reconstituted for administration. Precipitated mAb formulations are comprised of very fine particles which can normally be re-dissolved rapidly into aqueous diluent. XstalBio has developed formulations that also satisfy the other important criteria for subcutaneous injection which include exclusive use of parenteral excipients, syringability and osmolality.

Complementary to this, a new reconstitution protocol has been developed which can be used to accelerate the dissolution of a wide range of different biomolecule dry powders, including lyophilised cakes, to very high concentration without production of foam.

Another area of increasing interest for biopharmaceuticals is the development of methods for extending the PK. This may be achieved by covalent modification of proteins with, for example, PEG groups. However, it may often be preferable to administer unmodified biomolecules.

XstalBio has found that it is possible to convert the above described highly soluble PCMC into a sustained-release formulation, CaP-PCMC, by surface modification with an outer coating of calcium phosphate, a major constituent of bones and teeth. The inorganic coating is very thin but, because it is sparingly soluble in physiological fluids, can nevertheless significantly slow the rate of release of biomolecules into solution from being instantaneous to taking hours or days.

"ACHIEVEMENT OF COLD-CHAIN FREE SHIPPING AND STORAGE OF BIOMOLECULES IS A MAJOR TARGET FOR THOSE ORGANISATIONS AND COMPANIES THAT INTEND TO SUPPLY DIAGNOSTICS, MEDICINES AND VACCINES IN CHALLENGING ENVIRONMENTS"

Fast and intermediate release profiles of biomolecules can therefore be obtained with complete clearance of the depot. This is something which cannot be easily achieved with other commonly used matrices such as poly (lactic-*co*-glycolic acid) (PLGA) copolymers, which may take many weeks to breakdown. A further application of sustained release CaP-PCMC microparticles is in the field of vaccines where it has been demonstrated that co-immobilisation of antigen(s) with an immunostimulant can be used to provide enhancement of innate and adaptive immune responses.

The manufacture of PCMC suitable for inhalation was developed to pilot scale *via* a collaboration between XstalBio and Boehringer Ingelheim. The GMP-compliant process utilises a highly scalable, continuous-flow precipitation step followed by a drying step based on supercritical carbon-dioxide fluid extraction. Quality-by-Design principles were used to optimise the process, which can be implemented using off-the-shelf equipment.

For applications such as vaccines where costs may need to be minimised, a similar isothermal, continuous-flow precipitation approach can be used but coupled with a simpler vacuum drying process. In either case the footprint of the equipment is much smaller and the throughput much faster than conventional methods for preparing dry formulations such as lyophilisation or spray-drying. It is therefore anticipated that the technology will become increasingly used to bring forth improvements in the formulation and delivery of therapeutic biomolecules and vaccines.

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A NASAL DELIVERY SOLUTION TO THE CHALLENGES IN BIOTHERAPEUTIC DELIVERY

With an increasing number of biotherapeutics coming through to market, and the growing need for non-invasive self-administration options for patients to use in the home setting, nasal drug delivery provides a promising approach. Here, Dr Shunji Haruta, PhD, Executive Officer, SNBL, Ltd and General Manager, NDS Division, describes how the company's nasal powder delivery technology, μco™ System, can meet these requirements.

The cultivated use of biologics for therapeutic treatment has introduced a promising, albeit very difficult, route for the treatment of many serious illnesses with a high unmet need. Currently, market share is dominated by chemically synthesised, small-molecule compounds which are typically in pill form. As is well noted, recent years have introduced an increase in the development of biotherapeutics.

Having gained much attention, these medicines differ greatly from small molecules as they are made from human or animal proteins. These biotherapeutics include peptides which regulate physiological processes, from acting at some sites as endocrine or paracrine signals to acting at others as neurotransmitters or growth factors. Insulin is an excellent of example, and perhaps the most well-known, of a biotherapeutic, which has been used therapeutically for decades. Furthermore, applications within the fields of neurology, endocrinology and haematology already use various biotherapeutic treatments.

This emerging field is expected to grow, and many scientific breakthroughs have created hope for new therapies in what have historically been considered as difficult-to-treat diseases.

While new advancements do hold great promise, there remain many hurdles for the delivery of proteins and peptides which must be cleared before success in treatment is seen. For example, the larger molecular sizes typical of biologics make it more difficult for them to be absorbed into the body. Also, peptides are more susceptible to degradation by enzymes and acids that are present in the body which generally results in extremely low oral bioavailability. In fact, peptides are almost exclusively injected because they are degraded by gastro-intestinal (GI) acids and enzymes when taken orally. What is more, when biologics are administered *via* the GI tract, the first-pass metabolism can neutralise the therapeutic effect through breakdown and degradation. As a result, the drug development industry has had to utilise injections for the majority of biologic therapies so compounds are able to enter the bloodstream for systemic action with as little degradation as possible.

While injections have made biologic delivery possible, there remains a need for these therapies to be conducted out of the clinical setting and in the normal lives of patients. Natural next steps for the drug development industry are now to consider better, enabling routes of systemic delivery which can put the control of the therapy in patient's hands and make at-home care a reality. The means, ideally, non-invasive drug delivery systems.

The majority of non-invasive drug delivery solutions for biologics have generally come in

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two forms. One is the engineering of a more resilient formulation of the peptide through, for example, a protective coating, or the addition of protease inhibitors, or PEGylation. These methods act in reducing the effect of degradation on the peptide prior to becoming systemically available, such as an orally delivered PEGylated insulin which works by combating digestive acids prior to absorption.

The other common approach is to deliver the biologic through the mucosal membrane in the respiratory tract. The respiratory tract, especially the lung alveoli and nasal cavity, have superb potential as sites for delivery. Oral and nasal inhalation enables a biologic to avoid degradation by acids, enzymes, and first-pass metabolism which are prevalent for GI delivery. Furthermore, the wide mucosal surface is interlaced with a high-density of blood vessels immediately beneath the surface, which makes for quick and direct absorption into the blood stream. Lungs provide a large mucosal surface area for absorption (approximately the size of a tennis court), and although smaller (approximately the area of a bath towel), the nasal cavity has ample room for delivery and absorption.

Both respiratory delivery sites hold great potential, though challenges still exist. To begin, both delivery routes are critically dependent on reliable delivery devices. Delivery to the deepest part of the lung, where absorption occurs, remains relatively difficult. However, even if delivery to the desired absorption site is achieved, the lungs display a higher sensitivity, which then opens the possibility of safety issues.

As an alternative, the nasal membrane provides relatively easy and more convenient access for consistent and complete delivery to the absorption site, though nasally delivered drugs must fight the natural function of the body to clear the nasal cavity through mucocilliary clearance.

To date there have been biotherapeutic products which have attempted to address these issues, but there is still a need for improvement. For lung delivery, Exubera® (pulmonary delivered insulin), came to market and was then withdrawn a year later for many speculated reasons, including the not-so-easy to use device. For nasal delivery, there is calcitonin (Miacalcin®), desmopressin (Desmopressin®) and nafarelin (Synarel®). All three of these nasal products are in liquid form and suffer from low bioavailability of about 3%, which is mainly caused by the running and clearance of the liquid formulation from the nasal mucosa before it can be absorbed.

One company which offers delivery solutions for biologics is SNBL, Ltd. SNBL has developed a nasal delivery system technology which aims to address the needs of successful biotherapeutics delivery: *µco*™ System.

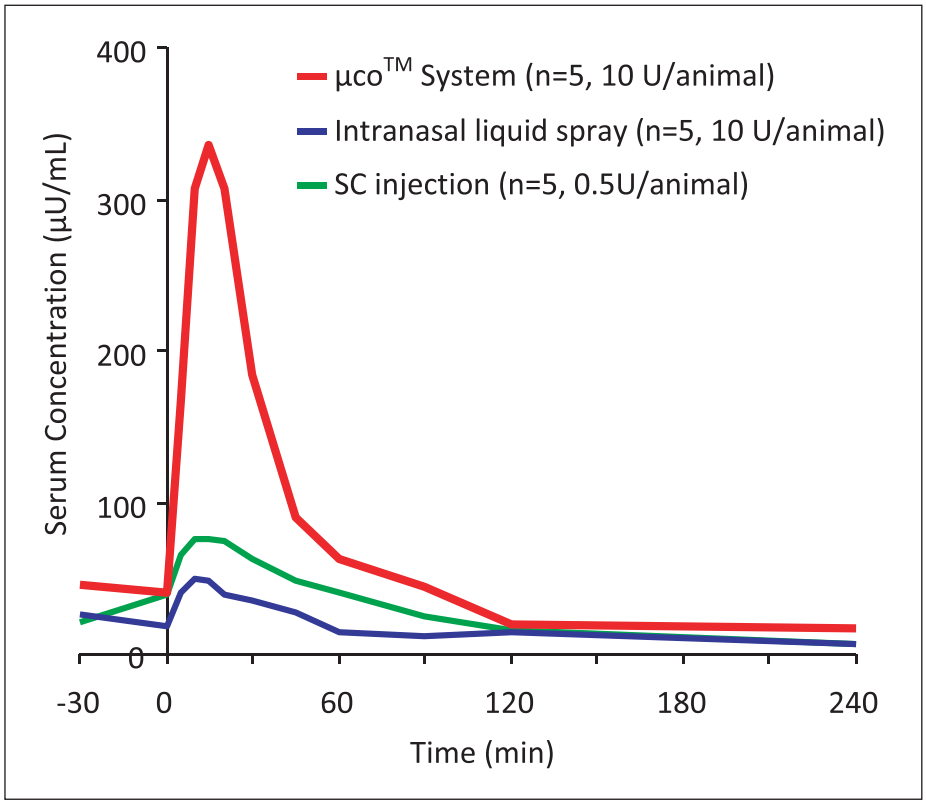

Figure 1: PK Profile of Insulin in NHPs.

µco™ System began development 15 years ago with the goal of systemically delivering biologics. At the time, SNBL recognised a significant unmet need within the pharmaceutical industry for better drug delivery technologies which could meet both industry and patient care needs. Initially developed for the delivery of insulin, *µco*™ System was designed specifically for overcoming the hurdles presented in the development of large molecules.

With great research and development capabilities stemming from SNBL's core CRO busi-

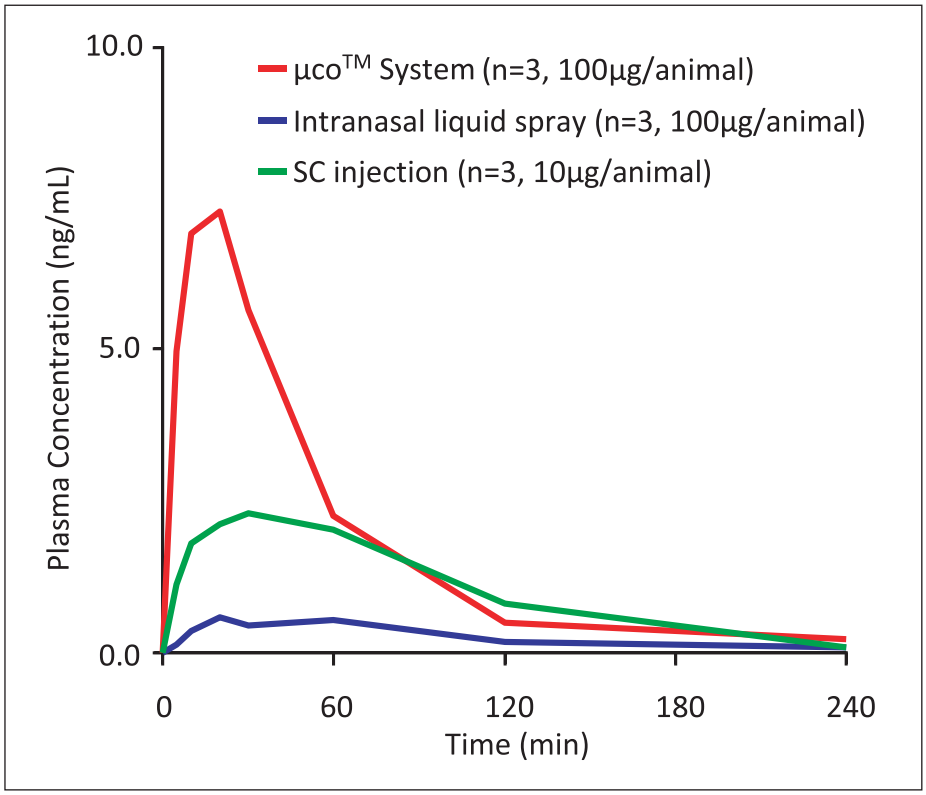

Figure 2: PK Profile of PTH 1-34 in NHPs.

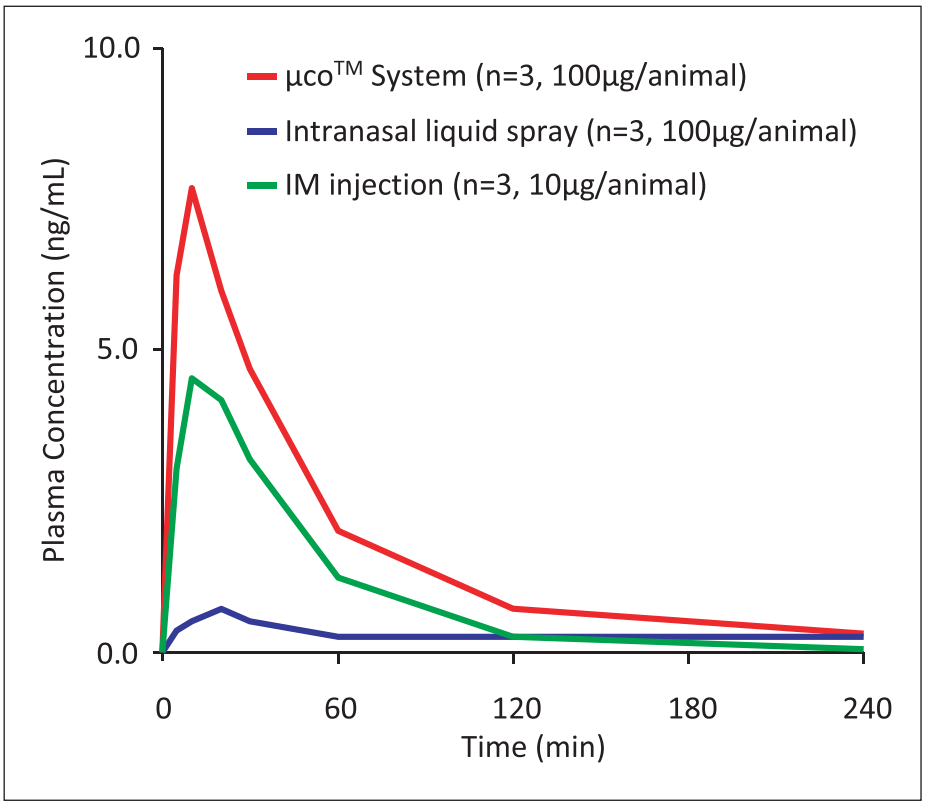

Figure 3: PK Profile of Calcitonin in NHPs.

ness, the resulting technology of µco™ System is ideal for partnership in the development of biologics. A two-part technology which helps to address development needs at an early stage, µco™ System provides a powder carrier and a line of powder nasal delivery devices to be used in conjunction.

CARRIER & DEVICE FOR ENABLING BIOTHERAPEUTICS

Taking advantage of the highly vascularised bed directly beneath the nasal membrane, which provides direct transfer into the blood stream, µco™ System's carrier is a novel technology. Consisting of GRAS materials, the carrier is a muco-adhesive which holds the compound on the nasal mucosa long enough to allow for absorption into the blood stream. As a muco-adhesive, the powder carrier sidesteps issues of running medications which are typically found with liquid applications.

After holding the compound on the mucosa for absorption, the carrier, which is insoluble and inactive in the body, is cleared by natural process from the nose and eventually excreted. A period of prolonged adherence to the nasal mucosa is especially meaningful in the delivery of biotherapeutics as molecule size is larger, and the prolonged time on the nasal mucosa in turn provides longer time for absorption. Also, because harsh detergents and absorption enhancers are not used in the carrier formulation, damage to the nasal mucosa is mitigated and caused only by any irritating factors of the API itself.

Key to µco™ System's successful delivery of biotherapeutics is its line of powder delivery devices, Fit-lizer™. With an understanding that practicality and convenience would be paramount in appeal to patients and thus the success of a product, Fit-lizer™ was designed with patient needs in mind. The device line offers a prefilled single-use device, or a capsule loading multiple-use device. Both devices are pocket-sized and extremely light weight. A patient can easily carry it in a purse or pocket, and thanks to its small size administration is discreet.

The device is hand-pump actuated, very easy to use, and provides nearly 100% delivery of the formulation every time. Aside from catering to patient needs, SNBL recognised a major issue with delivery devices is the consistent and full delivery of formulations, which inherently impacts performance and reliable therapeutic effect. A medication can only be as effective as the amount actually delivered, and Fit-lizer's ability to deliver nearly 100% is key to its success.

APPLICATIONS OF µCO™ SYSTEM IN BIOTHERAPEUTIC DELIVERY

For preclinical proof of concept studies utilising µco™ System's technology, SNBL has conducted PK studies in NHPs for nasal applications in the systemic delivery of biologics. The results across the board have consistently shown higher bioavailability of various biologics. A PK study with insulin gave relative bioavailability of 13% (see Figure 1). A PK study with parathyroid hormone (PTH 1-34) showed absolute bioavailability of 17%, as shown in Figure 2. Similarly, a PK study with Calcitonin showed absolute bioavailability of 17% (Figure 3).

A PARTNERSHIP FOR BIOLOGICS DEVELOPMENT

µco™ System is an enabling technology which SNBL offers for licensing. But licensing with SNBL is more than just an exchange. Through extensive experience and over 50 years in NHP studies, SNBL is a solution provider. From very early stage development to formulation optimisation and even regulatory filing, SNBL is a partner in development.

FEASIBILITY STUDY

As part of the revolutionary development of µco™ System, SNBL recognised a common, costly problem within the development of nasal drugs; the industry standard nasal dog model. Due to the anatomy of a canine nose, mucocilliary clearance is not representative of the human nose and canines also have a significantly higher amount of surface area for mucosal absorption. This dog model is a contributing reason why nasal drugs often make it into Phase I clinical trials, after costly safety studies and the expense of an IND filing, only to fall flat. SNBL took an innovative route and re-evaluated industry norms for nasal models. What was found is that NHPs provide a much better predictive model thanks to a more comparable nasal cavity. Mucocilliary clearance is closer to that of humans, along with a similar ratio of nasal surface area to body mass.

After recognising the benefit of replacing canines with NHPs, SNBL then developed and validated a unique model in-house. Building on decades of experience, the resulting model utilises unanaesthetised NHPs and a breat-synchronised device which enables precise delivery during the inhalation phase of the breathing cycle. This ultimately provides minimal variability, which means as few as three to four animals in a feasibility study can provide accurate, predictive results. This innovative study model is now a tool for assessment, and cost savings are gleaned from being able to make early-stage development decisions, to having fewer animals per study.

romeo & juliet

summertime & flip-flops

thunder & lightning

chicken noodle soup & crackers

batman & robin

peanut butter & jelly

movies & popcorn

campfires & scary stories

salt & pepper

baseball & hot-dogs

ken & barbie

tom & jerry

nuts & bolts

hot days & lemonade

rock & roll

wine & cheese

coffee & biscotti

warm cookies & cold milk

yin & yang

lock & key

good friends & belly laughs

golden retrievers & frisbees

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μco

by SNBL

BARRIERS TO BIOSIMILAR INSULIN TAKE-UP IN THE US AND UK: INSIGHTS FROM THE FRONT LINE OF DIABETES TREATMENT

In this article, Sarah Mackinnon, MSc, Quantitative Researcher, Creative Medical Research, provides an insight into the market for biosimilar insulins with reference to surveys of diabetes nurses in the US and the UK.

For 30 years, since the launch of Eli Lilly's Humulin (human insulin), the market for insulin has been dominated by three major players: Eli Lilly (Indianapolis, IN, US), Novo Nordisk (Bagsværd, Denmark), and Sanofi (Paris, France). Today, with patents having already expired for several human insulins and now looming for major insulin analogues, an opportunity has arisen for new companies to enter this market through the development of follow-on generic insulin products, known as biosimilars. This should make for an incredibly exciting time in the diabetes sector, for patients and pharma companies alike, as those new to the market will no doubt compete on price, driving established companies to innovate in order to stay ahead of the game.

So, given that some insulin patents have already expired, why are no generic insulins yet available?

Some manufacturers have certainly tried. In 2007, Marvel Lifesciences was the first to apply to the EMA to market three biosimilar insulins based on Lilly's Humulin. However, ultimately they withdrew their application in response to CHMP concerns that their products did not offer comparable efficacy in clinical trials. Further excitement was then speared by the

Figure 1: Insulin patents have already expired, so why are no generic insulins available?

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"RECENT US FDA GUIDELINES INDICATE THAT BIOSIMILAR DELIVERY DEVICES WILL BE PERMITTED TO EXHIBIT SOME DESIGN DIFFERENCES RELATIVE TO DEVICES USED TO DELIVER THE REFERENCE PRODUCT"

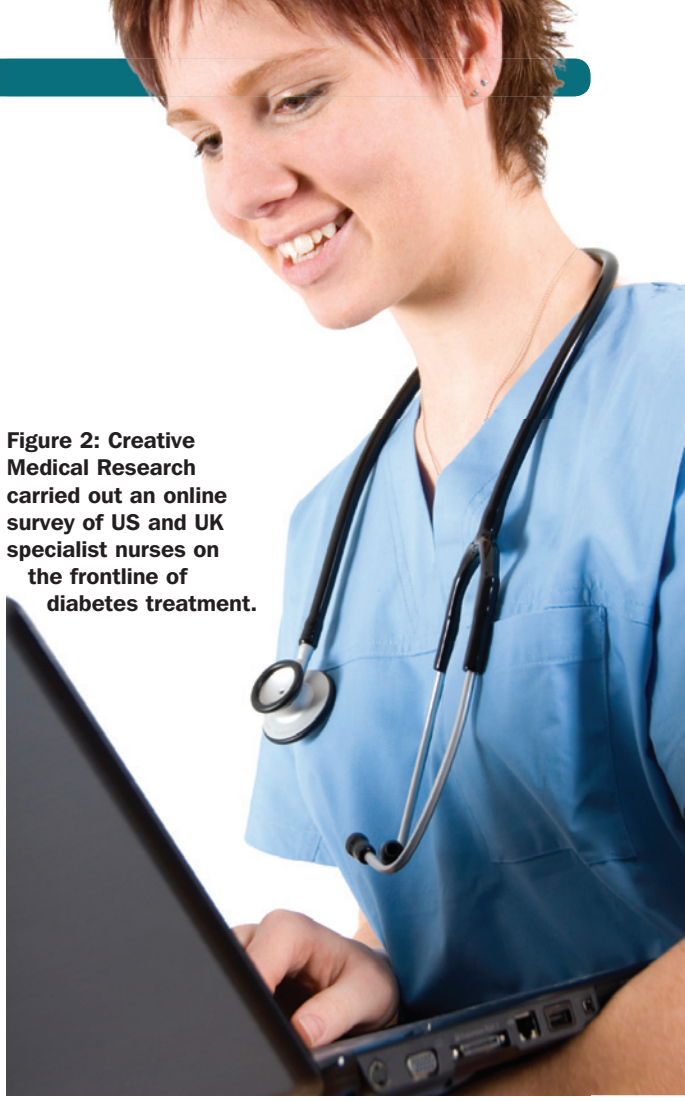

Figure 2: Creative Medical Research carried out an online survey of US and UK specialist nurses on the frontline of diabetes treatment.

announcement of a partnership between Pfizer (New York, NY, US) and Biocon (Bangalore, Karnataka, India) in October 2010, in which Biocon sold the rights to market their still-in-development biosimilar insulins to Pfizer.

However, the deal fell apart in March this year before any products made it to market, and while Biocon's products are likely to be approved in time, the Indian company may experience more difficulty selling their products to patients and clinicians without the might of Pfizer leading the way.

Why the difficulty? Well, because insulin is a complex biological molecule which can only be produced with the aid of living organisms, small differences during the manufacturing process can cause major variations in how the drug acts on the body. New insulin producers do not have access to the host cell lines or fermentation and purification processes used by current producers, making it very difficult to replicate existing products.

In fact, the best new manufacturers can feasibly hope for is to create a product which is only biologically similar to the original, hence the name "biosimilar". The significance of this is that biosimilar drugs are not necessarily interchangeable with innovator brands in the same way as typical generics are, and this has led to concern that biosimilars could initially appear equivalent to existing brands, but end up behaving quite differently post-approval.

Particularly for biosimilar insulin there is also another major hurdle to overcome – the development of a safe and effective delivery device.

Conventional wisdom suggests biosimilar delivery devices will need to closely mimic those offered by reference brands, as this will minimise the amount of device training and healthcare practitioner resources required for a patient to switch insulins. Furthermore, differences between innovator and biosimilar devices may foster doubt as to the true similarity between biosimilars and their reference products.

However, recent US FDA guidelines indicate that biosimilar delivery devices will be permitted to exhibit some design differences relative to devices used to deliver the reference product, and this flexibility may represent a considerable opportunity for biosimilar manufacturers, as development of a superior device could allow a generic product to gain a further advantage (other than cost) over existing brands. For example, where reference insulins are currently available only in vial form, a biosimilar manufacturer may be able to encourage existing users to switch by offering a well-designed pen as an alternative delivery device.

Taking this debate surrounding the issue of interchangeability into account, the EMA has stressed that once a biosimilar insulin has been approved, it will be down to healthcare professionals to decide whether they want to prescribe it to their patients. It will therefore be key to the success of any biosimilar insulin to win over healthcare professionals. With the aim of assisting manufacturers in this task by providing an insight into healthcare professional attitudes and expectations surrounding the issue of biosimilar insulin, Creative Medical Research carried out an online survey of US and UK specialist nurses on the frontline of diabetes treatment (Figure 2). The results are compelling.

Despite the ongoing debate, the survey showed that many diabetes nurses are still completely unaware of biosimilar insulin. Overall, almost half (47%) of UK and US nurses have not heard of it, compared with just 28% who are aware (see Figure 3). The proportion of informed nurses in each market differs only slightly, with only a quarter currently aware in the UK compared with almost a third in the US.

Given that diabetes nurses tend to have close, on-going relationships with their patients and are frequently turned to for advice and

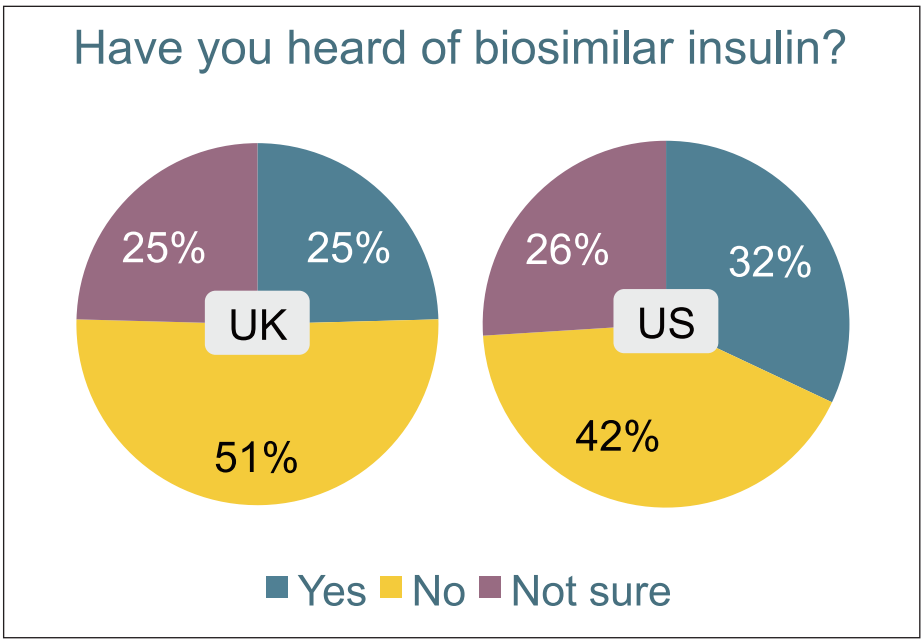

Figure 3: Proportion of nurses in the UK and the US who said they had heard of biosimilar insulin.

information, it will be essential for manufacturers to ensure nurses are fully educated about biosimilar insulin *before* their products come to market, so that patients in turn can be fully informed about their treatment options.

With regard to whether physicians are ready to prescribe a biosimilar insulin, 63% of nurses surveyed said that they believed doctors at their practice or hospital would be likely to prescribe a biosimilar insulin to a new patient, *versus* exactly half who believe this would likely be suggested to an existing patient (see Figure 4). Asked to explain their positive expectations freely, by far the most common reason given for the expected uptake of biosimilar insulin (unsurprisingly) was the assumed cost benefit; 34% of all nurses surveyed said either that they felt it was likely biosimilar insulins would be prescribed to new patients because they *would* cost less, or that they would likely be prescribed if the cost proved to be lower, with a quarter expressing similar viewpoints concerning prescription to existing patients.

However, nurses were also quick to mention that cost would not always be the deciding factor, with the great majority indicating other provisos would need to be met in order to ensure conversion. Most notably, one in eight nurses overall (12%) mentioned the need to see the efficacy of biosimilars proven in practice, whilst 9% cited the need for further research and clinical trials to establish safety. What is more, 4% also spoke about the need for a functionally equivalent or possibly even improved injection device. For example, one said: *"…Dependent on its use, if it worked as well as current insulins and was a cheaper alternative or possibly had different or improved injectable devices it would be worth consideration."*

As to why doctors might be more ready to offer a biosimilar to a new patient than an existing patient, one in ten nurses advocated the position that if a patient was experiencing good control on their current insulin, then there would be little incentive to risk a change to their regime unless cost pressure was sufficiently high to necessitate the switch. To quote one respondent: *"…To decrease cost, yes. This would only be if their current insulin is too expensive for the patient. If it is not, they will keep them on current insulins…"*

It will be imperative for biosimilar insulin manufacturers to overcome this barrier to take-up among existing patients in order truly to compete with innovator brands in the type 1 diabetes market. As mentioned, further research and personal experience are most likely to increase positive perceptions. However, results suggest new manufacturers may also be able to get ahead of the game by offering an intuitive delivery device which requires minimal patient training (facilitating switching by reducing the need for healthcare professionals' time and resources), or by trading on their 'good name' to foster confidence among healthcare professionals. Three nurses' responses were as follows:

"We definitely need more information about these products and the companies who would be entering the market with these insulins."

"If it isn't broke don't mend it. But cost is paramount so is our lack of diabetes nurses. It would involve re-educating the patient, which means time, hence things are unlikely to change."

"Yes, if the pen device was equal and there were no objections from patients."

Moving on to look at differences between the two markets studied, US nurses were generally more likely to believe doctors would prescribe a biosimilar insulin than nurses in the UK were. This was particularly true for existing patients. In the US, 58% indicated they felt doctors would be likely to prescribe to these patients, compared with 44% in the UK.

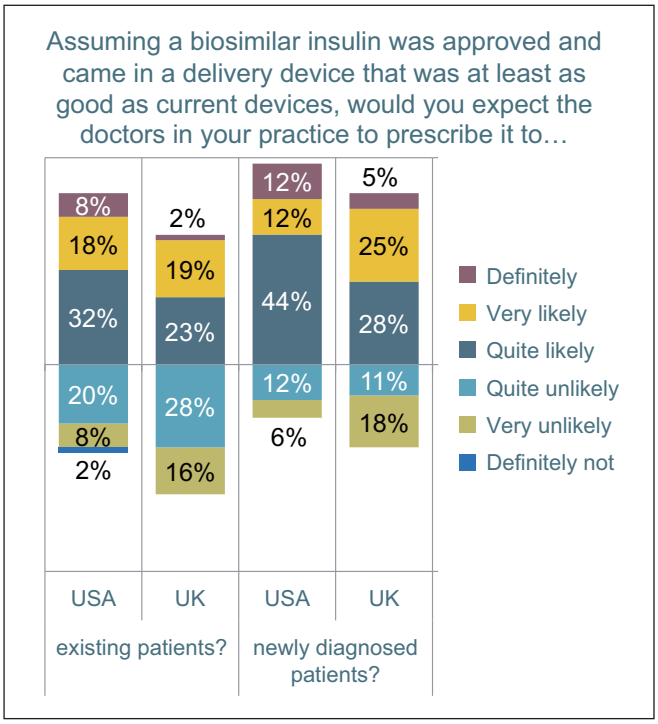

Figure 4: Responses from US and UK nurses to question regarding likely rates of prescription of biosimilar insulin to newly diagnosed patients compared with existing patients.

Given the clear expectation that biosimilar insulins will cost less than innovator brands, greater positivity surrounding their likely take-up among US nurses looks to be at least somewhat due to the fact that US patients are required to pay for insulin, while UK patients receive it free through the UK NHS. Indeed, one in eight (12%) US nurses spoke about how biosimilar insulin could lessen financial stress for patients, while one in ten mentioned that if biosimilars were covered by insurance (potentially with a lower co-pay), then doctors would be likely to prescribe them.

In conclusion, it seems likely that the lower cost of biosimilars will drive take-up through patient pressure from the 'bottom-up' in the US. Meanwhile, in comparison, any cost pressure in the UK is more likely to come from the top down, due to NHS budgetary constraints. As one nurse respondent commented: *"Prescription drugs are expensive. Generics offer the patient the ability to maintain their medications with less financial stress. Patients are asking for generics and now with the economy, many healthcare insurance plans require generics to be prescribed (1st tier). Deductables are very high and co-pays are high now also."*

Another said, "*Cost of products is a major consideration for the NHS at the moment so any generic product would be favoured over a branded product."*

Finally, as we have established that the key criterion for changing to a biosimilar insulin will most certainly be price, the next obvious question is: how much cheaper will a biosimilar insulin need to be in order to encourage healthcare professionals to prescribe it?

The answer from our nurses? On average, 30-40% cheaper, with little difference in cost expectation between the US and UK. Of course, new entrants to the market will not expect to be able to charge first-generation biologic prices for their follow-on products. However, given the relatively high cost of developing a biosimilar as opposed to a standard generic, they will certainly be looking for ways to maximise their margins and stand out from other biosimilar developers.

Creative Medical Research believes those who can offer the whole package on their entry to market – a lower cost, teamed with solid clinical research results, an equivalent or even superior delivery device, and the benefit of a good reputation – are likely to be first to the finish line.

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COMPANY PROFILE – NOVOZYMES BIOPHARMA

Novozymes Biopharma develops and manufactures high quality, animal-free, and regulatory-compliant recombinant ingredients and technologies to provide pharmaceutical and medical device manufacturers with the knowledge-based solutions needed to address their challenges and develop innovative, safer and more consistent products.

With more than 25 years' experience in the pharmaceutical industry, Novozymes is the world leader in the supply of recombinant products and technologies for drug delivery applications. Currently, 14% of Novozymes' total revenue is spent on research and development with more than 6,000 granted and pending patent applications, demonstrating a commitment to scientific innovation.

Novozymes' large-scale manufacturing facilities worldwide are run to cGMP/Q7 quality standards ensuring customers receive product quality and consistency, as well as the security of long-term supply. The company's customer-integrated approach combines Novozymes' scientific know-how with the specific needs of customers to deliver improved products and performance.

HALF-LIFE EXTENSION (HLE) TECHNOLOGY

Novozymes' tuneable half-life extension (HLE) technology can flexibly extend half-life to reduce the dosing frequency of drugs from "days to weeks". Based on albumin, Novozymes offers HLE by genetic fusion, as Albufuse® Flex, and by chemical conjugation, as Recombumin® Flex, enabling half-life to be modulated to meet the needs of a particular disease or application.

Leading the way in improving patient quality of life, Novozymes' technology is already being widely used in the fields of diabetes, haemophilia and neutropenia. Through the optimisation of drug half-life, dosing frequency and healthcare costs can be reduced while increasing patient compliance. Long patents until at least 2030 also provide manufacturers with a unique competitive edge in current challenging markets.

Albufuse® Flex

Albufuse® Flex is a new and improved albumin fusion technology. Through subtle modification of the albumin molecule this innovative technology aims to improve the circulatory half-life of the albumin molecule itself, resulting in these advantages being conferred to any fused or conjugated drug. The next-generation technology has been developed to tailor and control the pharmacokinetics of target proteins and peptides to enable a tuneable half-life that offers control and flexibility, improving overall treatment efficacy and patient compliance.

> "LEADING THE WAY IN IMPROVING PATIENT QUALITY OF LIFE, NOVOZYMES' TECHNOLOGY IS ALREADY BEING WIDELY USED IN THE FIELDS OF DIABETES, HAEMOPHILIA AND NEUTROPENIA"

Recombumin® Flex

By linking drugs to Novozymes' Recombumin® (Recombinant Albumin), their pharmacokinetic and pharmacodynamics properties can be dramatically enhanced. As a result manufacturers can benefit from the ability to tailor and control the half-life of drugs to fit specific medical needs.

RECOMBINANT ALBUMIN

Novozymes offers a range of recombinant albumins (rAlbumins) developed to provide customers with a safe and consistent regulatory-compliant product. The company's rAlbumins are manufactured to large-scale using a proprietary Saccharomyces yeast strain to cGMP/Q7 quality standards, free of animal- or human-derived products and supported by a strongly documented safety package and drug master file.

DRUG DELIVERY

Whether it is to improve the half-life of the active molecule or to increase the drug retention time for controlled release, Novozymes can help drug manufacturers with a solution suited to the desired application.

NOVOZYMES' rALBUMINS IN FORMULATION

As the purest and most homogenous rAlbumins available, Novozymes' Albucult® and Recombumin® (see Figure 1) are ideal for stabilising drug formulations and can help:

- Achieve liquid formulations in protein therapeutics
- Limit product loss due to non-specific adsorption
- Prevent functional or structural changes caused by oxidation
- Reduce aggregation and sub-visible particle formulation to minimise immunogenicity concerns
- Function over a range of formulation conditions, for example, pH and temperature.

Albucult® – Recombinant albumin USP-NF*

Suited to drug, vaccine, and device manufacturing

Expressed in a proprietary *Saccharomyces cerevisiae* expression technology and manufactured in a large-scale, cGMP-compliant facility, Albucult is designed with stringent quality requirements in mind. Albucult has been developed and supplied as an ingredient for the manufacture of pharmaceutical drugs, medical devices and advanced cell therapy products. It delivers quality and unprecedented performance benefits to customers' applications.

Recombumin® – Recombinant albumin USP-NF*

Ideal for drug delivery and formulation

Also expressed in *Saccharomyces cerevisiae*, Recombumin is the world's first and only commercially available, GMP-manufactured, animal-free rAlbumin developed specifically as a drug and vaccine manufacturing ingredient.

Figure 1: Novozymes' Albucult® and Recombumin® are ideal for stabilizing drugs in a range of formulation conditions.

Figure 2: Novozymes' Hyasis® offers safety, consistency and performance, all in one raw material.

Recombumin has been fully approved for use in the manufacture of human therapeutics. The product's batch-to-batch consistency and regulatory compliance reduces processing and testing times to drive product efficiency.

HYALURONIC ACID – HYASIS®

Novozymes' cGMP-grade hyaluronic acid (HA), Hyasis (see Figure 2), has been designed to fill a gap in the market for biomedical and pharmaceutical manufacturers looking for Q7 regulatory compliant ingredients with superior performance benefits.

Novozymes' focus on improving processes for customers has resulted in a HA that offers unmatched benefits. Superior heat stability permits autoclaving without significant loss of product viscosity, and tight control of molecular weight during production allows for excellent control in formulations. Hyasis can also dissolve five times faster than other sources, reducing processing times by up to 50%.

Produced using a fermentation process of the safe bacterial strain, Bacillus subtilis, Hyasis is free of animal-derived components and organic solvents, ensuring superior purity and reducing contamination risks. Hyasis can be customised using Novozymes' proprietary crosslinking technology to achieve a specified viscosity. This enables the product to be adapted for drug delivery and medical device applications across ophthalmology, dermal fillers and osteoarthritis.

HYASIS® LINK- HYALURONIC ACID CROSSLINKING TECHNOLOGY

Novozymes has introduced a new crosslinking technology for preparing hyaluronic acid (HA) hydrogels. The versatile and proven Hyasis Link technology enables Novozymes' cGMP-grade Hyasis HA to be customised to achieve specific visco-elastic properties. The new technology will expand opportunities for the use of HA across multiple therapy areas, creating improved products with real benefits for patients.

"LONG PATENTS UNTIL AT LEAST 2030 ALSO PROVIDE MANUFACTURERS WITH A UNIQUE COMPETITIVE EDGE IN CURRENT CHALLENGING MARKETS"

The new Hyasis Link technology can be adapted to display a longer in vivo residence time according to the needs of a range of drug delivery and medical device applications, including ophthalmology, dermal fillers, osteoarthritis, adhesion prevention, coating and wound healing. The technology is based on a reproducible and safe process that does not employ any organic solvents. Owing to an effective purification step, the resulting transparent and homogeneous hydrogels do not contain any residual crosslinking agent, ensuring safety and biocompatibility.

The technology offers superior heat stability and permits autoclaving and extrusion through clinical needles of different gauge sizes without significant loss of product viscosity, ensuring enhanced control in formulations. Hyasis Link is available through a licensing agreement in which customers gain access to the technology as well as support to develop their final hydrogel formulation.

EXPERIENCED REGULATORY SUPPORT FOR RECOMBINANTS

Novozymes offers up-to-date and efficient regulatory support services to fast track customers' regulatory filings through:

- Experienced dealings with regulatory agencies, including US FDA, EMEA, TGA, Health Canada
- Support of Novozymes' animal-free recombinant products and technologies
- Preparation and maintenance of regulatory support dossiers; e.g. drug master files, clinical trial applications, product dossiers
- Application of QbD principles, removing animal-derived materials from manufacturing processes

QUALITY ASSURANCE AND CONSISTENCY

Novozymes' quality assured, consistent products and technologies are designed with an understanding of the regulatory landscape. Dedicated product support and expertise delivers a rapid response to regulatory queries facilitating the regulatory process of customers' products and technologies.

** Meets National Formulary (NF) standards as published by the US Pharmacopeia (USP).*

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