DELIVERING INJECTABLES

SAFETY, EFFICACY AND CONVENIENCE IN TODAY'S COMPLEX MARKET

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"Delivering injectables: safety, efficacy and convenience in today's complex market"

This edition is one in a series of sponsored themed publications from ONdrugDelivery Ltd. Each issue will focus on a specific topic within the field of drug delivery, and contain up to eight articles contributed by industry experts.

Full contact information appears alongside each article. Contributing companies would be delighted to hear from interested readers directly. ONdrugDelivery would also be very pleased to pass on to authors, or answer as appropriate, any queries you might have in relation to this publication or others in the series.

Forthcoming editions cover: nasal drug delivery; safer injections; advanced transdermal drug delivery; drug delivery in diabetes; pulmonary deilvery; advanced oral drug delivery needle-free injection; and prefilled syringes. To find out more about receiving or participating with any of these issues, please contact ONdrugDelivery Ltd.

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"*Delivering injectables: safety, efficacy and convenience in today's complex market*". Published by ONdrugDelivery Ltd, Cedar Cottage, Newtimber Place Lane, Newtimber, West Sussex, BN6 9BU, United Kingdom. Registered in England: No 05314696.

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INTRODUCTION

There was a time during the mid-1990s when it seemed possible that the needle and syringe, which had served the medical world so well for more than one-and-a-half centuries, was nearing the end of its days. Non-invasive drug delivery routes, such as systemic administration via the lung and nasal delivery, were emerging and offered painless, convenient and safe self-administration options. They were set to eclipse needle-based devices, but they have not done so.

It was not that these novel systems did not exist, nor were they ineffective; indeed many of them are applied in products that are either already available or nearing the market today. However, almost as soon as the buzz about non-invasive delivery had started, it became clear that for many products, injection – even though it had some drawbacks – was the most attractive administration route, and would remain so for the foreseeable future.

The over-optimistic period about non-invasive drug delivery in the late 1990s, although eventually dampened, nevertheless had a powerful effect on the injectables market. Having been presented, albeit temporarily, with the possibility of readily available alternatives to needles, the pharmaceutical industry, medical community and government regulators worldwide no longer seem as content to settle for the traditional needle and syringe design, and traditional formulations, without questioning every detail. They are constantly asking themselves and each other what aspects of injectable delivery should be improved and how this might be achieved.

Boosted significantly by other factors such as: the emergence of biopharmaceutical companies and the large, fragile and expensive therapeutic molecules they produce; the introduction of sharps injury prevention legislation; and global efforts to eradicate the dangerous practice of needle- re-use in the developing world, there has been a wholesale shift in attitudes towards injections. The effect on the injectables sector has been positive – particularly driving the development of technologies designed to improve injections. The market continues to grow fast and, indeed, technological innovations have enabled injectable administration to expand into completely new areas.

Acceptance that injections are here to stay as a mainstream route of administration mixes with a climate that is more questioning and demanding of injection systems, prompting an explosion of new ideas and technologies. Some of these involve the drug delivery device and others the formulation itself, but all are aimed at improving the safety, efficacy and convenience of products given via the injectable route.

In this edition in the sponsored series of specialist publications from ONdrugDelivery, we have articles from some of the leading companies in the field of injectable drug delivery.

SkyePharma reports on formulation-based approaches for reducing frequency of injection, the benefits of which, we shall see, can extend far beyond convenience. Diatos describes its conjugation and prodrug systems, which include intracellular delivery technologies, for targeting cancer therapies precisely to the required site to reduce injection site reactions and systemic toxicity.

Meanwhile, companies involved on the device side of injectable drug delivery also appear. Vetter Pharma gives a run-down of its syringe filling capabilities, including details of its dual-chamber Lyo-Ject technology for lyophilised formulations. Ticona outlines its vision for the future of injection device manufacture using polymers instead of glass, opening many new design possibilities.

I hope that you will find the articles that follow to be useful and enlightening accounts of the technologies and products under development or marketed by each company featured. Additionally, it is our intention that this edition as a whole serves as an informative glimpse of the current trends and latest advances within this sector. It demonstrates clearly that while injection is a long-established delivery route, the market – full of inspired new ideas – is more important than ever for healthcare today.

Guy Furness
Managing Director, ONdrugDelivery Ltd

MEETING THE CHALLENGE OF DELIVERING COMPLEX INJECTABLES:

INJECTABLE SUSTAINED-RELEASE SYSTEMS

The great majority of drugs have relatively short residence times in the body after administration, generally on the order of a few hours. This in turn requires that these products be administered frequently or continuously. Many parenterally administered drugs require frequent injections or continuous infusion to be therapeutically effective. This is particularly true for macromolecular agents such as therapeutic proteins (which generally cannot be administered orally for systemic effect), but also applies to classical small-molecule drugs. Daily injections, for instance, are not only inconvenient, but also can give peak blood levels that cause unwanted side effects and/or blood levels that drop to sub-therapeutic concentrations before the next dose is administered. Continuous infusion can obviate these difficulties, but this is more invasive, expensive, and risky. Dr Richard Jones, senior vice-president, R&D at SkyePharma, explains how sustained-release injection technologies can overcome some of these problems.

Sustained-release injectable systems are designed to provide sustained availability and activity over several days to several weeks or more after a single injection. The ideal system will achieve a more constant delivery rate of the drug – such that a flatter pharmacokinetic / pharmacodynamic profile is maintained for a longer period of time – and reduce the frequency of injections. This can increase patient convenience and compliance, reduce cost, and improve efficacy and safety.

SkyePharma has been active in the design, development, and manufacturing of sustained-release injectable systems, based on its proprietary DepoFoam® and Biosphere® technologies.

DEPOFOAM®

DepoFoam® is a non-classical liposome technology designed for sustained release of therapeutic agents following injection into sites other than the bloodstream. DepoFoam® products are sterile suspensions of spherical microscopic multivesicular liposome (MVL) particles in water. Particles are generally in the 10 to 40 μm diameter size range, and are suitable for administration via the subcutaneous, intramuscular, intrathecal, epidural, intra-articular and intra-ophthalmic routes, among others. Needles as small as 30G are feasible for DepoFoam® injections. However because of the size of the MVLs, DepoFoam® is not suitable for intravascular administration.

Unlike classical liposomes, where the lipid bilayers are in concentric shells, each MVL particle is a honeycomb of numerous non-concentric aqueous chambers surrounded by lipid bilayers (see figure 1). The drug is contained in solution within the aqueous chambers. The lipids, which are naturally occurring materials or close analogs thereof, constitute approximately 4-5% of the total particle volume. The duration of release of the encapsulated drug is generally determined by the lipid composition, and can be modified to provide release durations from a day or two up to two to four weeks.

Due to the innocuous nature of the constituents of the particles, the system is highly biocompatible and fully biodegradable. Since the drug is dissolved in the water in the aqueous chambers, it must be water soluble and water stable.

Confocal photomicrographs of an MVL particle are shown in figure 2. In this example, the lipid phase of the particle has been labelled with a red-fluorescent dye and the aqueous phase has been labelled with a green-fluorescent dye. The images clearly show the multivesicular nature

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of the particle. The difference between the multivesicular DepoFoam® liposomes and conventional liposomes is illustrated in figure 3.

Typical pharmacodynamic profiles for a model protein (leridistim, a fusion protein of IL-3 and GCSF) administered subcutaneously in an animal model in vivo are shown in figure 4. In this example, the unencapsulated protein provides only a day or two of activity, whereas DepoFoam® formulations can provide more than a week of sustained activity after a single subcutaneous injection. Also shown is the ability to tailor the system to provide a range of delivery profiles.

... MARKETED DEPOFOAM® PRODUCTS

The first DepoFoam® product to be approved by the FDA and the EMEA was DepoCyt®, a sustained-release form of the antineoplastic drug, cytarabine, administered intrathecally for the treatment of lymphomatous meningitis. It is currently marketed in the US by Enzon Pharmaceuticals, and in Europe (as DepoCyte®) by Mundipharma.

The half-life of unencapsulated cytarabine administered by this route is only 3.4 hours, but in DepoCyt® the effective half-life is 142 hours. DepoCyt® therefore needs to be injected only once every two weeks (compared with every other day for unencapsulated drug) thereby allowing the patient to be treated on an outpatient basis, and reducing the frequency of a very uncomfortable procedure.

A second DepoFoam® product, DepoDur™ (morphine sulfate), was approved in the US in May 2004, where it is marketed by Endo Pharmaceuticals. A UK marketing application is currently under review by the UK MHRA and, once approved, DepoDur™ will be marketed in Europe by Zeneus Pharma. DepoDur™ is injected epidurally, for the relief of moderate-to-severe post-surgical pain for up to two days after a single injection. Such pain relief with a conventional aqueous solution of morphine would require an indwelling epidural catheter, which has attendant risks of displacement of the catheter and/or infection.

Several other DepoFoam® products are in development, and are designed to provide delivery profiles from 2-3 days up to one month, depending on the product.

... MANUFACTURE

The manufacturing process is a multi-step aseptic double-emulsification process, involving formation of a water-in-oil-in-water emulsion, solvent removal, and microfiltration/diafiltration to produce the final aqueous DepoFoam® suspension product. The process generally results in no damage to complex macromolecular drugs such as therapeutic proteins. The finished product is filled into vials using standard aseptic filling equipment. The entire process from initial emulsion formation to final product fill is carried out under aseptic conditions. The process has been scaled up to commercial levels and the process and the San Diego commercial manufacturing site have passed both FDA and EMEA inspection. Broad patent protection on the technology extends to 2014 and beyond.

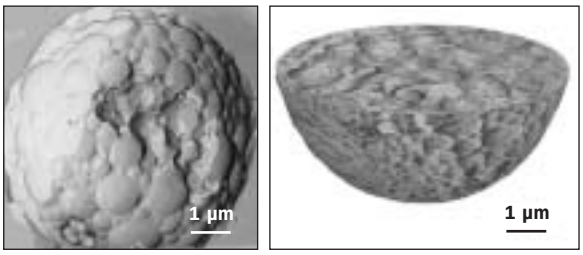

Figure 1: FF-SEM image (a) and computer-generated section (b) of a DepoFoam® particle

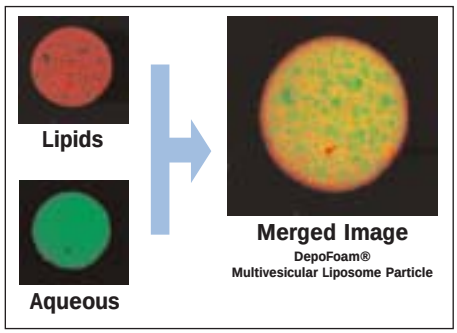

Figure 2: Confocal photomicrographs of an MVL particle

BIOSPHERE®

Biosphere® is a microparticle technology and, like DepoFoam®, is designed for the sustained release of drugs following injection into sites other than the bloodstream. Biosphere® products are provided as sterile, dry powders for reconstitution into aqueous suspensions just prior to administration. Needles as small as 23-25G can be used for delivery.

The Biosphere® particles (see figure 5), about 40-100 μm in diameter, are made up of a central core of a highly purified parenteral-grade starch containing dispersed drug. A polymer (polylactide-co-glycolide, PLG) coating surrounding each particle helps determine the release rate of drug. Release rates are varied by selection of the molecular weight and the lactide/glycolide ratio of the PLG, and can be modified to provide release durations from 1-2 days up to as much as 2-4 weeks. The starch and the polymer are fully biocompatible and biodegradable. Because the product is stored in the dry state, the technology is particularly well suited for drugs that are not fully stable in water for long periods of time.

Typical delivery profiles in a recent Phase I pharmacokinetic/pharmacodynamic study in man with a Biosphere® formulation of a model protein (hGH) are shown in figure 6. In this example, serum hGH concentrations were maintained well above baseline for at least two weeks after a single dose. In addition, unlike other microsphere delivery systems, the degree of "burst" release at short times was considerably attenuated. The pharmacodynamic effect (elevation of serum IGF-I levels) was also maintained for at least two weeks or longer.

The manufacturing process for Biosphere® products involves two major steps: microsphere formation and microsphere coating. The first step is an aqueous precipitation of starch microparticles under controlled mixing conditions during or after which the drug is incorporated into the particles. The microparticles are collected and dried, then coated with PLG in a fluid-bed system. The exposure of the microparticles to organic solvent during the coating process is very brief. Particularly important to note in the case of proteins is that since the drug is encapsulated in the starch microparticles, it is not ever exposed directly to the solvent. The coated microparticles are collected, further

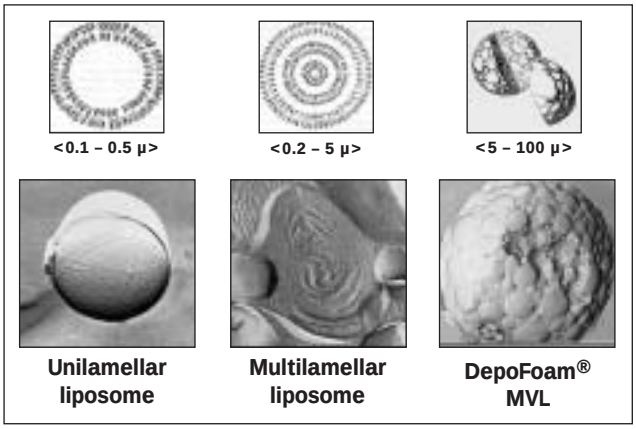

Figure 3: Conventional liposomes and DepoFoam®

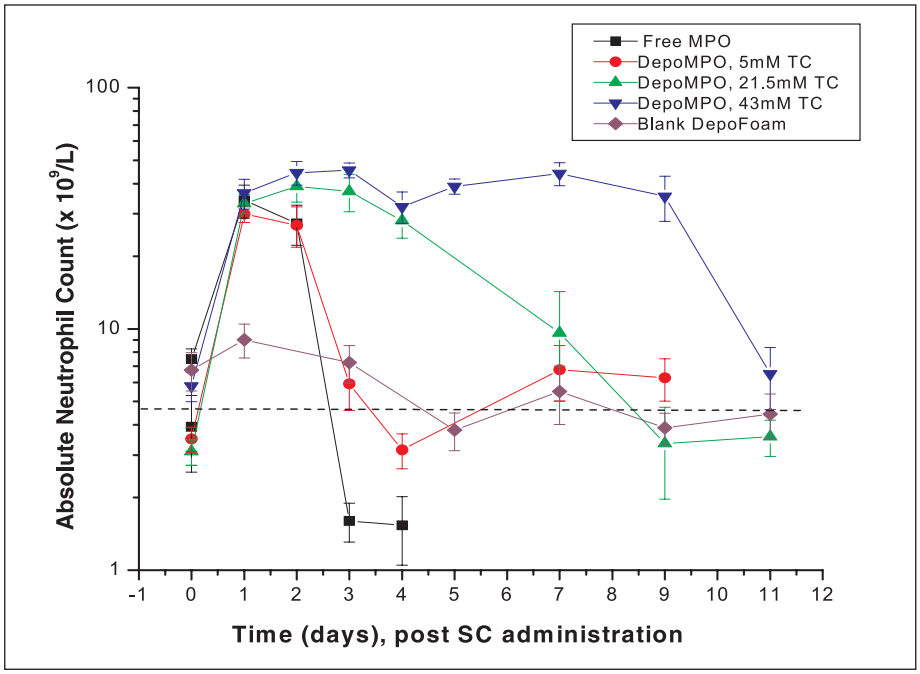

Figure 4: Sustained pharmacodynamic effect of DepoLeridistim (myelopoietin, "MPO")

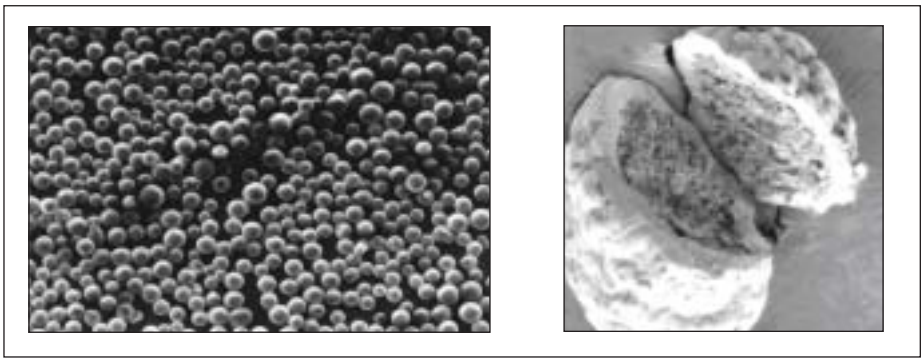

Figure 5: Electron micrograph of Biosphere®

dried, and then filled into vials using standard aseptic powder filling equipment. The entire process from initial aqueous precipitation to final product fill is carried out under aseptic conditions. Patent protection on the technology extends to 2021.

Therapeutic protein products using the Biosphere® technology are manufacturable at pilot scale (for clinical studies) at SkyePharma's R&D site in San Diego, California, US. A single-step increase in scale would be adequate for entry into commercial manufacturing, which could take place at SkyePharma's commercial pharmaceutical manufacturing facilities in San Diego or Lyon, France.

CONCLUSIONS

Sustained-release injectable technologies offer significant benefits in increasing patient convenience and compliance, reducing cost, and improving efficacy and safety of drug therapy. SkyePharma's DepoFoam® and Biosphere® technologies are good examples of such delivery systems, and have been shown to provide potential with both conventional small-molecule drugs as well as large, more complex protein therapeutics.

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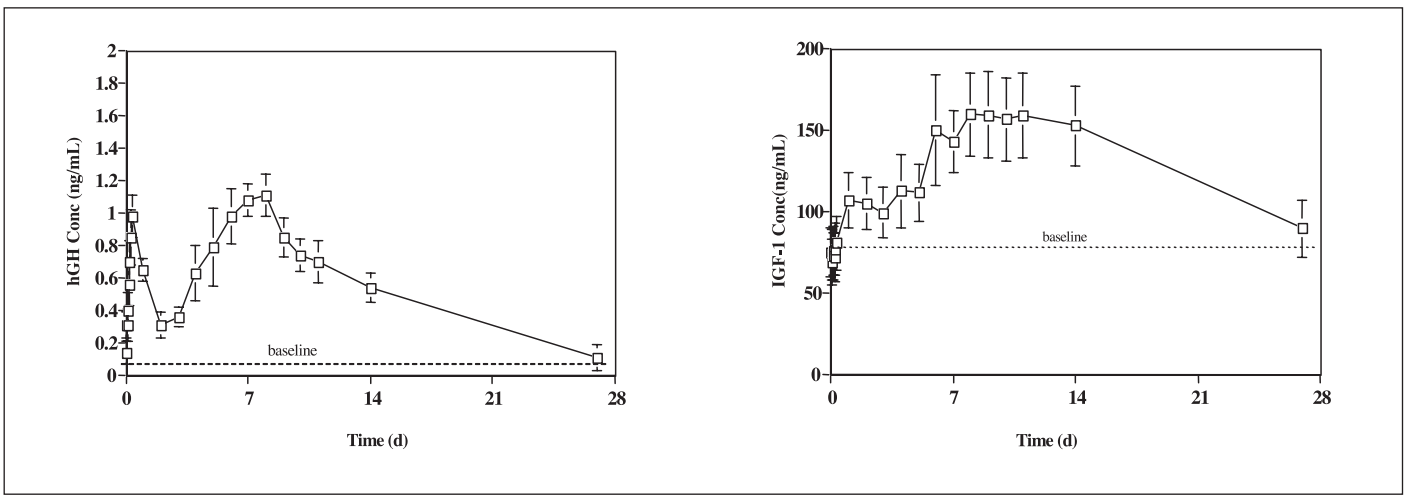

Figure 6: hGH-Biosphere pharmacokinetics/pharmacodynamics in man

INNOVATIVE INJECTION DEVICE DESIGN:

UNIQUE POLYMERS THAT BREAK THROUGH THE GLASS CEILING

In this article, Deven Patel, Market Development US, Topas, and Michael Grimm, Market Development EU, Topas, both of Ticona, explain how a family of Topas® cyclo-olefin-copolymers, when used for injection devices, can overcome many of the problems associated with traditional materials, and also open up new and exciting opportunities in device design functionality.

After a period of amazing claims by the drug delivery industry towards the end of the 1990s, during which many believed that non-invasive delivery systems were set to run injectables out of the market in the decade ahead, the reality dawned that many products would be suitable only for administration by injection for the foreseeable future at least. Indeed, according to figures from Thomson Scientific's IDdb, almost a quarter of drugs in clinical trials or awaiting approval or launch that have a disclosed route of administration are injectable formulations. Injection is still the chosen delivery route for these products on account of its efficacy in getting the active compound to where it is needed quickly and in therapeutic quantities.

The healthcare community has accepted that injections will remain one of the most important methods of drug delivery and, far from shrinking as other delivery routes take over, the injectable drug delivery market is predicted to grow. According to Datamonitor, from a value of $83 billion in 2002, the sector will enjoy a compound annual growth rate of 10% to 2008. Nonetheless, the days when the shortcomings of conventional needle-and-syringe systems could be overlooked, accepted as unavoidable, and left unchallenged, are over. There is demand from all quarters – the pharmaceutical industry, its regulators, medical practitioners and patients – for every aspect of injection devices to be revisited, and improved upon wherever possible.

CHOICE OF OPTIMAL MATERIALS IS CRUCIAL

When considering potential improvements to the design and manufacture of injection devices, or indeed the development of entirely original injectors, choice of materials available is one of the most important – if not the most important – and fundamental factors. However, when it comes to choosing materials for syringes, the common perception is that there is really no decision to be made.

Glass is the material that has been traditionally used for syringes for many years, and so glass is the material that is chosen again and again, almost as a subconscious, habitual reflex. This decision is often made without considering the hugely beneficial – perhaps previously unimaginable – opportunities that could be pursued if viable alternatives to glass were made available.

Yet, for some years now, Topas® cyclo-olefincopolymers, a class of unique polymer materials, have been emerging as exactly such an alternative to glass. These materials have the potential to revolutionise injector device design.

Cyclo-olefin-copolymers (COC) are crystal-clear amorphous materials based on cyclic and linear olefins. This family of engineering resins, developed and marketed as Topas by Ticona GmbH, exhibits a unique combination of properties including high transparency, low density, excellent moisture barrier capabilities and resistance to aqueous and polar organic media. These qualities, together with the polymers' good mechanical characteristics – which include high rigidity and strength – and their high purity, very low level of extractables and biocompatibility, mean that they represent the material of choice for an increasing number of applications in the medical and diagnostics sectors.

When it comes to examining and revisiting conventional injection devices for possible areas of

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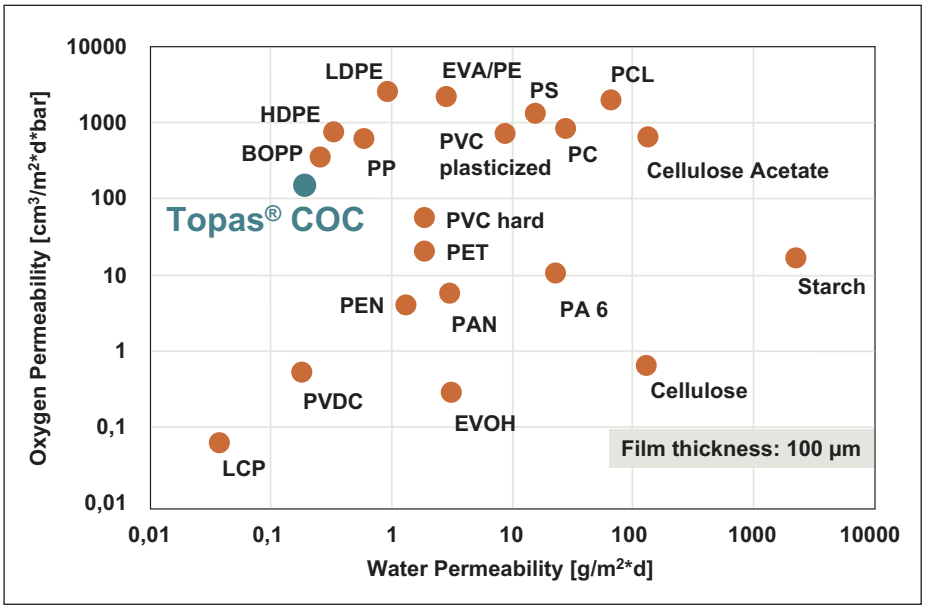

Figure 1: Topas barrier properties (relative humidity: 85%, temperature: 23°C)

improvement, Topas COC polymers, which can be applied in syringes, vials, small bottles (and even non-injectable applications such as blister packs), open up new opportunities at almost every turn.

As a basic measure, simply replacing glass syringes with plastic, which is more shatter resistant, immediately reduces the risk of accidental breakage and therefore carries a significant safety advantage. However, although this in itself is a major benefit, the advantages of Topas run far deeper.

Typically, Topas components in injection systems are manufactured using injection molding, injection blow molding and injection stretch blow molding. Manufacturing using plastics is much simpler and units, in most cases, are ready to fill resulting in overall lower system cost compared with glass, which requires cleaning prior to filling process. Tighter tolerances than glass tubes of up to 3% allow precise volume and delivery to patients.

Also manufacturing with plastics confers design versatility in a different league to that possible with glass, allowing manufacturers to differentiate their product and gain a significant competitive edge.

For example, greater design flexibility allows more complex shapes to be introduced, enabling additional functionality to be engineered into the design. Plastic materials such as Topas polymers therefore are not simply an alternative, but can be an equivalent or better material than glass. They can overcome many of the problems associated with the use of glass in injection devices but, furthermore, plastic opens avenues that were not even explored previously.

New ideas are not limited to application in needle and syringe design, but also have been usefully applied to overcome the technical challenges of injector pens, auto-injectors and needle-free injectors, all of which have several moving parts, and many of which must tolerate

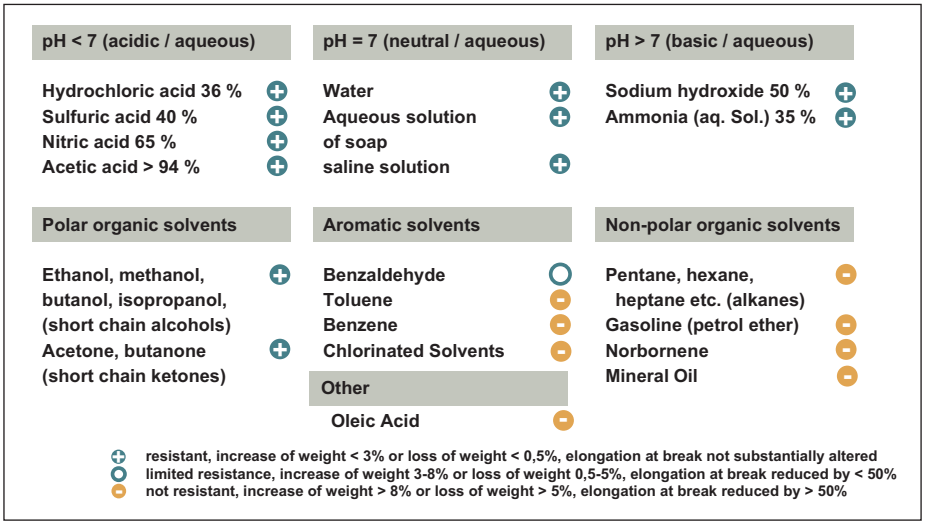

Figure 2: Topas chemical resistance

substantial pressures and accommodate variable dosing and dose counting mechanisms.

Additional functionality, such as moving parts, is currently typically achieved by "bolting on" additional mechanisms to the central core of the device – the drug container – which is made of glass and the versatility of which is therefore restricted. More of the functionality could be incorporated into a single functional drug container component if a polymer such a Topas was used, therefore potentially reducing the total number of components, and with it the complexity and cost of the device.

THE EMERGENCE OF PREFILLABLE DEVICES

One of the most apparent trends in today's injectable drug delivery market is the adoption of prefillable systems, across a range of therapeutic areas. The advantages of these systems are manifold and include the fact that they are quicker, more convenient and safer to use than formulations presented in a vial. They also reduce the incidence of dosing errors and can contain the precise amount of drug required, eliminating drug wastage through overfill.

A common characteristic of all prefillable delivery devices is that they must play a dual role, as both drug container and delivery system. They must therefore meet the functional and regulatory requirements of both roles, and this often presents engineering and design challenges. Topas can help overcome and in some cases completely avoid many of these obstacles.

HIGHLY IMPERMEABLE TO WATER

One key requirement is that product stability must be maintained. Topas exhibits exceptional moisture barrier qualities to the extent that it can extend shelf life compared with products stored in other transparent polymers. In permeability studies, Topas 8007 film of thickness 100 μm exhibited water permeability in the region of 0,28 g/m²*d (see figure 1).

MINIMAL INTERACTION WITH PROTEIN COMPOUNDS

Biocompatability, especially with reference to fragile protein therapeutics, is another prerequisite for an appropriate drug container. Protein solutions can behave like colloidal suspensions, being always on the verge of a phase change, leading to aggregation, precipitation or gel formation, for example. Proteins are very sensitive to surfaces – they undergo adsorption to the container surface, where chemical reactions can be catalysed. Protein denaturation can occur after adsorption,

causing protein aggregation both at the surface and in the solution, or protein precipitation.

The first of three studies that demonstrated the biocompatibility of Topas was carried out by LMU Munich, Professor Winter, Germany, in 2002 and compared the adsorption of 200 μg/ml solutions of bovine serum albumin (BSA) and of interferon alfa-2α in containers made from borosilicate, siliconised borosilicate and Schott's TopPac vials, which are made from Topas, after 24 hours and 72 hours of storage.

The study revealed that similar amounts of BSA adsorbed to the Topas container and the siliconised borosilicate container after 72 hours. However, interferon alfa-2α showed significantly lower adsorption in Topas compared with both siliconised and non-siliconised borosilicate containers.

The second study, conducted by Boehringer Ingelheim, involved a liquid formulation of highly potent, small (< 9,000 Da), positively charged therapeutic protein. While significant adsorption to Type I glass vials was observed, there was very low absorption to Topas vials. This particular protein is given at a very low dose after dilution for infusion (0.1 μg/ml), meaning that any mechanism for reducing the degree of adsorption would be therapeutically advantageous.

In the third stability study, an immersion test of polio vaccine stored in a Topas vial for three months showed that there was no decline in recovered potency at 4˚C. Indeed, potency remained well above the specified limit.

In addition to being biocompatible, Topas has excellent chemical resistance properties. It is resistant to acids, alcohols, bases and polar solvents, as shown in figure 2.

IMPROVED CONTROL OVER PH OF WFI

While glass performs well in terms of its high chemical resistance and low moisture permeability, one of its major drawbacks arises when it is used in storage containers for water for injection (WFI), the most common diluent for reconstituting lyophilised formulations. Specifically, the problem is that glass has a reactive internal surface, which, in the presence of WFI, releases hydroxide ions making it difficult to maintain the pH within the limits set out in the US and other Pharmacopoeias.

A recent study carried out by Aseptic Technologies monitored the pH of WFI at 4˚C and 20˚C in a Topas vial for three months. It found that pH remained within the specified limits throughout the period, tending to stabilise at around 6.8. When buffers were used, no change in pH was observed.

Area	Regulatory Authority	Pharmacopeia	International Standards
EU	EMEA	European (EP)	International Organization for Standardization (ISO)
Japan	MHLW	Japanese (JP)	
USA	FDA	United States (USP)	

Figure 3: Regulatory status of Topas

READILY STERILISABLE

Topas can withstand high-energy radiation (gamma rays and electron beams) and ethylene oxide. Different grades of Topas with varying glass transition temperatures can easily be produced. Grades with a high glass-transition temperature can be used in applications where steam sterilisation is required.

BEST PLASTIC FOR PHARMACEUTICAL APPLICATIONS

So far we have concentrated on comparing the benefits of Topas over traditional glass materials. Topas also has significant advantages over other polymers that might be considered for injectable devices. For example, with polypropylene clarity is reduced; with polymethylpentene strength, weight and water barrier properties are not optimal; polycarbonate is not selected because of poor water barrier properties and chemical resistance; and polyethylene cannot be sterilised by steam autoclave.

In contrast, Topas does not encounter any of these drawbacks. On the contrary, it is the plastic with the best combination of properties for pharmaceutical containers.

STRONG GLOBAL REGULATORY POSITION

The finished product of primary pharmaceutical packaging is subject to regulation, rather the constituent materials, therefore it is not possible to obtain a general approval for plastics in these applications. However, Ticona has placed Topas in the strongest possible regulatory position in order to support manufacturers and users of its products.

Drug Master Files and Device Master Files have been established with the US FDA, and the relevant grades of Topas conform to the US, European and Japanese Pharmacopoeias as summarised in figure 3, and with ISO10993-4 and 10993-5.

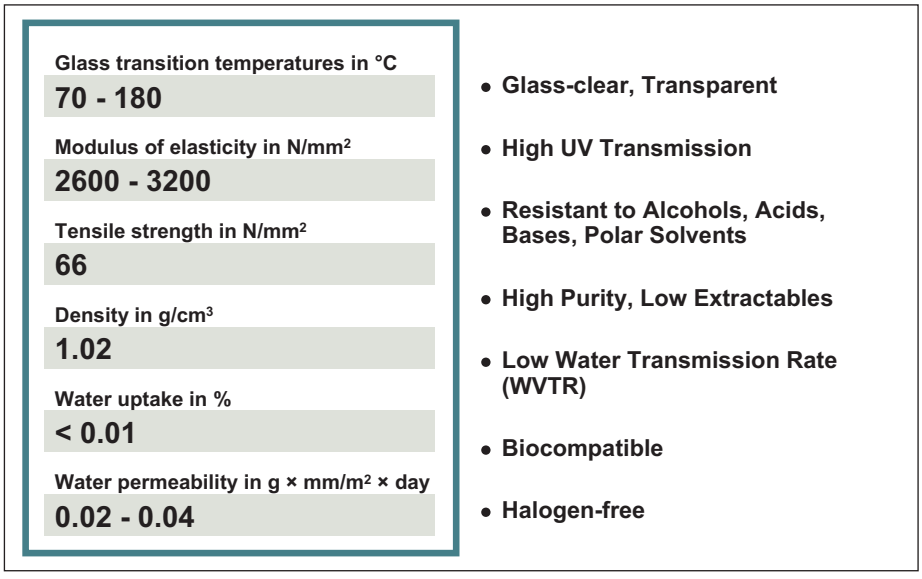

Figure 4: Summary of basic properties of Topas

HISTORY, MANUFACTURING AND CHARACTERISTICS OF TOPAS COC POLYMERS

"Cyclo-olefin copolymers (COC) with α-olefins have been known for about 50 years but new synthetic production methods, initially using Ziegler-Natta catalysts and then metallocene catalysts, enabled commercially viable manufacture.

After COC development projects began in 1990, the production plant in Oberhausen, Germany, with a capacity of 30,000 tons/year, came on stream in October 2000. It is the largest COC plant in the world.

The production plant is completely controlled by a Process Control System (PCS), which maintains a stable process, ensuring product uniformity. A data management system allows continuous monitoring and optimisation of the process and gives traceability.

Various grades of Topas are produced, each with different molecular weights and glass transition temperatures and each being tailored for specific pharmaceutical applications. The basic properties of Topas are summarised in figure 4."

BEYOND THE GLASS CEILING

The trouble with glass ceilings is that those underneath them seldom realise that the glass ceiling is even there, preventing them from reaching their full potential. Such is the case in the injectable devices market, where the use of glass is itself the glass ceiling.

So entrenched is the tradition of glass syringes and vials that other materials, and the promise they hold to transform the quality and functionality of injection devices, often remain unseen.

With its Topas COC polymers, Ticona believes that it can show those involved in the injectables market that the glass ceiling does exist but that there are viable possibilities beyond it that would readily be transformed into real technological breakthroughs. Topas COC polymers represent an ideal material for use in a broad range of injection devices and containers. Employing Topas enables manufacturers to overcome many of the problems associated with traditional injection devices, and creates new opportunities for such devices to undergo significant improvements, setting them in a class above other devices in the marketplace.

DELIVERING COMPLEX INJECTABLES:
PROCESS CHALLENGES AND SOLUTIONS

As a leading partner for the pharmaceutical industry in the field of aseptically prefilled systems, Vetter Pharma-Fertigung GmbH and Co KG, along with its customers, has developed a number of tailor-made solutions that have proven to be highly successful. Joerg Zimmermann, Head of Production at Vetter, uses the following case studies to illustrate some of the company's solutions.

The development of sophisticated medications for previously unmet medical needs has created a whole new breed of challenges for the pharmaceutical industry. The very sophistication of these new drugs has dramatically changed the processes required to produce them. By the same token, the products themselves must be differentiated in the marketplace in order to achieve commercial success. The standard ampoule, for example, might still be appropriate for a low-price, generic drug that is widely known and has attained general acceptance. Innovative drugs, on the other hand, such as recombinant proteins and monoclonal antibodies, among others, require much more sophisticated packaging and presentations if they are to achieve breakthrough.

THE PROCESS OF SYRINGE FILLING

While the filling of vials and bottles is a well-known process in both the food and pharma industries, the filling of syringes is something different and highly specialised. The steps of the process are as follows:

WASHING

Syringe barrels, rubber stoppers and closure parts have to be washed and cleaned before sterilisation. This is usually done on washing machines using purified water for the first washing steps, followed by a final rinse with water for injection. The final step of this process is the lubrication of the parts. Lubrication is in most cases based on medical-grade silicone oil. Processes have been fine-tuned to provide enough silicone to allow movement of the stopper in the syringe, while keeping the quantity to the absolute minimum.

STERILISATION

If possible, the syringes are sterilised using dry heat tunnels (see figure 1), since this also removes pyrogens, which could cause fever in the patient (depyrogenisation). If this is not possible, for example when the syringe has a staked needle, steam sterilisation is used. In this case, a more sophisticated washing process is needed that already reduces pyrogens on the glass. At Vetter, the pyrogen removal has been validated by demonstrating an endotoxin removal exceeding 3 log.

FILLING

The filling can be done using various pumping technologies and will be suited to the product's needs: rotary piston pumps, rolling diaphragm pumps or peristaltic pumps (see figure 2) are some of the possibilities.

As a principle, Vetter applies an inline filtration of the product on the filling line as close as possible to the point of fill. This reduces the critical area within the clean room to a minimum.

STOPPERING

The stopper is introduced into the syringe using a stopper placement tube with a slightly smaller diameter than the syringe. The stopper is compressed through the tube with a placement pin. When the stopper has reached its final position, the tube is retracted first, letting the stopper expand. With this technology, no overpressure is created within the syringe.

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Figure 1: Automated heat tunnel unloading

CASE STUDY 1: MICROPARTICLES

Microparticulate dosage forms have been developed as depot formulations for long-release of drug substances. These microparticles are typically based on biodegradable macromolecules such as lactic and glycolic acid copolymers. The microparticles can be manufactured either by spray drying under aseptic conditions, or using solvent-detergent based processes. For the fill-finish section of the process, the challenge lies in the aseptic transfer into the classified area (class A/B) with subsequent resuspension.

In this particular case, the microparticles manufactured by spray drying are collected in a small stainless steel vessel. This is then transferred into a La Calhène box, which is transported to the site of filling and coupled to the cleanroom wall. During this step, the outer side of the cleanroom door is fixed tightly to the outer side of the transfer box, therefore sealing the unsterile faces of both doors. The door then opens into the cleanroom providing access to the stainless steel vessel.

The vessel is transferred into an aseptic work place equipped with RABS (Restricted Access Barrier System). Here, the microparticles are resuspended into a buffer solution just prior to filling.

CASE STUDY 2: VETTER LYO-JECT® SYRINGES

The second part of the process described above is the filling of the microparticle-suspension into Vetter Lyo-Ject® dual-chamber syringes (see figure 3). Vetter developed its patented, award-winning Vetter Lyo-Ject® syringe specifically to meet the requirements of certain types of formulations whose components must be combined just prior to administration, such is the case with a freeze-dried active substance and its diluent.

The Vetter system involves placing a stopper inside a syringe. The diluent is then filled into the top segment, and the active substance into the bottom segment. Prior to administering the drug, the doctor or nurse activates a mechanism on the plunger to mix the two substances. The actual process for filling was also developed by Vetter, including the filling machines themselves (see figure 4). The steps involved are depicted in figure 5.

The major hurdle when filling the suspension is to avoid sedimentation of the suspension if the filling is interrupted. Moreover, all connections have to be performed with special care as the suspension cannot be filtered.

To avoid sedimentation, Vetter has developed a special system of recirculation from the filling needles to the product-holding tank, providing conforming product throughout the fill.

Due to the abrasive nature of the particles, ceramic pumps have to be used instead of the usual stainless steel ones.

This particular product has been in commercial production for seven years already and has been performing on the market to the customer's complete satisfaction.

CASE STUDY 3: OXYGEN-SENSITIVE PRODUCTS

For oxygen-sensitive products, the filling has to be done in a protective atmosphere. In most cases, a nitrogen-rich gas mixture replaces the air bubble in the filled syringe. Depending on the detailed layout and construction of the filling machine, this can be done on various workstations. For some processes, it is sufficient to provide nitro-gen into the stopper placement tube during sealing of the syringe. For others, pre-purging of the empty syringes coupled with filling under nitrogen might be called for.

Using these techniques, oxygen levels of less then 8% in the air bubble are obtained. Final proof for the effectiveness of these steps, however, can only be ob-tained from stability studies.

Figure 2: Filling operation via peristatic pump

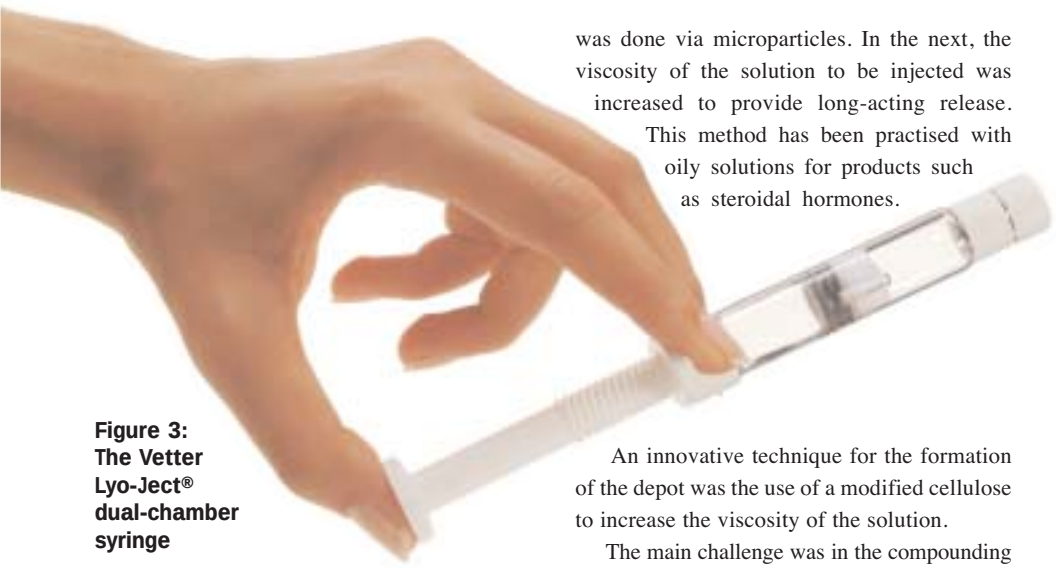


Figure 3: The Vetter Lyo-Ject® dual-chamber syringe

CASE STUDY 4: VISCOUS SOLUTIONS

Controlled release of injectable products is usually achieved by establishing a depot within the tissue. In the above-mentioned case, this was done via microparticles. In the next, the viscosity of the solution to be injected was increased to provide long-acting release. This method has been practised with oily solutions for products such as steroidal hormones.

An innovative technique for the formation of the depot was the use of a modified cellulose to increase the viscosity of the solution.

The main challenge was in the compounding process. If not mixed and milled properly, the cellulose-derivative would form insoluble particles. The solution was found in a set-up with a rotor-stator mixer providing a high shear force. The mixer is used as an external mixer, linked to the compounding tank by flexible tubing of a considerable diameter. The modified cellulose is fed into the rotor-stator via a funnel and a venturi-pump. With this set-up, several kilograms of cellulose can be homogenised into solution within minutes in a validated and reproducible way.

Sterile filtration prior to filling of the product is mandatory as it cannot be heat-sterilised. Again, due to the viscosity of the product, a special pre- and sterilising filter skid had to be developed resulting in a sterile filtered solution of defined viscosity.

The filling process itself is then standard procedure using rotary piston pumps. Here, the process has also been in commercial production for a few years.

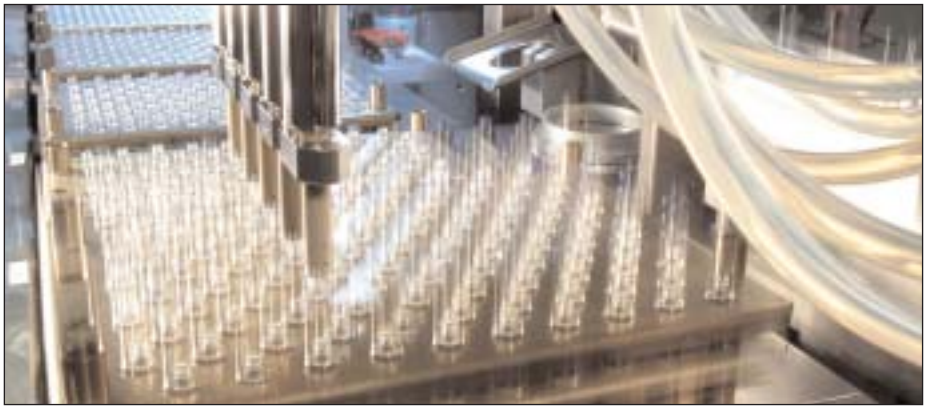


Figure 4: Filling of dual chamber cartridges

CONCLUSION

As these four case studies show, the delivery of complex injectables requires tailor-made solutions. Vetter works closely together with pharmaceutical companies to find the perfect match between the active substance and administration system.

Vetter conducts feasibility analyses and determines which injection system best suits the drug to be produced. During the clinical production phase, all necessary tests are carried out on the product to ensure sterility, stability and even viability for scale-up.

All documentation necessary for international approvals is also prepared during this phase. Vetter has worked with the FDA and the EMEA as well as other regulatory authorities throughout the world, giving Vetter's customers a marked time advantage. When it comes to sophisticated drugs, experience in the aseptic filling process is crucial. Vetter, with more than 25 years as a leading contract manufacturer, has what it takes.

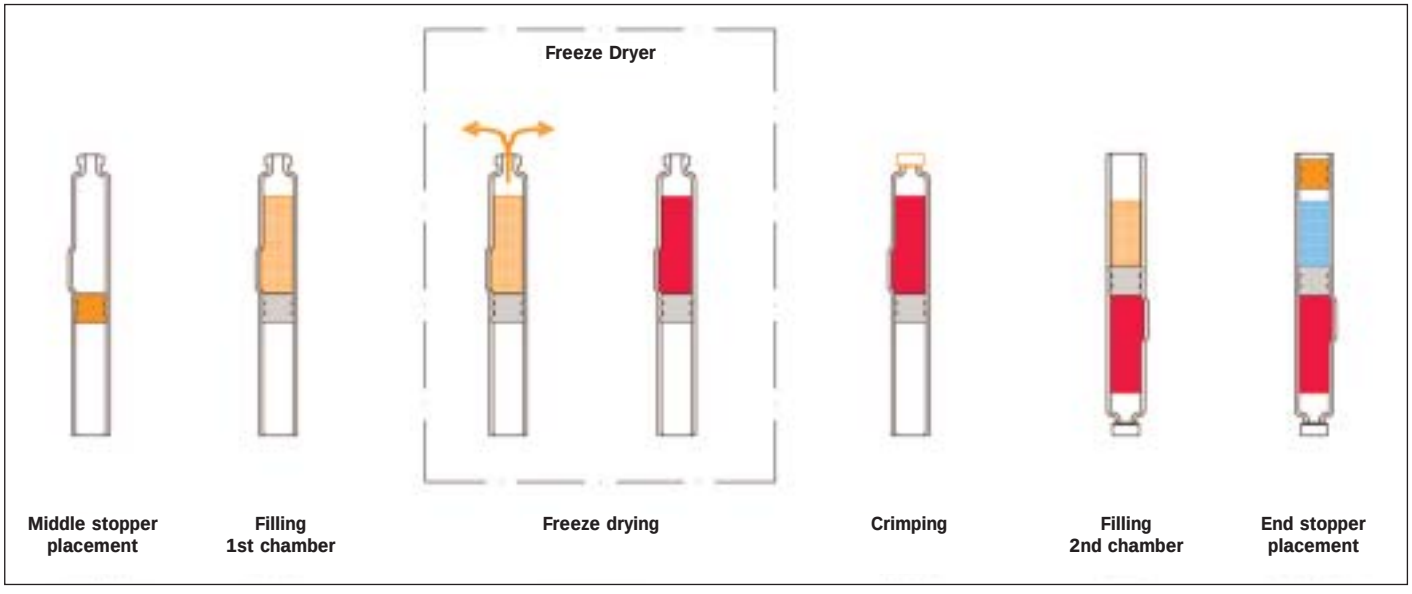
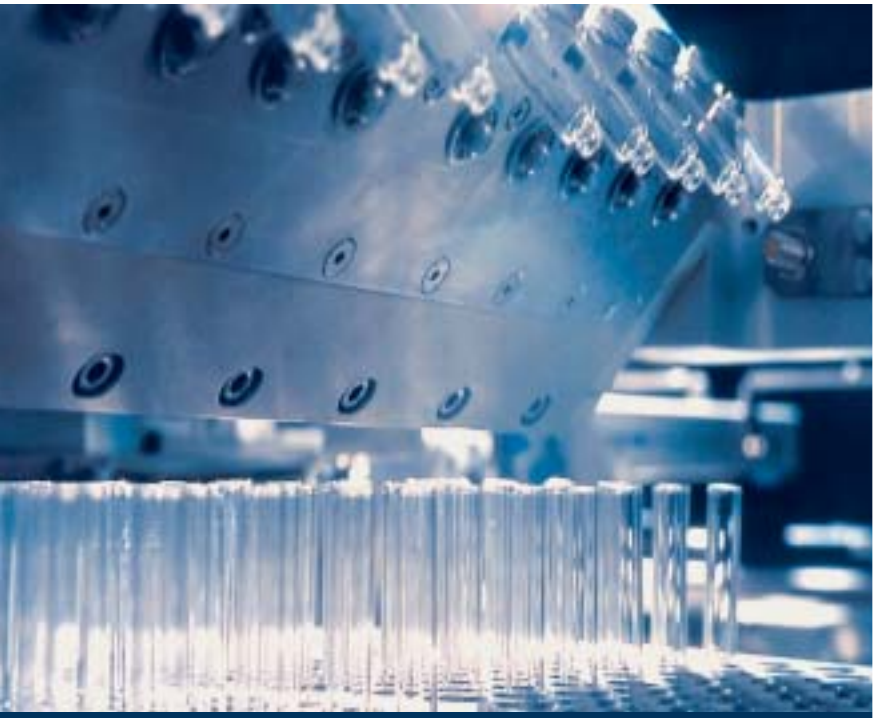


Figure 5: Steps involved in filling dual-chamber syringe



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NOVEL DELIVERY STRATEGIES FOR INJECTABLE CYTOTOXICS

Cancer remains one of the main causes of death in the developing world. Many cancer treatments involve chemotherapy and most cytotoxics are administered by injection. In the past few decades, there have been significant improvements in cancer patient survival rates, but the side effects of chemotherapy limit the therapeutic index of these agents. Dr Sancha Salgueiro, Senior Manager, Business Development Europe at Diatos, describes some of the company's innovative approaches to reduce the undesirable side effects of cytotoxics, without compromising efficacy and in some cases increasing it. They include new types of formulations of well-known cytotoxics, and the development of prodrugs with a widened therapeutic index and better tumour targeting abilities.

In cancer treatment, the large majority of available therapies are administered by injection. Traditional methods of injectable drug administration have a number of advantages that include manageability of dosing volume, stability, convenience and bioavailability. However, there are also important limitations, including undesirable side effects due to poor targeting and poor patient compliance. In cancer, the latter is not a common problem, but the toxic nature of the drugs used exacerbates the direct injection-related side effects.

There are two types of injection site reactions: one is a local allergic reaction, also called a flare reaction, and is caused by drugs that are irritants.

The other, more serious, is called extravasation. Symptoms of a flare reaction include tenderness, warmth, redness along the vein or at the site of the injection and itching. Extravasation may initially have the same signs as a flare reaction, but will worsen to include pain at the site of the injection, blistering and severe skin and tissue damage.

To improve the therapeutic index and to reduce the toxicity of these drugs even at high doses, several strategies – including the use of combination therapy, modification of the cytotoxic molecules, and modification of their physical state or changes in the drug delivery system – have been used.

New passive drug delivery systems, such as liposomal formulations, lipid complexes, lipid emulsions, and colloidal dispersions, have been introduced. However, due to the side effects mentioned above, the development of novel, effective, parenteral drug delivery systems is still of great importance.

DIATOS APPROACHES

Diatos is an international biopharmaceutical company that focuses on researching, developing and commercialising innovative targeted anticancer therapies. Diatos bases its product development efforts on its proprietary Tumor Selective Prodrug (TSP) and Vectocell® technology platforms and on selective in-licensing of high-quality anticancer drugs. Diatos has generated enhanced versions of established cytotoxic drugs with improved biodistribution and tumour specificity and, consequently, widened therapeutic window.

Diatos is using a variety of approaches to reduce toxicity of well-know injectable cytotoxics. These approaches should result in increased tolerance, even at higher dosages. Three examples of the applications being developed by Diatos are described here.

DTS-301 – INTRATUMOURAL INJECTION WITH PACLITAXEL

The anticancer agent Paclitaxel (Taxol®) is active against a number of the most common human cancers. Systemic chemotherapy with agents such as paclitaxel has been shown to prolong patient life as well as reduce spread of cancer to other organs, but side effects can be severe, leading to therapy interruption.

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Paclitaxel is difficult to administer because it is formulated in Cremophor, a solvent that is a blood vessel irritant. It may also cause allergic reactions and may require an intravenous (iv) infusion of up to 24 hours.[1]

Several companies have developed or are developing paclitaxel formulations that do not require such solvents. Diatos is performing clinical research using DTS-301, a unique Cremophor-free polymer depot gel formulation of paclitaxel based on a patent-protected biodegradable polymer known as ReGel ® in-licensed from MacroMed .

The basic requirements for new formulations are that the excipient materials used are acceptable for parenteral application and that the materials used are biodegradable and biocompatible. The materials must be tolerated well and biodegradation must produce innocuous compounds that are either eliminated from the body or incorporated in the intermediary metabolism. ReGel has been shown to fall well within these requirements.

DTS-301 is designed for use as an antineoplastic agent by intratumoural depot injection. By administering DTS-301 intratumourally the toxicity associated with traditional iv paclitaxel therapy should be eliminated or significantly reduced. Additionally, the slow release of paclitaxel from DTS-301, combined with paclitaxel's high protein binding affinity effectively concentrates the drug in the tumour area. [2] Injected DTS-301 degrades over a period of several weeks. As it degrades, the properties of ReGel stabilise paclitaxel allowing controlled release within the tumour.

This innovative formulation should thus fulfil the double objective underlying Diatos' approaches: to lower the toxicity and to increase or maintain efficacy of the drug

Another critical requirement in new formulations is that there is sufficient control of the drug release. It is generally important to maintain the concentration of the drug within the therapeutic window for a time period sufficient to achieve the desired therapeutic effect and to avoid excessive concentrations, which may lead to toxic side effects.

A Phase I dose-escalation study was conducted in 16 patients with 18 superficially accessible solid malignant lesions. Four paclitaxel dosages, from 0.06 mg/cm3 to 0.24 mg/cm^3, based on tumour volume were administered. Blood samples were collected at pre-dose and at different times post-dose. Nine patients had no detectable plasma levels of paclitaxel and four others had <2 ng/mL in 5 of the 153 plasma samples analysed. Of 103 adverse effects reported, 12 mild or moderated adverse effects were considered to be related to the drug. A proportion of these were indeed sensitivity at the injection site, but the benefits of the Cremophor-free formulation, plus the absence of systemic paclitaxel, represent important advantages for DTS-301 in comparison with Taxol®, where the Cremophor formulation can induce severe side-effects.

The conclusions from the Phase I study were that the drug was well tolerated, maintained paclitaxel at the injection site and suggested efficacy.[2] Diatos is currently conducting a Phase IIa trial in Europe, using DTS-301 as a neoadjuvant in breast cancer treatment.

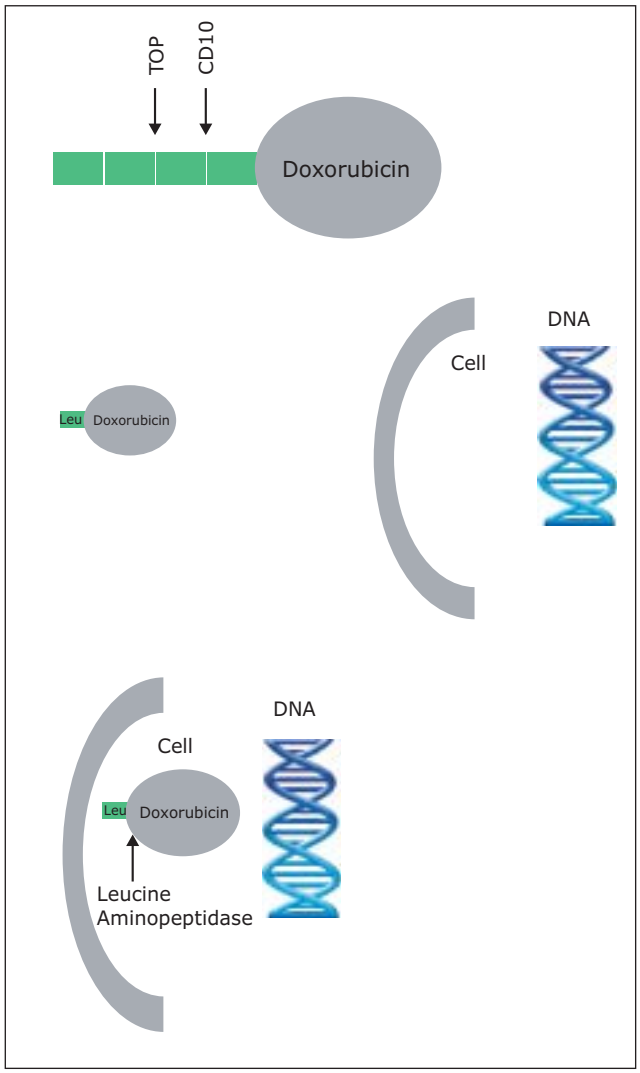

Figure 1: Activation of DTS-201

DTS-201 – A DOXORUBICIN PRODRUG/TSP TECHNOLOGY

The efficacy of doxorubicin is restricted due to its toxic profile. Doxorubicin like other anthracyclines is usually administered intravenously. Extravasational injury (inflammation, ulceraition and necrosis of the tissue around the administration site) have been associated with these agents, all of which can persist in local subcutaneous tissues at the injection site. Likewise, anthracyclines also cause extreme irritation when injected locally, as in superficial bladder cancers.

The prodrug DTS-201, based on Diatos' TSP concept, is unable to enter cells until it is activated into a cell-penetrating entity (L-Dox) in the vicinity of tumour cells (see figure 1). As a result, a low exposure to doxorubicin of normal tissues is observed in animal models[4].

Diatos expects that DTS-201 will improve the local tolerance of doxorubicin, avoid the dose-limiting toxicities of both doxorubicin (cardiomyopathy) and Doxil (cutaneous hand-foot syndrome) and thus allow doxorubicin to be used in a more effective way.

Toxicity studies of DTS-201 in rodents and dogs, where the equivalent doses of doxorubicin injected were significantly higher than doxorubicin at its maximum tolerated dose, did not lead to unusual injection-site adverse reactions, confirming Diatos' expectation that DTS-201 would be less toxic at the injection site as well as to healthy organs.

DTS-201 is being tested by Diatos in a dose-escalating Phase I study in Europe.

ONE MIGHT ASK, IF SOLUBILITY WAS NOT AN PROBLEM, WHICH ONE OF THESE REJECTED NMES WOULD HAVE BEEN THE NEXT BLOCKBUSTER DRUG?

VECTOCELL® – A CREMOPHOR-FREE FORMULATION OF PACLITAXEL

More than 40% of newly discovered drugs have little or no water solubility representing a serious challenge to their successful development and commercialisation. If a new molecular entity (NME) is not available in solution at the site of action, it is not a viable development candidate even if it is highly active. As a result, the development of many exciting NMEs is stopped before their potential is realised or confirmed. One might ask, if solubility was not an problem, which one of these rejected NMEs would have been the next blockbuster drug?

Aqueous solubility can also be an issue for some marketed drugs. More than 90% of drugs approved since 1995 have poor solubility, poor permeability, or both.[1,3] Approximately 16% have less-than-optimal performance specifically because of poor solubility and low bioavailability[3]. A marketed drug with poor water solubility can still show performance limitations, such as poor bioavailability, an unfavourable pharmacokinetics profile and slow onset of action, and it may be necessary to increase the dose of a poorly soluble drug to obtain the efficacy required. Effectiveness can also vary from patient to patient.

Vectocell® is a proprietary product-generating technology that relies on the conjugation of therapeutically active molecules with specific human protein-derived peptides, termed Diatos Peptide Vectors (DPVs). These positively charged, short DPVs can alter biodistribution and pharmacokinetics, are not immunogenic in animal studies, and widen the therapeutic window of drugs conjugated with them. In addition, it has been observed that Vectocell can solubilise certain insoluble compounds. The peptides are chemically conjugated with small molecules and the stability of the linker in plasma can be increased or decreased, according to the particular application.

Diatos has conjugated Vectocell with insoluble anticancer molecules and demonstrated activity of the conjugate in several cancer cell lines. The ability of using Vectocell to solubilise molecules, and alter their pK and biodistribution may be exploited with selected drugs.

CONCLUSION

There are countless examples of the limitations associated with drug injection, which can lead to poor performance of the molecules, severe injection-related side effects, and poor patient compliance. Diatos is using a variety of innovative strategies in cancer to achieve tumour targeting, increase efficacy and to lower drug toxicity and overcome some of the most serious limitations.

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COMPANY PROFILES

Company Description

The Medical House (TMH) has developed a range of devices that enable safe, comfortable and simple self-injection of liquid drugs. Our current portfolio includes re-usable and disposable, needle-based and needle-free injection systems. A number of these devices have been licensed by pharmaceutical companies in order to create and maintain competitive advantage. Our systems are typically designed to accommodate existing drug presentations and formulations, ensuring efficient regulatory approval processes and commercialisation timescales.

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TMH has a growing reputation for providing innovative, cost-effective injection systems that can be brought to market in short timescales creating competitive advantage for any product portfolio. Please contact us to discuss your specific requirements.

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Company Description

Buender Glas GmbH is the world's second-largest manufacturer of prefilled syringe systems, and also supplies the pharmaceutical industry with glass cartridges, specialty vials, ophthalmic dropper bottles and inhalers. The company has invested heavily in the production of presterilized prefilled RTF® syringes, which compare with HypakTM SCF syringes. Our RTF® syringes conform to US, European and Japanese pharmacopoeias.

Buender Glas GmbH is part of the Gerresheimer group, headquartered in Dusseldorf, Germany. Buender Glas, together with Polfa in Poland, comprises the Gerresheimer pharmaSystems division of the group.

Our cross-functional project teams are capable of adapting your product's drug delivery requirements to meet local needs. Through more than 50 years of experience in the market for injectable drugs, which have given it a thorough understanding of market trends for parenteral delivery systems, Buender Glas has built an impeccable reputation as one of the major players in this specialist global industry.

Our plant is highly flexible and able to accommodate special customer demands. In the area of RTF® syringes our latest innovation is a controlled production set-up to customize baked on silicone syringes. We have responded quickly to a rapidly increasing demand for biotechnology drugs. Many of these are best presented in prefilled syringes - but show extreme sensitivity to the sprayed silicone used on conventional devices.

High expertise in the area of plastic molding allows Buender Glas to make concepts, develop and manufacture devices around the area of drug delivery. This applies for injectable drugs, but as well for ophthalmic, nasal and pulmonary drugs.

Buender Glas collaborates with all major machine makers and contract fillers to meet all your requirements in the area of product processing. This statement is valid for all steps throughout the project.

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- Child-resistant, tamper-evident closures
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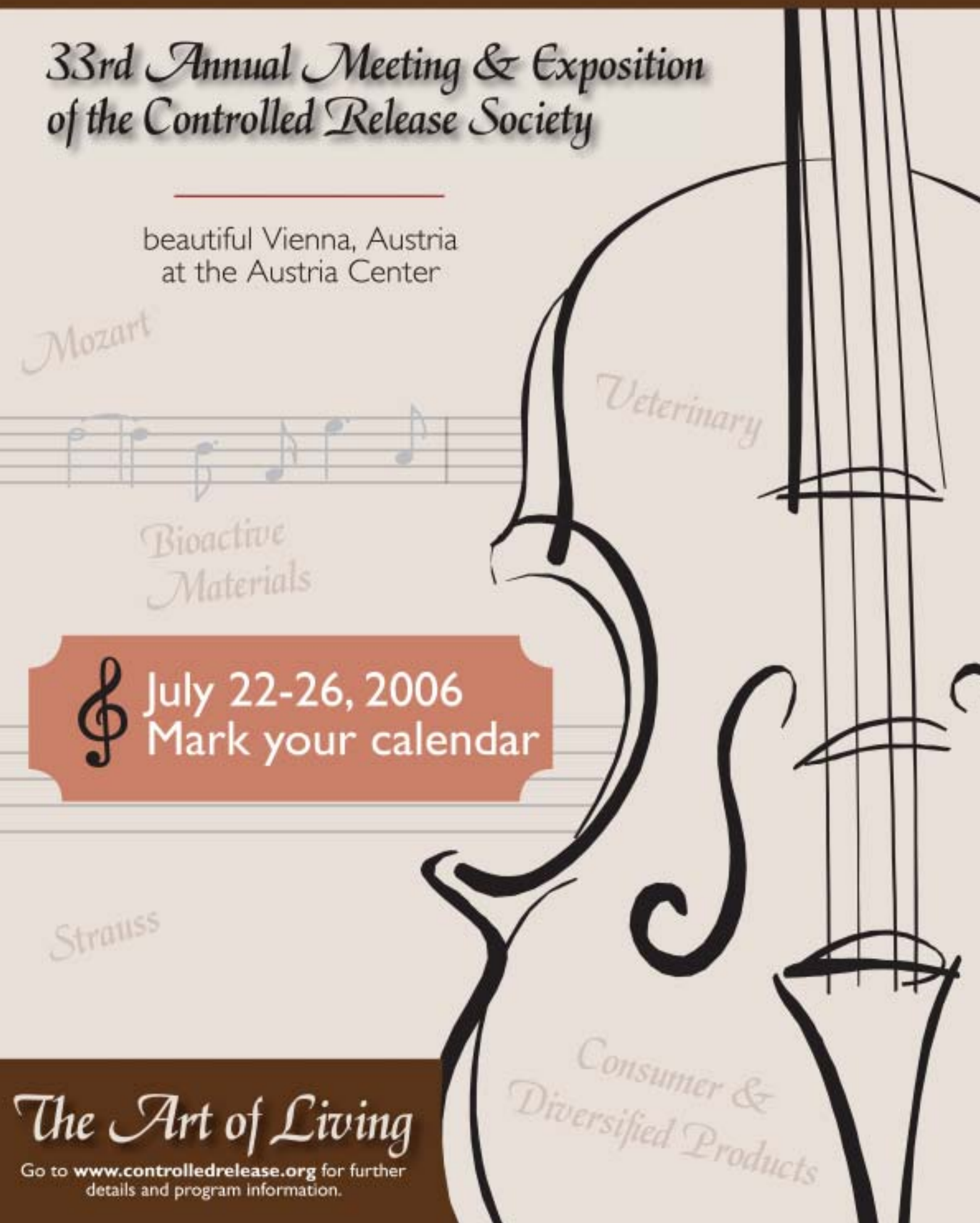

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