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CONTENTS

Introduction: FDA Releases a Draft Guidance on Injection Devices

Dr Michael Gross
Biologics Consulting Group, Inc

4-5

Advanced processes, controls and inspection innovations for prefilled syringes

Dr Andrea Sardella
Stevanato Group S.p.a

8-11

Focusing on the expertise in prefilled syringe components

Stelmi S.A.

12-14

The advantages & challenges of developing a drug product in prefilled syringes

Dr. Gerald Hofer
Fresenius Kabi Product Partnering

16-18

Company profile

Ypsomed AG

21

The Importance of Extractables & Leachables Testing for Injectable Drug Delivery Systems

Fran L. DeGrazio
West Pharmaceutical Services, Inc

22-24

Company profile

The Medical House Plc

25

Equipping a complete syringe line, from filling to palletisation

Mr Pietro Tomasi and Massimo Pannini
Marchesini Group S.p.a.

26-30

synchronized solutions

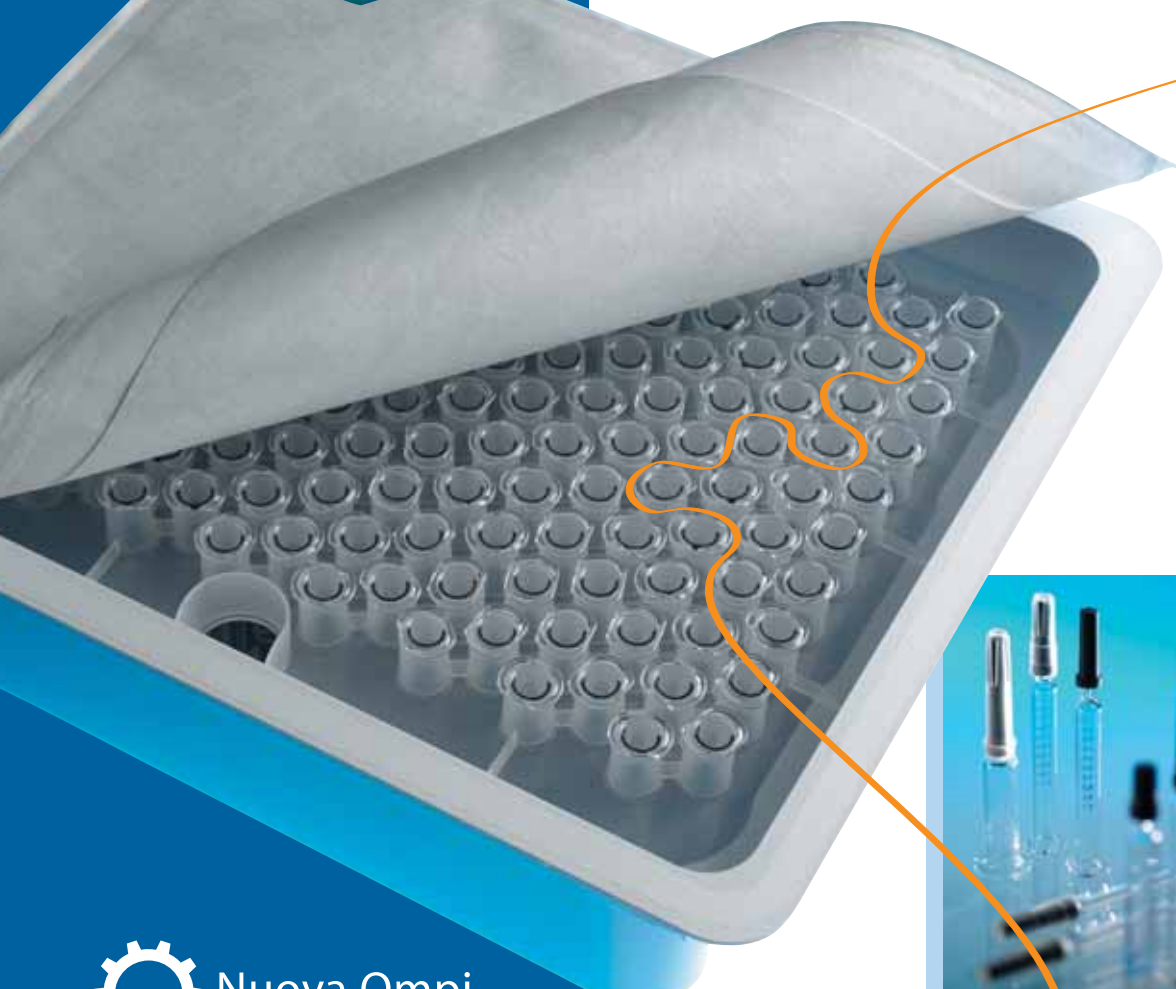


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INTRODUCTION

FDA RELEASES A DRAFT GUIDANCE ON INJECTION DEVICES

The US FDA has announced the availability of a draft guidance that should be of interest to anyone reading this issue of ONdrugDelivery. “*Draft Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products*” was published for comment on April 26, 2009. The comment period closes on July 27, 2009.

The draft guidance describes the FDA’s initial thinking on the development and registration of all unfilled and prefilled, single-use, multi-use, reusable and disposable drug delivery devices that utilise injection technology, including piston syringes. It pertains to injectors that are stand-alone general use medical devices and those that comprise the device constituent parts of a combination product.

Following consideration of public comments, when the FDA finalises the guidance it will then describe FDA’s current thinking on technical development and regulatory considerations for virtually all drug delivery devices intended to deliver drugs and biologics via injection.

“LEFT UNCHALLENGED, THE PHARMACEUTICAL AND MEDICAL DEVICE INDUSTRIES MAY RISK HAVING TO RESPOND TO A BURDENSOME REGULATORY STANDARD FOR THE CONTENT OF INJECTOR APPLICATIONS”

Many points in the document merit review and comment. Interested parties should carefully read the draft guidance document and provide their perspectives to the FDA. The following is intended to point the reader to parts of the draft guidance that may have important ramifications for injector marketing applications.

Typically, general-use injection devices intended for the delivery of a variety of drugs and biologics, are cleared for marketing by FDA through the 510(k) pre-market notification process. On the other hand, an injection device intended to deliver a specific drug or biological product is regulated by the FDA as a combination product and these typically gain marketing approval through an NDA or a BLA.

The pre-market notification process and the pre-market approval process are different; the

applications are different and their information requirements are different. At the core of the pre-market notification process for a general-use injection device is the substantiation of a claim of *substantial equivalence* to a previously marketed injection device. At the core of the pre-market approval process for an injection device that is part of a combination product is the quality of the product and substantiation of a claim of its safety and effectiveness.

While the draft guidance aims to describe the least burdensome approach to addressing relevant technical and scientific development considerations for injectors, it includes a comprehensive list of technical information that might be included in an application.

The FDA has reviewed numerous pre-market notification and pre-market approval applications for injection devices. The list is useful for identifying all of the technical and scientific issues that should be considered during the development and registration of an injection device. However, the purpose of a guidance document for industry and FDA staff should be to reduce regulatory uncertainty.

Listing in the guidance all possible information that might be included in a marketing application for an injector may not fulfil this purpose. A comprehensive list could become a standard for FDA reviewers. For example, the draft guidance suggests that it may be useful to include information in NDAs and BLAs which compares and contrasts similarities and differences between the subject injector and previously marketed injectors. These comparison tables are common to medical device pre-market notification applications. The FDA notes that when this information is included in an NDA or BLA, it would not be used to establish substantial equivalence. Yet, how this information would be used in the review of an NDA or BLA is not specified.

For an application for an injector that is a combination product the draft guidance suggests that a single marketing application covering both the injector and the pharmaceutical constituents should be sufficient unless FDA determines that more than one application is needed. But, the number of applications submitted to support the marketing a combination product in general is not established in FDA regulations or guidance.



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An informal concept paper on this topic was issued several years ago. How marketing applications are structured could impact how manufacturing and design changes are reported and how safety reports are filed with FDA. Providing specific guidance for an injector-drug or injector-biologic combination product should be delayed until the pharmaceutical and medical device industries have had the opportunity to review and comment on a draft guidance or a proposed regulation on general principals for combination product applications.

It seems reasonable that the draft guidance would apply to prefilled syringes since these container-closure systems are injectors themselves or may be components of injectors. Since prefilled syringes and prefillable syringe components are or form piston syringes it follows that the draft guidance should apply to piston syringes. But since the draft guidance also pertains to unfilled injectors, the draft guidance may also apply to disposable syringes. FDA Guidance on the content of pre-market notification applications for piston syringes already exists. Whether or not additional guidance is needed needs to be considered.

The spectacular growth of the injection device market is being fueled by the growth of the market for biotech-derived drugs and biologics. Whereas once they were merely a convenience that was

nice to have, injectors are now an essential tool in product differentiation and marketing.

Today, most biotech-derived therapeutics are being developed in a variety of injector presentations. Once finalised, the FDA's injector guidance will be a key regulatory reference on the content of applications that support the marketing of these devices. Left unchallenged, the pharmaceutical and medical device industries may risk having to respond to a burdensome regulatory standard for the content of injector applications.

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Responses to the Draft Guidance and submitted in writing to:

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Food and Drug Administration
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Rockville, MD 20852
United States

Alternatively, responses can be submitted electronically via <http://www.regulations.gov>.

ABOUT THE AUTHOR

Michael Gross, PhD, RAC, is an industry consultant specialising in quality, regulatory and technical issues for combination products. Over his 30-year career, he has worked for the US FDA, as well as for pharmaceutical and biological product manufacturers and medical device companies. He has spent more than 20 years working on combination

product problems. Dr Gross recently joined the Biologics Consulting Group as a Senior Consultant.



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It is the goal of the conference to give an update of the relevant aspects of pre-filled syringes and parenteral injections in general. It will cover technical issues from the development to manufacturing, quality and engineering, supplier issues, regulatory topics and inspections, handling and use of devices. As always a focus is given to practical information and case studies. We invite you to send an abstract for a presentation or a poster to Graeper@pda.org. The conference will have on October 26 a pre-conference workshop together with "The International Commission on Glass" on "Glass containers for Pharmaceuticals".

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ADVANCED PROCESSES, CONTROLS AND INSPECTION INNOVATIONS FOR PREFILLED SYRINGES

The US FDA mainly regulates prefilled syringes under pharma product regulations, and in the EU they are considered to be pharmaceutical components. As such, the glass supplier becomes the starting point in the pharma customer production chain. Glass container suppliers thus share responsibility for the drug integrity and efficacy with the pharma company. As Dr Andrea Sardella, R&D Manager at S.P.A.M.I. explains, this has put great pressure on glass converters for providing a well controlled production process with the same quality level as in the remaining part of the pharmaceutical chain.

The Stevanato Group sterile syringes production facility – EZ-Fill™ – started with an in-depth risk analysis of the glass converting and sterilisation process and ended with the implementation of several new controls and the redesign of some line components.

TUBE PROCESSING

When comparing the average specifications of glass tubing suppliers with the requirements of the pharmaceutical market it may be seen that the starting quality of glass tubing can be insufficient (see Table 1).

Glass tubing particles are a relevant source of contamination for the final glass containers,

Composition (w %)	Borosilicate Glass Type I
SiO ₂	72.0-75.0
B ₂ O ₃	10.0-11.5
Al ₂ O ₃	5.0-7.0
Na ₂ O-K ₂ O	7.0-8.5
MgO-CaO-BaO	0.5-3.0
Working point	1260 °C
Transformation Temp.	525 °C
Thermal Expansion Coeff. (α*10 ⁻⁶)	5.0

Table 2. Chemical composition of type I borosilicate glass

MAJOR CRITICAL DEFECTS:	Glass tubing supplier		Current Japan Quality Requirements	
	Defect definition	AQL	Defect definition	AQL
Cracks	-	0.025	-	0.01
Fissures	>2mm	0.65	-	0.1
Stones / knots	>0.5 to 0.8 mm	2.5	> 1 mm	1.0
	>0.5 to 0.8 mm and more than 10 pieces	1.0	> 1 mm	1.0
Glass particles	> 0.2 to 25mm (9 max)	0.65	> 0.3mm	0.4
	>0.5mm (1 max)	0.65		
Scratches	Longitudinal: Width>0.2 mm and length >30 mm	1.0	Length > 5mm	1.0
	Radial: wider more than 0.1mm for half of the circumference	1.0	Width > 1mm	1.0
Airlines	> 400mm	0.4	> 1 mm	0.25
	Aggregate >15mm length and width > 0.01mm	0.4		
	Width > 0.1 mm	0.4		
Surface impurities	Outer surface > 2mm	0.1	Not removable > 0.1 mm ²	0.01
	Inner surface > 0.5mm	0.1	Not removable > 0.1 mm ²	0.01

Table 1: Comparison between glass tubing supplier specifications and Japanese pharmaceutical market requirements.



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Figure 1: Syringe Machine GS36-15.

therefore a pre-processing automatic station to remove them is required together with a special loading tray system for automating the tubing insertion into the forming machine.

A precise and reliable system for the full evaluation of the tubing glass by measuring outer diameter, inner diameter, defects and paneling all along each tube is also required in order to reject “out-of-specs” tubing before the converting phase.

FORMING MACHINE AND CLOSED-LOOP CONTROLS

The forming machine is the core business of Stevanato Group’s Engineering division, Spami, and the GS36-15 is the state of the art among our glass forming machines with its high productivity and high precision (see Figure 1).

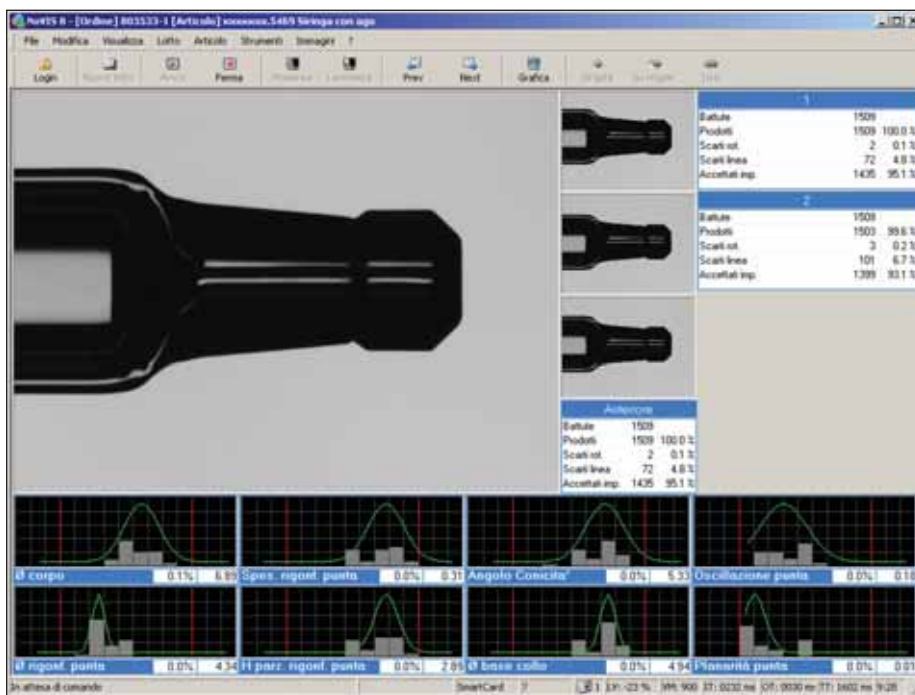


Figure 2: Novis Camera System output

All process variables are controlled and the forming tools are regulated in a closed loop between the dimensional vision system and the multi-axis electronic tool actuators for producing using the tightest possible dimensional tolerances. Figure 2 provides an example of output from the Novis camera system.

Gas flow and burner regulations are programmed and controlled by optical pyrometers in order to guarantee the most accurate control of glass converting temperature in the different machine sections.

By redesigning the cutting device we obtained a relevant reduction of particle production during tube segmentation improving the consistency of the product’s final cosmetic quality.

A very recent upgrade, driven by the ever increasing request for the best chemical

neutrality of the primary packaging for the biotech market, has been the development of new tools for funnel forming. Combined with a lower forming temperature it provides the lowest available content of Tungsten. A thermal image of optimised funnel forming is shown in Figure 3.

AMMONIUM SULPHATE TREATMENT, COATING AND ANNEALING CONTROL

The chemical composition of a typical Type I borosilicate glass presents a percentage of about 7% Na_2O , necessary to reduce the glass melting point (see Table 2 on page 8). The heat-forming process facilitates the migration of Na_2O from the glass bulk to the surface potentially altering the hydrolytic losses of

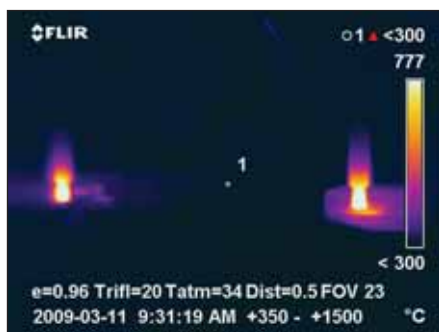


Figure 3: Thermal image of optimised funnel forming

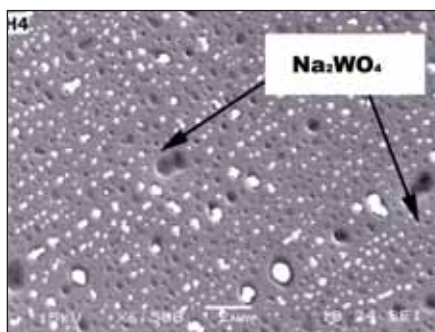


Figure 4: Scanning Electron Microscope (SEM) image of visible Na_2SO_4 on syringe surface, Na_2SO_4 contamination fill micro-cavities on the glass ranging from 1 to $5\mu\text{m}$ in diameter



Figure 5: SEM image of flakes formed by delamination

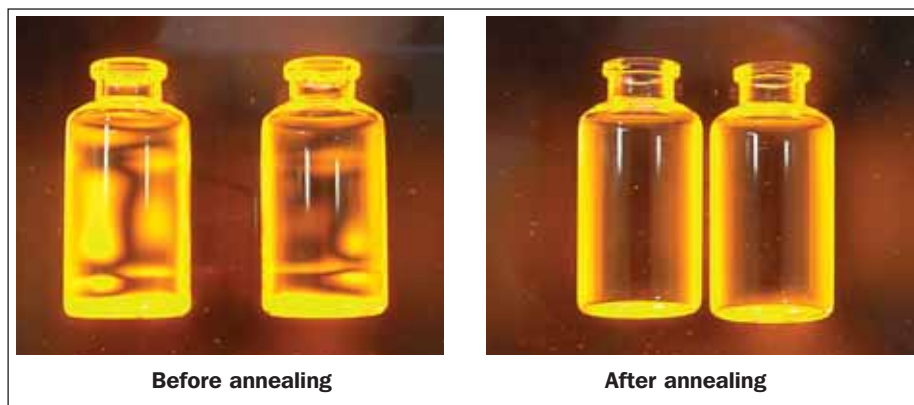


Figure 6: Effects detection due to annealing phase

the container. The interaction of ammonium sulphate ($(\text{NH}_4)_2\text{SO}_4$) with Na_2O at high temperatures gives rise to easily washable sodium sulphate (Na_2SO_4) a SEM image of which is provided in Figure 4.

The de-alkalized layer is highly beneficial to the hydrolytic resistance but if its thickness is $>1\mu\text{m}$, a delaminating effect may occur with the formation of tiny particles or flakes (Figure 5).

Consequently the accuracy of the sulphurisation system and the control of the temperature and concentration of the ammonium sulphate solution are critical.

To reduce even more the alkali release several SiO_2 coating processes can be used on the internal surface of the container.

After annealing, glass containers are inspected for residual stress presence in order to guarantee the best mechanical/thermal resistance (see Figure 6). This is particularly important in freeze-drying processes.

LEACHABLE AND EXTRACTABLE ANALYSIS

Every batch is tested, in accordance with the sampling plan, for the quality of the inner surface of finished containers by using an alkali release test




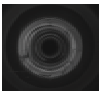

BODY	CONE	SHOULDER	TIP	FLANGE
Contamination	Contamination	Contamination	Micro-cracks	Contamination
Air lines	Stains, dirt on the neck	Deformation		Breakages
Scratches	Folds and incision	Incisions		Deformation
Cracks	Chipped glass	Circular crack		Chipped glass
Glass fragments	Cracks on the cone	Tail heel		Cracks
Printing control	Cracks on the base of the cone			
Stains of color	Glass threads			
Dimensional	Dimensional	Dimensional	Dimensional	Dimensional
				

Table 3: Classification of critical cosmetic defects

following ISO International Standards and as recognized by the EU pharmacopeia surface test. A titration method measures the pH of combined extract solutions from several containers and AAS analysis measures the alkalinity of individual containers.

DIMENSIONAL AND COSMETIC INSPECTION

The dimensional and cosmetic inspections in the ISO 8 Clean Room are the final controls of the glass containers. Dedicated equipment with a double turret for inspecting the whole container without mechanical interference of the handling system is used (see Figure 7).

As shown in Table 3, the Critical cosmetic parameters are classified as per the PDA Lexicon defect classification manual while the dimensional measurements verify URS of the pharmaceutical customer.

An extended number of parameters, other than those required by international standards, are currently used. The system has built-in redundancy since more than one camera covers the same area, and syringes must pass inspection to continue.

For selected critical cosmetic defects, a Japanese quality standard of 0.04 AQL is used, which is more stringent than international standards.

On request, optional controls can be added by using customer inspection algorithm in order to match the results of the customer inspection machines and reduce false rejects in its production lines.

NEEDLE ASSEMBLY CONTROL

The needle assembly phase is critical and requires precise mechanical

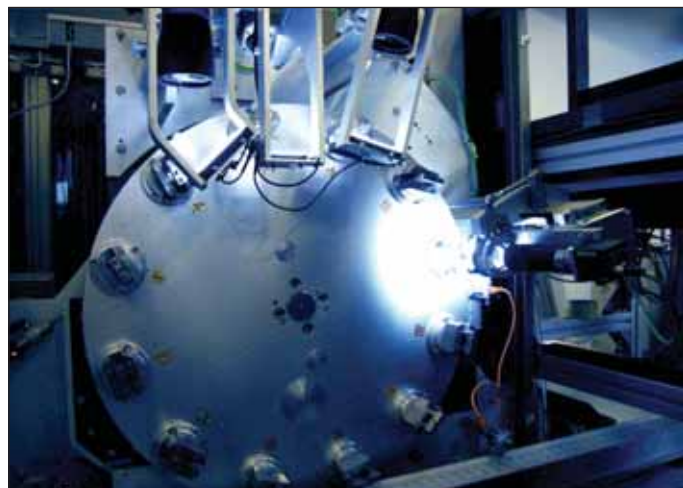
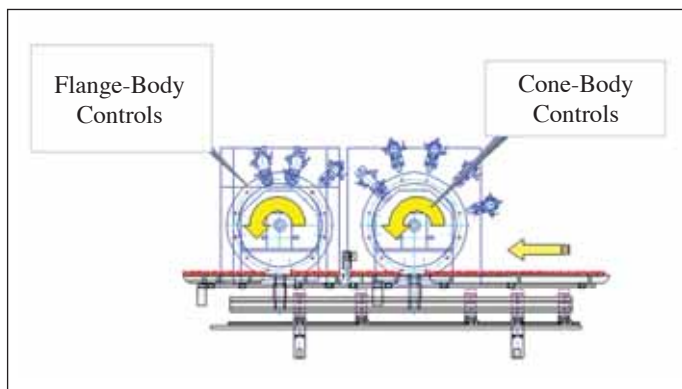


Figure 7: Double-turret equipment general scheme (left) and frontal photograph (right)

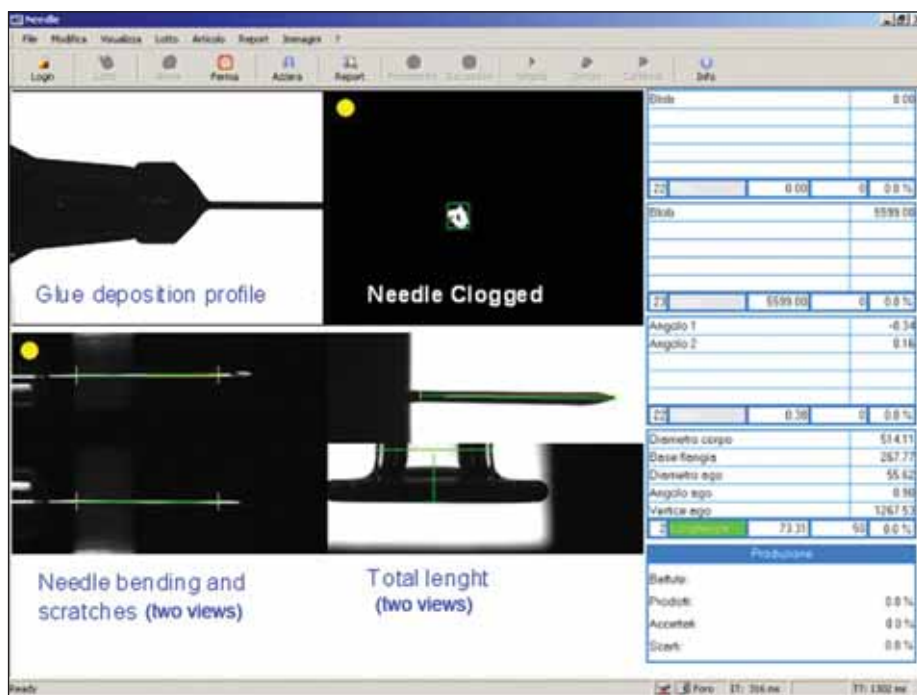


Figure 8: Polymerisation evolution in time measured by Near Infra-Red (NIR)

handling, exact glue dosing, curing-light control and gentle handling of the needle's micro-tube.

Spami has developed a dedicated machine for this assembly operation, integrating the most sophisticated assembly and inspecting technologies.

Glue distribution, and needle position and integrity, are controlled using vision systems and special optical layout directly on the assembly machine to give fast feedback to the system in case of anomalies (Figure 8).

Blowing tests and "pull-off" tests are also integrated for verifying needle functionality and mechanical resistance (Figure 9). The "pull-off" test is not well accepted by customers (even if required by regulations) because of the potential risk of damaging the needle during the operation. For this reason alternative methods such as optical can be used to measure glue polymerisation; in particular

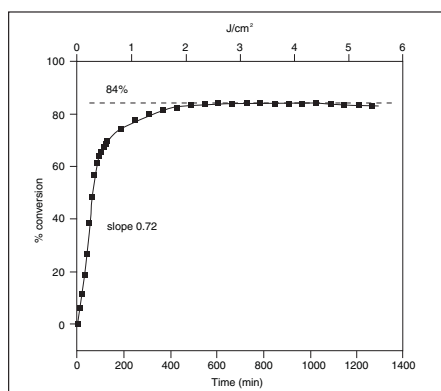


Figure 9: "Pull-off" test results graph

on the inner surface of the cone which could come in contact with drug.

WFI WASHING, SILICONISATION, SHIELD ASSEMBLY AND NESTING

After needle assembly, the syringes are transferred in an ISO 7 clean room with an ISO 5 washing and siliconising machine integrated with a nester. For the sterile line, the equipment from a company with a good reputation in sterile machinery is used.

The line is equipped with an optical system for sprayed silicone distribution control and pressure control for blocked needle and needle shield integrity control.

Presence and pop-off of shield is checked with an optical laser system. Presence of glass fragments during unloading is detected with an optical barrier.

At the out-feed a Bausch & Stroebel nester collects the syringes and a vision system verifies the presence and the integrity of the syringes before sealing the tub.

Finally, the sealed tubs are sent for EtO sterilization.

CONCLUSIONS

Requests for ever increasing quality pose new challenges to the processing and control of sterile containers. The synergy between the glass converting division and the engineering division is an important advantage in meeting these challenges.

ABOUT STEVANATO GROUP

S.P.A.M.I. and Optrel comprise the Engineering Division of the Stevanato Group, which is among leading suppliers of glass primary packaging for the global pharmaceutical industry.

The Engineering Division is strongly linked with the Glass Division, consisting of Nuova Ompi, Alfamatic, Medical Glass and Ompi of America. These companies specialise in the design, manufacture, installation and after-sales support of high-speed precision machinery for the production and control of glass containers as well as vision inspection systems.

S.P.A.M.I. is the technological leader in the design and production of machinery for glass tubing converting for the production of vials, cartridges, syringes, ampoules and special devices.

Optrel has a long tradition in the inspection machine market for the pharmaceutical industry including parenteral drug, injectable and solid dosage inspection with automatic and semiautomatic equipment.

Following its acquisition by the Stevanato Group, Optrel has developed, based on the same field-proven technology, a range of inspection machines for empty glass articles: ampoules, vials and syringes. The range of defects covered matches the requirement from the PDA glass task force and comprise also metrological controls recorded in a SCADA-like interface for production control. The system is 21CFR11 compliant relating to recipes and batch recording.

Stevanato Group produces a full range of glass packaging including important traditional products such as vials and ampoules and also strong growth products such as cartridges for pen-injection systems and auto-injectors as well as prefillable syringes. Syringes are available in both bulk (stake needle & luer finish) as well as from the EZ-fill™ line.

EZ-fill™ offers clients an important new source for reliable, flexible supply of prefillable syringes packaged in convenient nested tub formats (washed, siliconized, sterile).



FOCUSING ON THE EXPERTISE IN PREFILLED SYRINGE COMPONENTS

Since 1964, Stelmi has been dedicated to the research and development of elastomeric rubber components of unsurpassed quality and cleanliness for the pharmaceutical industry. In this short article, the company provides a brief rundown of its current product offerings in the area of prefilled syringes.

Stelmi manufactures prefilled syringe components (plungers, flexible and rigid needle shields, tip caps) (see figure 1) and stoppers for infusion, antibiotic, lyophilization, and diagnostic use that are compliant with all pharmacopoeias.

Over many years, Stelmi has developed a high level of expertise in the field of elastomeric components for prefilled syringes, constantly innovating in every aspect of this area, notably offering:

- innovative designs
- formulations with a very low level of extractables
- increased cleanliness
- ready-to-use sterile components

PLUNGERS

High purity formulation: Ultrapure 6901 for improved contact conditions

The aim in developing formulation Ultrapure 6901 was to reduce interaction between the organic and ionic substances from the stopper and the medication, leading to a better container-drug compatibility.

The syringe plunger is in prolonged contact with the drug product and requires a



Figure 1: A selection of Stelmi's tip-cap, needle-shield and plunger products

solutions, and allow an excellent compatibility with water for injection and sensitive products such as biotech drugs.

Sterile plungers

Since the end of 2003, Stelmi has been offering guaranteed sterile plungers, greatly simplifying use for its clients. The sterile plungers are

delivered in double polyethylene bags or containers for isolators, limiting the risks of possible contamination to handling during the transfer of components to a sterile area. Stelmi is in charge of the indispensable validation and re-validation and has developed

a process and the appropriate documentation, including the registry in a Type V Drug Master File (DMF) with the US FDA, to provide the highest degree of quality assurance.

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formulation with a low level of extractables. The excellent properties demonstrated by formulation Ultrapure 6901 allow it to be suitable for long-term contact with aqueous

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RIGID AND SOFT NEEDLE SHIELDS

Formulation 4800GS developed by Stelmi for soft and rigid needle shields is the standard for needle shields on the market.

Stelmi's Rigid Needle Shield: the successful concept with the anti pop-off patented design

Developed at the end of the 1990s, the rigid needle shield is the mechanical assembly of a soft needle shield in a polypropylene cover, combining the sealing properties of rubber with the rigidity of polypropylene.

It has advantages from the production process by improving the machinability and reducing the sterilisation time by a substantial permeability of formulation 4800GS and by reducing the risk of pop-off.

An article describing Stelmi's Rigid Needle Shield in detail was published by ONdrugDelivery in the 2008 issue, "Prefilled Syringes: the container of choice for today's injectables".

A full-text pdf of the article can be viewed (free of charge) via the following link:

www.ondrugdelivery.com/publications/Stelmi_Rigid_Needle_Shield_Article_2008.pdf

TPE-based formulation: a new option for the rigid needle shield

The rigid needle shield has originally been developed with synthetic thermoset rubber as the soft part of the rigid needle shield. Another option of Stelmi rigid needle shield is also available in a new formulation made of ThermoPlastic Elastomer (TPE).

TIP CAPS

Formulation 6580GS for tip caps: all the properties required for tip-caps combined in one formulation

Apart from the functional properties such as adapted pull-off forces, good resistance to aging or good machinability on assembly line, two major elements have been considered when developing a formulation for tip caps: good chemical inertness and high permeability to steam and ethylene oxide.

Thus, Stelmi has developed formulation 6580GS to meet the specific required properties of tip-caps as 6580GS combines the optimised permeability of polyisoprene with the good chemical properties of butyl.

UltraClean 6 evolution, the highest particulate and microbiological cleanliness

The cleanliness of elastomeric components is particularly important for prefilled syringe components and especially plungers. All of Stelmi's prefilled syringe components are washed with UltraClean 6 evolution, providing the highest particulate and microbiological cleanliness.

In accordance with FDA regulation, UltraClean 6 evolution finishing is a validated washing process which is carried out entirely in a controlled atmosphere. The registration of the UltraClean 6 evolution washing process in a single Type V DMF for all production sites ensures the rigorous application of Good Manufacturing Practices (GMPs), offers the additional safety assurance of a multiple source supplier, and meets the strictest requirements of pharmaceutical laboratories.

Stelmi continues to invest heavily in increasing its production capacity, especially for prefilled syringe components. Its products are present in the global marketplace and customers grant Stelmi their trust in more than 70 countries, from national pharmaceutical laboratories to the largest global pharmaceutical groups.

*Stelmi is a registered trademark of Stelmi S.A. in various countries.
Stelmi's rigid needle shield is a registered patented design.*



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Product Partnering

THE ADVANTAGES & CHALLENGES OF DEVELOPING A DRUG PRODUCT IN PREFILLED SYRINGES

The rapid and continuing rate of growth of the prefilled syringes industry has exceeded the initial expectations of those who were involved in this sector in its early years. In this article, Dr Gerald Hofer, Senior Director of Global Manufacturing at Fresenius Kabi Product Partnering, outlines the advantages of prefilled syringes that drive this growth, and balances them with an examination of the challenges that companies wishing to benefit from employing prefilled syringes will likely have to face. Dr Hofer describes how Fresenius Kabi's Product Partnering division is well placed to help its partners overcome the challenges and thus realise the benefits that this product presentation and delivery method can bring.

The parenteral route of drug application has significantly gained in importance over the years. A great number of newly developed drugs, in particular the many new biological molecules such as proteins, pushed this trend as they almost always require application by injection or infusion. New, highly potent drugs have increased the pressure on the pharmaceuti-

cal industry to provide safe and efficient delivery systems. One container form that enables parenteral application either through injection or infusion and combines easy administration with safety for the patient as well as the healthcare professional is the prefilled syringe.

past. For many years the prefilled syringes application system was only chosen for specialty drugs – today the syringe market shows annual growth rates of up to 25% and there is no sign that this development may slow down over the next years. Syringes are now available in many different sizes and a variety of materials, making them an option for a great range of products – liquid and even lyophilized – in various stages of their life cycle.

**"SOURCING PREFILLED SYRINGES
MEANS NOT ONLY PURCHASING AN
EMPTY SYRINGE; PREFILLED SYRINGES
INCLUDE A VARIETY OF COMPONENTS
SUCH AS STOPPERS, PLUNGER RODS,
TIP CAPS, AND NEEDLE SHIELDS"**

cal industry to provide safe and efficient delivery systems. One container form that enables parenteral application either through injection or infusion and combines easy administration with safety for the patient as well as the healthcare professional is the prefilled syringe.

THE RISE OF THE PREFILLED SYRINGE

Prefilled syringes are not a recent development but have actually been in use since World War II. The growth the prefilled syringe market has undergone in recent years, however, is tremendous and unparalleled by anything the sector has seen in the

THE ADVANTAGES

Undeniably, the great popularity of prefilled syringes today has its roots in some essential advantages this container type has over more traditional ones such as vials and ampoules (figure 1). The convenience and safety of

the prefilled syringe makes it the preferred choice of healthcare professionals and in the end for the patients themselves. A great number of risky needle-stick injuries can be prevented as prefilled syringes simplify the application of injectables. The time-consuming procedure of transferring the drug product from its original container to a syringe is completely avoided. In emergency situations this can save lives.

Avoiding the transfer of the drug product means also that it can be more accurately dosed in the original container. This means no overfill is required and the valuable drug substance is not wasted – an important factor in times of



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continuously increasing cost pressure in the public healthcare sector.

Prefilled syringes come ready to use, which guarantees sterility, and labeled, which prevents misidentification and mix-ups which are particularly dangerous when highly potent drugs are in play.

A variety of safety devices can be used in combination with prefilled syringes to make them even safer and minimise the risk of the needle coming into contact with medical personnel. A lot of development is going on in this field accounting for a product range from quite simple solutions to highly sophisticated devices. Safety devices are currently only mandatory in the US, but also in Europe it is becoming more commonplace to include them in prefilled syringe products.

This improvement in the safety of handling prefilled syringe systems, makes them a viable option for home-use products and self administration. This trend is strongly supported by the increasing availability of self-administration devices such as auto-injectors and pens for use in combination with prefilled syringes.

From a marketing point of view, the use of the prefilled syringe as a container allows pharmaceutical and biotechnology companies to differentiate their drug products from the competi-

tion, opening up new opportunities for lifecycle management, not only for newly developed drugs but also for well established products.

During the last few years, innovations in plastic syringes have considerably broadened the possibilities for prefilled syringe products. The use of the previously predominant glass syringes is limited to small volumes of up to 20 ml. Also many highly sensitive drug products are not compatible with glass. Plastic syringes made of COC (cyclic-olefine-copolymer) or COP (cyclic-olefine-polymer) have the advantage that they are as clear as glass and can be used in larger sizes. They are starting to become commercially available from most of the established suppliers in sizes up to 50ml.

THE CHALLENGES

The advantages of prefilled syringes seem overwhelming; nevertheless there are also some drawbacks to be taken into consideration when assessing prefilled syringes. For one, prefilled syringes are complex medical devices and as such they are more expensive than simpler container forms. It has to be carefully evaluated whether the higher cost of the container can be compensated by the advantages such as the reduction of waste and product differentiation.



Figure 1. Prefilled syringes (left) have manifold advantages over traditional vials (right)

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An issue weightier even than the cost is the strained supply situation. There are only few well established suppliers in the market and due to the current big demand, prefilled syringes are not easily available. Extremely long lead times may have to be taken into account. Sourcing prefilled syringes means not only purchasing an empty syringe; prefilled syringes include a variety of components such as stoppers, plunger rods, tip caps, and needle shields. It is essential to be aware that these components are not equally available

"A PREFILLED SYRINGE IS USUALLY A VERY ATTRACTIVE OPTION. AT THE SAME TIME IT IS A FACT THAT HIGHLY SPECIALISED KNOW-HOW IS NECESSARY FOR THE SUCCESSFUL IMPLEMENTATION OF SUCH A DEVELOPMENT PROJECT"

for all materials and the complete range of sizes. Despite the fact that recent developments in plastic materials have increased the volume range of available syringes significantly, the filling volumes of commercially available empty prefilled syringes are still restricted to a maximum of 50 ml (starting at 0.5 ml).

The strained supply situation is particularly problematic if a prefilled syringe product is still in the development stage and the different containers available are under evaluation. In these cases small quantities are required to produce small-scale trials to test and compare different options without knowing the outcome of such studies. For this purpose a strong relationship to all potential suppliers is an advantage not to be underestimated.

For pharmaceutical manufacturers to implement prefilled syringe technology new equipment is required. At first sight prefilled syringes may appear to be fairly similar to the conventional vial with glass container and plastic stopper, but the prefilled syringe being the primary packaging material adds a lot of complexity to the manufacturing processes and the testing of drug products. Not all stopper materials avail-

able for vials are also available for syringes. Prefilled syringes are not only sealed by a stopper but have a second opening closed either by a needle plus needle-shield or a tip-cap. Both the needle-shield and the tip-cap may be made from a material different to that of the stopper.

Testing material compatibility and leachables/extractables studies are far more complex and, with the needle, might even include a metallic component in addition to a variety of plastics and rubbers. Material compatibility may become a huge problem and mean a no-go for your prefilled syringes project. Incompatibilities have, for example, been reported for proteins and residues of Tungsten, the material used for fusing needle and glass. Also the compatibility of the drug product with the silicone layer that is usually used to maintain break-loose and gliding forces may become an issue.

The good news is that the huge demand of prefilled syringes has pushed the rate of development in recent years, also changing some mechanical parameters. Now different technologies for siliconisation are available and the first syringes without any silicone at all are appearing on the market.

Nevertheless, the material compatibility as well as the functionality of the prefilled syringes has to be verified in addition to the stability of the drug product itself throughout the whole shelf life. The functionality concerns in particular the break-loose force and gliding force parameters; tests for which special equipment and know-how is necessary.

Related to the additional testing required for stability studies are the general regulatory requirements. If a drug is newly developed the situation is quite clear: the prefilled syringe is the primary packaging material and all the relevant data has to be supplied as in the case of a vial, with the additional emphasis also on the syringe functionality.

The situation is different if a variation from a vial to a syringe is planned in order to custom-

ise the product or to introduce the innovative container for lifecycle management reasons. In this case the requirements are different for Europe and the US. While in Europe it is recommended to contact the EMEA early on to clarify whether a supplement to the existing dossier is sufficient, the requirements in the US are clearly defined and differ from NDA to ANDA. In the case of an NDA it is possible to file a supplement for the change in container; in the case of an ANDA a new ANDA has to be submitted.

THE SERVICE OF FRESenius KABI PRODUCT PARTNERING

Essentially, for parenteral products, the development of a drug in a prefilled syringe is usually a very attractive option. At the same time it is a fact that highly specialised know-how is necessary for the successful implementation of such a development project.

For the pharmaceutical industry specialised in drug development it therefore makes sense to work with a partner who has the required know-how and to choose a contract development/contract manufacturing approach.

Through its Product Partnering division, Fresenius Kabi is able to provide this service, having built up the required expertise in the course of the implementation of the prefilled syringes technology for its own portfolio.

Recently, the Fresenius Kabi facility in Graz, Austria, has been working with well established partners to set up a syringe-filling line laid out aseptically to process plastic and glass syringes with filling quantities ranging from 0.1 to 50ml.

At Fresenius Kabi, the prefilled syringes technology teams up with long-standing experience in aseptic filling, preparation of complex aqueous solutions and fat emulsions, in oxygen control and purification technologies such as ultrafiltration and distillation.

The prefilled syringe technology complements a wide range of capabilities that may be of interest for your prefilled syringes development project. Fresenius Kabi Product Partnering may well be your solution to tackle the challenges faced in the world of prefilled syringes.



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THE IMPORTANCE OF EXTRACTABLES & LEACHABLES TESTING FOR INJECTABLE DRUG DELIVERY SYSTEMS

Judging the correct approach to addressing extractables and leachables testing in the development of prefilled syringe products can prove to be a challenge, and getting it wrong can cause major set-backs in product commercialisation when it comes to the regulatory process. Here, Fran DeGrazio, Vice-President of Marketing and Strategic Business Development at West gives examples of how and why confusion can arise, and suggests strategies for making sure the right decisions are made.

Suppliers of pharmaceutical packaging components and delivery devices have been working closely with the industry in an effort to provide solutions for mitigating the risk associated with extractables and leachables. This effort includes managing both the technical and regulatory aspects of the subject. The following example illustrates the challenges faced by the industry.

A company that produces and fills an injectable drug product wanted to move from a glass vial with a bromobutyl stopper to a prefilled syringe delivery system. With a prefilled syringe system, there is direct contact between the elastomeric plunger and the drug product in the syringe system. The same bromobutyl elastomer used for the vial stopper was also used for the syringe plunger.

"THE MAJOR DRIVER FOR CONDUCTING EXTRACTABLES/LEACHABLES TESTING IS DUE DILIGENCE IN ASSURING APPROPRIATE SUITABILITY FOR INTENDED USE OF THE PACKAGING COMPONENTS OR DELIVERY DEVICES"

A major extractable ingredient in the elastomeric formulation was zinc ions from zinc oxide, which was used as part of the cure system. The drug company completed stability studies of the prefilled syringe format and supplemented their work with leachable testing for Zn⁺. However, the US FDA rejected their appli-

cation because it lacked sufficient extractables and leachables testing.

The drug company had assumed that since the elastomeric formulation was the same for both the vial stopper and the syringe plunger, the limited leachables work they had completed would be acceptable. As they found out, this was not the case.

The Chemistry, Manufacturing and Controls (CMC) reviewers at the FDA are asking for similar information from other companies as a part of their drug applications. Initially these requests were inconsistent. The topic of extractables and leachables had been initiated with inhalation and nasal drug dosage forms, and so those CMC reviewers more familiar with these types of drug products began to bridge these requests into injectable drugs. These same reviewers were also responsible for the initial internal education of the FDA on this issue.

Since there was no written guidance on this subject, the industry was confused about a path forward. One point of confusion was the belief that compendial testing was an acceptable way to address the extractables issue.

The US Pharmacopeia (USP) is the major compendium of standard testing requirements for the pharmaceutical industry in the US. USP Section 381 defines physicochemical testing associated with elastomeric closures used for injectable drug products. Although



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this compendium is currently going through a major update that will bring it much closer in requirements to the European Pharmacopeia, the test series that has been in place does not even have specifications defined for the physicochemical series. Additionally, the series of tests are antiquated, wet-chemical methods that are nothing more than a gross type of chemical testing. This testing bears no relationship to true extractables testing.

From an industry standpoint, one major hurdle was defining how to test for extractables. Once this was understood, the next question was how to test and what to test for leachables. The questions then became, "How do we quantify?" and, "What do we quantify?"

The industry came to realise that the FDA did not consider leachables in the same category as a drug degradation product. As a result, the ICH guidance, "Q3B Impurities in New Drug Products" was not applicable to leachables. This guidance had at one time been thought of as an answer to quantification limits.

The first written guidance the industry received on the subject was the FDA's "Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics", published in 1999.

The guidance defined *Suitability for Intended Use* as consisting of:

- Protection
- Safety
- Compatibility
- Performance

In recent years, there has been a tremendous amount of progress made by the industry in an effort to standardise the definitions and the approach to the extractables and leachables issue.

Understanding this issue is critical because the risk of delaying a drug application approval can have a dramatic negative effect on a pharmaceutical or biotechnology company.

For this reason, extractables and leachables should be addressed before the pharma/biotech company submits a drug application to the regulatory agency. In addition, an understanding of the reasons why the regulatory agencies are requesting these studies is also important.

So, why are the FDA and other regulatory agencies around the globe concerned with extractables and leachables?

Although the most obvious reason is patient safety, the major driver for conducting extractables/leachables testing is due diligence in assur-

ing appropriate *Suitability for Intended Use* of the packaging components or delivery devices. Due diligence helps assure that there is a basic understanding of the extractables species that could leach into and are present in a drug or biologic product over its shelf life.

THERMOSET COMPONENTS INJECTABLE DRUG PRODUCTS

Thermoset elastomers used for the pharmaceutical industry consist of the same raw materials that are commonly used for products such as tyres and in electronics. There are no "pharmaceutical grade" elastomeric raw materials. Suppliers to the pharmaceutical industry must understand the raw material production process and conduct a thorough analytical evaluation of the raw materials used in these components.

Thermoset elastomers, which are commonly used for sterile, injectable drug applications, are typically composed of six to ten raw materials. Under the heat and pressure of component manufacturing, breakdown products and reaction products of the raw materials are formed. Additionally, each raw material has its own combination of additives or process aids that could lead to a leachable in a drug product.

Extractables and leachables

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An example is the polymer used as the base of an elastomeric formulation. Table 1 shows a list of

POLYMER POTENTIAL EXTRACTABLES

- Oligomers
- Calcium stearate
- Antioxidant (BHT, etc.)
- Epoxidised soybean oil
- Halide ions

Table 1: Potential extractables from a general raw polymer used for a typical pharmaceutical application.

potential extractables from a general raw polymer used for a typical pharmaceutical application.

Other common sources of extractables from the finished elastomeric formulation are the cross-linking system, which is composed of a series of curatives, accelerators and activators, along with plasticisers, process aids and reaction products of these materials.

Among the reasons the FDA is asking for extractables data on components are qualification and quality control of the components.

Pharmaceutical component suppliers have continued to adjust to the market and to the regulatory environment. Initially, suppliers developed potential extractables lists on every formulation. The lists were created from a theoretical standpoint, not an experimental standpoint. All raw materials were considered, along with any process aids or other materials relating to the raw materials, as were possible reactions or by-products from the manufacturing process.

As time went on, suppliers provided more support for pharmaceutical companies. The pharmaceutical/biotech industry's core knowledge is around drug development, not packaging materials and their extractables and related leachables. In an effort to expand the level of support for their customers, some component suppliers developed laboratory services to provide both extractables and drug leachables testing.

An experienced component supplier such as West can advise and consult with customers to assist with their testing program. Potential extractables lists can be used to help determine what leachables testing to initiate. A formal extractable testing program should provide scientifically sound data to support what leachables are tested in a drug product.

Component suppliers have also introduced products that can help pharmaceutical and biopharmaceutical companies meet current quality requirements for finished pharmaceuti-

cals. For example, West's NovaPure® components can provide a ready-to-use solution that is certified on a lot-to-lot basis for extractables, and includes an extractables profile and extractables specifications.

Certification helps assure pharmaceutical companies that the composition of the closures, and the closure manufacturing processes, are uniform from laboratory-scale studies until commercialisation. NovaPure® components can minimise the risk of extractables in the drug solution because they are manufactured with a barrier film. In addition, the closures are vision inspected to minimise defects and subvisible particle specifications are applied to assure consistency as an input to the finished drug product fill/finish process.

"TO SUPPORT THE PHARMACEUTICAL AND BIOTECH INDUSTRIES EFFECTIVELY, SUPPLIERS MUST STAY ON THE LEADING EDGE OF THE EVOLVING REQUIREMENTS IN THE AREA OF EXTRACTABLES AND LEACHABLES"

These types of product/service offerings address several industry challenges, including giving the customer the ability to move quickly into a leachables testing program. It also provides assurance of change control around the component itself. This is critical when the drug development and commercialisation cycle can take years to complete.

RISK FACTORS REGARDING EXTRACTABLES AND LEACHABLES

The industry has progressed to a common-sense approach of deciding, "What to test" and, "How much to test". Through a combination of regulatory guidances and industry knowledge, a risk-based approach is now used to address these questions.

The key factors are:

1. Potential for extraction
 - The degree of contact between drug and container closure system
 - The ability of the drug formulation to enhance extracts from the container closure system
2. Route of administration (for example, IV, inhalation)
3. Patient population
 - Chronically ill, paediatric, geriatric, etc.
 - Treatment duration (acute vs long-term)

CASE STUDY

The following case study illustrates the impact of extractables and leachables on drug products delivered in prefillable syringe systems. In 2003, a safety issue led to a market recall of Eprex, a recombinant human erythropoietin (EPO), by Ortho Biotech (a division of Johnson & Johnson).

A news report from Reuters, London, summarises the incident:

"August 12, 2003 – Johnson & Johnson said on Tuesday it was recalling certain batches of its anaemia drug, Eprex, in most countries outside the US after discovering they were tainted by chemical reactions with stoppers. Details of the recall emerged after Britain's Medicine and Healthcare Products Regulatory Agency issued an alert on its website saying the company had found low levels of "extractables" in the product."

The drug was packaged in a pre-filled syringe format with an uncoated plunger. A change was made to the drug product by incorporating Polysorbate 80 to replace Human Serum Albumin in the drug product. This changed the migration potential of extractables in the elastomeric formulation, leading to a higher level of leachables. Interaction between the extractables from the elastomeric syringe plunger and the drug product formulation caused the adverse event of pure red cell aplasia in certain patients.

The resolution for this issue was a move to a barrier-coated plunger to minimise migration of extractables into the drug product.

MINIMISING RISK

To support the pharmaceutical and biotech industries effectively, suppliers must stay on the leading edge of the evolving requirements in the area of extractables and leachables. Although tremendous progress has been made over the last decade, this issue continues to evolve.

Direct suppliers to the industry play an important roll in transforming raw materials into components that are critical to the delivery of life-saving pharmaceutical and biotechnology products. By working closely with their component suppliers from the earliest stages of drug development, pharmaceutical and biopharmaceutical companies can mitigate regulatory and product-related risk related to extractables and leachables.

NovaPure® is a registered trademark of West Pharmaceutical Services, Inc, in the US and other jurisdictions.

COMPANY PROFILE – THE MEDICAL HOUSE PLC



The Medical House PLC (TMH) specialises in the design, development, licensing and supply of innovative self-injection devices for pharmaceutical industry clients. The proprietary, patented ASI™ disposable auto-injector is TMH's lead platform technology, on which the company has based a range of delivery devices, each designed to address specific challenges associated with self-injection. TMH can offer clients both a standardised disposable auto-injector device product and bespoke solutions to their injectable drug product requirements.

As well as stand-alone provision of its auto-injector devices, TMH can also provide a comprehensive solution for development, manufacture and supply of drug/device combination products, through collaboration with Catalent Pharma Solutions, a leading provider of technologies and development, manufacturing and packaging services.

ASI™ Disposable Auto-injector

The ASI™ is a disposable auto-injector which typically incorporates drugs in prefilled syringes, enabling patients to undertake fully-automated injections in a convenient and safe manner. The ASI™ auto-injector ensures that patients never see the needle, thereby reducing the anxiety associated with injection, whilst a passive needle safety feature eliminates the risk of accidental needlestick injuries. With a viewing window for checking the drug before injection, ASI™ auto-injector also provides audible, visual and tactile feedback during the injection.

TMH's ASI™ disposable auto-injector can be customised according to:

- Primary packaging
- Drug viscosity
- Needle length and gauge
- Depth of injection
- Speed of injection
- Delivered volume

Advantages of the ASI™ auto-injector include:

- Choice of simple, intuitive operating systems
- Fully automated injection process
 - Needle insertion, delivery of dose and needle retraction
- Adaptable to a wide range of injection challenges, including delivery of viscous formulations



"ASI™ disposable auto-injector design variants"

Choice of Device Operation

The ASI™ auto-injector offers the choice of either "Push-actuation" or "Button-actuation" operation.

The two-step Push-actuation system requires removal of the device's safety cap and pushing of the device against the injection site to initiate the automated injection process. This simple operation is particularly advantageous for patients with limited dexterity, such as those with rheumatoid arthritis.

The Button-actuation system involves pushing a button to initiate the injection, once the device has been applied firmly at the injection site. Button-actuation provides users with a greater sense of control and may be more suitable for patients likely to experience discomfort at the injection site during the delivery process.

Automated Needle Retraction

The ASI™ auto-injector provides a choice of whether the fully-automated needle retraction processes is triggered immediately following

completion of delivery or is initiated by the user (allowing for a needle dwell period following completion of injection).

Delivery of Viscous Formulations

There are increasing numbers of viscous injectable drugs, often with sustained release characteristics, which generally require high forces to achieve acceptable injection duration with narrow gauge needles. An auto-injector can overcome strength and dexterity challenges resulting from viscosity, although the use of high forces in an auto-injector is known to increase risk of breakage of glass syringes. TMH's VISC-ASI™ device is an auto-injector for viscous drugs, with a proprietary Syringe Protection System to protecting glass syringes against damage from the applied high forces.

The range of ASI™ auto-injector devices are designed to address a number of self-injection needs:

- **SQ-ASI™**
Subcutaneous delivery.
- **IM-ASI™**
Intramuscular delivery.
- **RECON-ASI™**
"Wet & Dry injector" with integrated reconstitution system.
- **JR-ASI™**
Compact injector for drugs which must be carried by the patient (e.g. for emergency administration).
- **VISC-ASI™**
Viscous formulations.

TMH has achieved a number of US and European regulatory clearance (including CE-mark and 510(k)) for several ASI™ auto-injector device variants.

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EQUIPPING A COMPLETE SYRINGE LINE, FROM FILLING TO PALLETISATION

Marchesini Group is a multinational, multidivisional organisation specialising in the supply of innovative packaging machinery to a range of industry sectors. In the past few years, significant investment in providing equipment for syringe filling lines means that now the Group can provide all of the machines needed for a complete syringe line. In this article, Mr Pietro Tomasi, Commercial Director, and Mr Massimo Pannini, Product Manager, describe the syringe-filling process from beginning to end, detailing how Marchesini Group equipment can be employed at each stage.

In recent years, prefilled syringes have become an increasingly important area of focus for Marchesini Group, which has concentrated considerable technological efforts on this type of packaging system. Strategic investments, including the addition of two specific organisations to the Group, are of particular significance, and alliances between the various enterprises that have become part of the Group since 2000 have been of great importance.

In 2002, the Group acquired Farcon (Carpi, Italy), which specialises in deep-draw thermoforming machines, with applications in packaging ampoules, vials, needles and, of course, syringes. Then in 2004, Corima (Monteriggioni, Italy) joined the Group. Corima brought with it extensive experience and capabilities in filling, handling, labelling, plunger-insertion and nest-handling machines.

The Group's know-how has expanded to the extent that today Marchesini's capabilities incorporate the production of the machines required to form a complete syringe line: from filling to palletising.

Not only does the Group produce all the machines, but it also boasts a complete range of accessories required for handling and assembling the syringes with conventional but also new components, such as backstops or needle-safety devices, amongst others, which are foreseen in new international standards concerning the safeguard and protection of healthcare workers.

How is a conventional filling and packaging line structured?

Naturally, the first stage in a conventional filling and packaging line is the filler (**Series**

FSP by Corima) that fills the syringe in an aseptic and controlled environment and applies a rubber stopper. A true concentration of technology, the FSP machine is equipped with an innovative and extremely flexible robotic system that is able to process various sizes of syringes. Controlled totally by brushless motors, it guarantees maximum batching precision and is manufactured to fit all types of conventional protection systems, laminar air flow or the more advanced barriers for restricting access (RABS) to the processing area, either open or closed.

Once filling and stoppering is complete, the nest, containing the filled syringes, sealed with a rubber stopper, are placed back inside the container to then be transferred towards the subsequent secondary packaging steps.

The secondary packaging phase of the syringe lines requires the obligatory installation of a de-nester (**Series MP by Corima**). This unit automatically picks-up the filled syringes from the nests and feeds them to an inspection machine or to the plunger insertion and labelling machine (**series AEC by Corima**).

The insertion of the plunger on the syringe, likewise for the syringe pick-up and handling functions, is precise and safe and designed to avoid damage to the syringes (including aesthetic damage). The plunger is inserted perfectly vertical thanks to controlled distribution on just one line. Equipped with a complete set of controllers, the AEC machine is offered in different rig-outs based on the production requirements involved and is integrated with the most popular types of printers and vision systems available on the market.



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Figure 1: The Corima APS Combi syringe assembly machine

Downstream from the plunger insertion and labelling machine, the assembly machine for syringes with back-stop (**Series SMB by Corima**) or the assembly machine for syringes with safety device (**Series APS by Corima**) can be installed alternatively.

The safety devices are designed to prevent all possibilities of the operator accidentally coming into contact with the potentially contaminated used needle. These safety devices normally trigger automatically, isolating the needle inside at the end of the injection, and are becoming increasingly popular. Indeed, they are becoming a permanent obligation in safety standard protocols in many countries worldwide. Both the SMB machine and the APS machine are designed and pre-arranged to be connected in line with other machines of the plant. They are reliable and versatile and can process the various sizes and shapes of back-stops and safety devices presently offered on the market.

Alternatively to separate machines, Marchesini Group offers Corima's APS



Figure 2: In detail, a section of the APS Combi machine in action

Combi machine (see figure 1), the first machine in the world designed and manufactured to assemble syringes with plungers, to label the plungered syringes and to assemble them with the safety devices. Compact and extremely reliable, the APS Combi machine is appreciated by many major enterprises in the industry. Available with various production rates, the APS Combi carries out all the steps automatically and avails of special solutions

so that it can be easily integrated with the machines downstream.

A more detailed photograph of the APS Combi machine in action is shown in figure 2.

The **SMB Combi** is similar to the APS Combi, but is designed to apply the label, the plunger and the backstop on the syringe.

FIRST-CLASS LINE-INTEGRATION EXPERIENCE

Once this last phase is complete, the filled, labelled and assembled syringe is picked-up by the Farcon thermo former. The operational phase between Corima and Farcon machines features dynamic robotic connection systems manufactured by Marchesini, increasingly frequently integrated with buffering systems that drastically reduce machine downtimes and increase the overall performance of the line.

Marchesini Group has substantial comprehensive line-integration experience and is consequently able to offer highly customised con-



Figure 3: The Robocombi robotic feeder places syringe trays in the cartoning machine



nection systems. For example, using special shuttles that carry the syringes together with secondary components, such as spare needles.

Syringe packaging in thermo formed containers is fulfilled by Farcon, which offers customers machines made entirely with balcony structure and in full compliance with the strictest of pertinent safety standards.

Farcon's most recent innovation to reach the market is the **FB320** machine. It is a totally mechanical thermo former controlled by brushless drives. Featuring many technological innovations, the FB anticipates the assembly of front-on sizing parts, which enables the operator to change size without using tools, simply and in just 20 minutes, with pitch selection from the operator panel.

With a forming area and depth of up to 42 mm, the FB unit is also available in the zero-reject version (**FBZ**).

The syringes, enclosed and protected in the tray, continue at this stage towards the final packaging step. The FB unit is then backed-up by the most advanced transfer system available; the **Robocombi**, Marchesini's cutting-edge robotic feeder, which places the syringe trays in the containers of the cartoning machine with tracking motion (see figure 3 on page 27).

The **Robocombi** system is able to pick up 400 pieces per minute, consequently guaranteeing production speed. It also features pick-up flexibility. In the case of containers with lids (either in PVC or paper), the pieces are picked-up with normal suckers from the top. If, on the other hand, the container is open without a lid, the suckers are replaced by side pick-up grippers.

Another important feature is the possibility to turn the container, either flat or upright in rows, before placing it in the boxes. This ability to handle the container in a very small space, together with outstanding reliability, is another of the system's strengths.

Together with the possibility to create the required number of stacks in the boxes of the cartoning machine, Robocombi can also place them in an especially designed mobile box system, to create a buffering system for accumulation or inspection purposes off-line.

The choice of the cartoner (**series MA by Marchesini**) is comprehensive and guided based on the various characteristics required: number of trays to be stacked, their size, and any other components to be added to the carton, such as leaflets or booklets, and the requested production speed.

To overcome the need to safeguard the integrity of the package, Marchesini also offers a series of labellers produced by another of the Group companies, **Neri** (Barberino di Mugello, Italy), which not only apply normal

"MARCHESINI BOASTS AN UNPARALLELED & UNRIVALLED OFFER, GUARANTEEING AUTOMATIC CONNECTIONS BETWEEN ALL THE MACHINES MAKING UP THE LINE ... STANDARDISING ALL THE ELECTRICAL & PNEUMATIC COMPONENTS ... GUARANTEEING UNIFORMITY OF THE DESIGN AND SUPERVISION OF THE PRODUCTION CYCLE."

labels on the carton body but also tamper-evident labels on the side flaps.

Made entirely with balcony structure, the labelling machines of the **BL series** by Neri are again a true blend of technology and versatility.

After identifying the product and checking the integrity of the package, it can be sent to the next step. The cartons can be bundled and wrapped in heat-sealed film (**series MF**), or bundled and wrapped in heat-shrink film (**Multipack**), even if the most popular type of packaging method for syringes is just cardboard cartons.

Controlled by brushless motors and made with balcony structure, the case-packers and palletisers of the **MC series** complete the line. These can be installed as separate machines (**MC820 and MP830**) or as a single monobloc structure (**MCP840 or MCPV840 Top Loader**) guaranteeing a compact and efficient end-of-line solution for speeds of up to 10-15 cases per minute.

In the handling compartment of all the components, and likewise for all of the machines just listed, Marchesini Group boasts an unparalleled and unrivalled offer, guaranteeing automatic connections between all the machines making up the line, not only standardising all the electrical and pneumatic components but also guaranteeing uniformity of the design and supervision of the

production cycle. All this at various production speeds: **from 2,000 to 24,000 pieces per hour.**

THE SIGNIFICANCE OF INTER-MACHINE CONNECTIONS

Having travelled along the syringe line, from filling to case-packing, describing the various stages and machines we can now focus specifically on the connections between each stage. The connections are as important as the stages themselves.

Of critical importance are the buffer systems designed to ensure correct feeding continuity throughout the various steps of the packaging line. Strategic steps are, for example, those between the plunger inserter and the thermo former, which must never stop because, unlike many other machines, stoppages could compromise operation, even causing serious damage.

To pre-empt this problem arising and thus avoid it, a buffer is installed upstream from the thermo former to create a stock for the required number of minutes, that the thermo former can exploit if the machine upstream should stop. This guarantees regular operation of the line.

The buffers offered do not have a permanent structure, but each unit has its own configuration, designed to meet individual lay-out requirements.

The common feature of all the machines is the robotic system, manufactured by Marchesini. Robocombi, Robovision and Robomaster (see figure 4), all fill and empty the buffer containers with PC logic.

The Robovision is a second-generation top-loader robot with four axes that can be integrated with a vision system. Developed to pick-up loose objects sent randomly from a belt and to feed them to the cartoning machine with continuous motion, Robovision can pick **up to 120 pieces per minute.**

Thanks to the camera and software with which it can be equipped, this innovative robotic solution recognises the image of the product to be fed and is able to turn the product itself to be able to insert it correctly in a conveyor, for example, that of a cartoning machine.

Complete with tracking motion, thanks to the characteristic bridged structure, it can also be slaved with a parallel belt and also a trans-

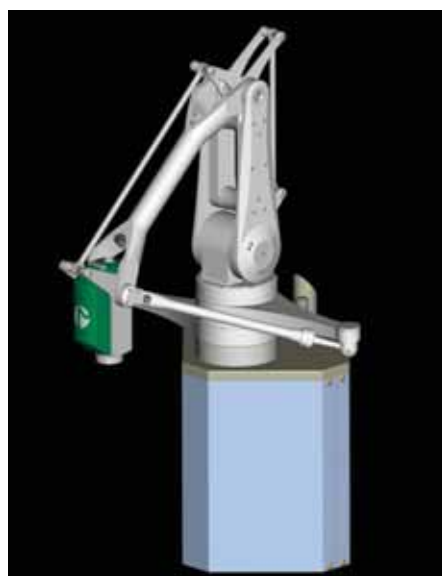


Figure 4: The Marchesini Robomaster feeder

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- Feeding syringes from hypak nest
- Feeding syringes or safety device from rondo flat tray traditional or robotized systems
- Retrayer: handling equipment to collect syringes into rondo flat
- Traybuffer "FIFO": handling equipment to buffer syringes into tray
- Renester: handling equipment to collect syringes into nest
- Safety device assembling machine
- Backstop assembling machine
- Plungering, labelling and assembling machines combi
- Filling and stoppering machines
- High speed labelling machines
- Deep draw thermoformers
- Cartoner with Robotized automatic syringes loading systems
- Robocombi
- Robovision
- Robomaster
- End of line equipment



verse belt. Maximum lay-out versatility, a large work area and precision are the special features of this product, whose software, just like the whole project, is developed entirely by Marchesini. Thanks to this special feature and to its impressive adaptability, Robovision can be implemented for a large number of applications, in both the pharmaceutical and cosmetic field.

Robomaster is perfect for requirements of higher speeds and more advanced dynamics; this robot also has four axes and features a cutting-edge design, studied specifically by Marchesini Group to feed syringes and ampoules for thermo formers (see figure 5). It works at a maximum speed of **400 pieces per minute** and can be equipped with an integrated vision system, just like the Robovision unit.

ROBOCOMBI, ROBOVISION, ROBOMASTER: ADVANTAGES IN 7 MOVES

The most innovative syringe-handling and feeding products from Marchesini are two – Robovision and Robomaster – and they are paired with unique specifications compared with what the rest of the market has to offer:

1) They are not just commercial robots simply adapted to a certain pharmaceutical product, but are designed right from the very start exclusively for the world of syringes; they merely enhance the specifications required for this type of product.

2) Since they are exclusive products of Marchesini's development department, which also supervises the design of the machines themselves, they are extremely compact in order to better adapt to lay-out configurations that may require



Figure 5: The Robomaster feeder, photographed in action

a considerable level of complexity and cannot be standardised. They are also all integrated for the optimum handling of the actual syringes.

3) Compared with a conventional mechanical feeding system, Marchesini's robots drastically reduce transfer movements performed by complex mechanical parts, consequently drastically reducing size-changing times.

4) They enable positive conveyance; consequently the syringe is always accompanied throughout the whole route and is subject to fewer transfer movements, which could be rather critical for the integrity of the product itself.

5) They enable outstanding cost reductions compared with a conventional mechanical feeder,

in terms of the structure's extreme simplicity, which is consequently maintenance free, and in terms of a much longer lifetime.

6) Extreme flexibility and precision in transferring the syringes.

7) A final yet extremely important aspect is the fact that the Software and Hardware of Marchesini Robots are integrated in the same PC.

The last point should be stressed. In line with the overarching integration philosophy that characterises the lines produced by Marchesini, an outstanding strong point of the machines is that they all use the same PC, with the same operator interface. This naturally makes the entire line extremely user friendly.

Summary of Marchesini Group machines mentioned in the article, with web references:

Name/Series	Function	URL
Series FSP (Corima)	Filling machine	http://www.marchesini.com/prodotti/liquidi/riempitrici-siringhe/
Series MP (Corima)	De-nester	http://www.marchesini.com/prodotti/liquidi/syringe-assembler/mp1-p-mp2-p/
Series SMB (Corima)	Syringe assembly	http://www.marchesini.com/prodotti/liquidi/syringe-assembler/smb/
Series APS (Corima)	Syringe assembly (with safety device)	http://www.marchesini.com/prodotti/liquidi/syringe-assembler/aps1/
APS (Combi)	Syringe assembly, plunger insertion and labelling (with safety device)	http://www.marchesini.com/prodotti/liquidi/syringe-assembler/aps-combi/
FB320 (Farcon)	Thermo former	http://www.marchesini.com/prodotti/packaging/termoformatrici/fb320/
series MA (Marchesini)	Cartoner	http://www.marchesini.com/prodotti/packaging/astucciatrici/
BL series (Neri)	Labelling machine	http://www.marchesini.com/prodotti/packaging/etichettatrici-astucci/
series MF	Wrapping	http://www.marchesini.com/prodotti/packaging/wrapping-overwrapping/mf910mini/
MC820 & MP830	Case packer and palletiser (separate machines)	http://www.marchesini.com/prodotti/packaging/cartonatrici-pallett/mp830/
MCP840 or MCPV840 Top Loader	Case packer and palletiser (mono-block)	http://www.marchesini.com/prodotti/packaging/cartonatrici-pallett/mcp840/

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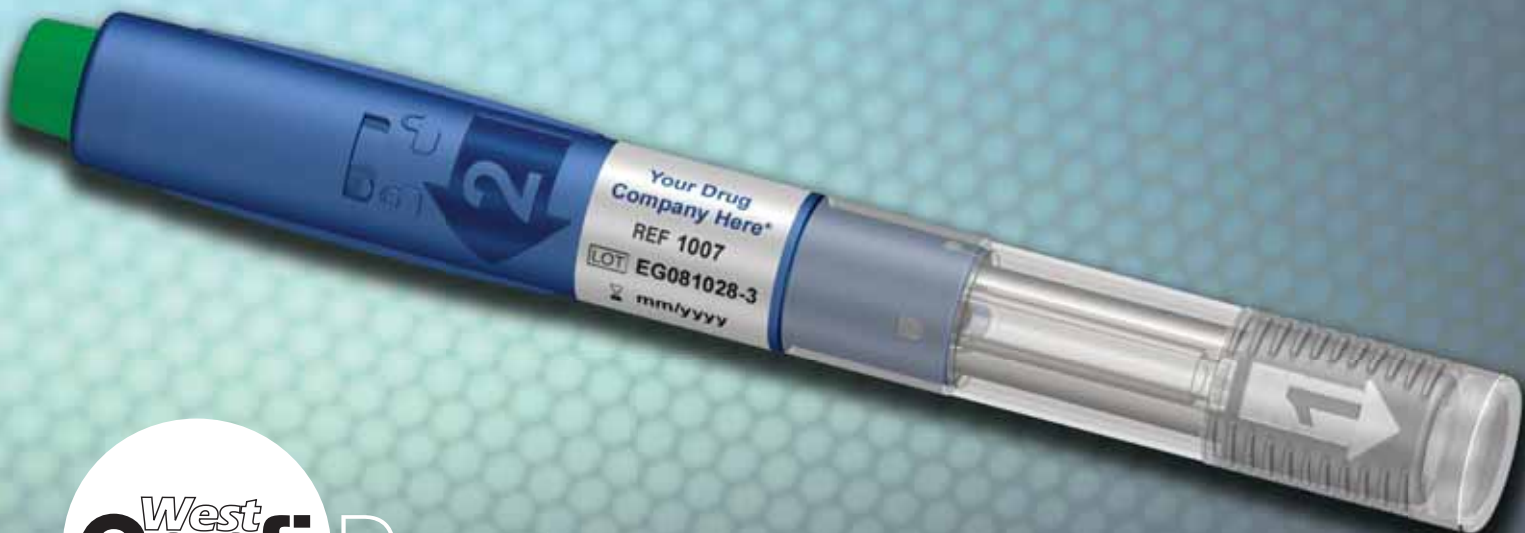
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