

PREFILLED SYRINGES: NEW IDEAS FOR THE NEW DECADE



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“Prefilled Syringes: New Ideas for the New Decade”

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Guy Furness, Publisher
T: +44 (0) 1273 78 24 24
E: guy.furness@ondrugdelivery.com

MAILING ADDRESS:

ONdrugDelivery Publishing
48, Albany Villas
Hove
East Sussex
BN3 2RW
United Kingdom

PRODUCTION/DESIGN:

Mark Frost
E: mark@frostmark.co.uk

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UNILIFE – DEVELOPING PREFILLED PRODUCTS OF CHOICE

Based in its market driven approach to product commercialisation, Unilife has developed a new prefilled syringe. The Unifill syringe is the first known ready-to-fill syringe which has all safety features fully contained within the glass barrel. Stephen Allan, Vice-President of Marketing and Communications at Unilife, explains.

There are more than 20 pharmaceutical companies using prefilled syringes as a preferred delivery device for at least 50 injectable drugs and vaccines that have total combined annual sales of approximately US\$50 billion. Prefilled syringes are now used across a wide array of therapeutic sectors outside of the traditional domains of anti-coagulants and vaccines (see figure 1). In particular, their usage in areas such as haematology, multiple sclerosis, arthritis, oncology and human growth hormones is expected to accelerate over the coming decade.

For pharmaceutical companies, the advantages of prefilled syringes in minimising drug wastage, increasing product lifecycles and enhancing levels of market share are driving market demand. As such, countless pipeline drugs and vaccines are also targeted to be launched in a prefilled syringe format over the coming decade.

By healthcare workers, prefilled syringes are recognised as an efficient, reliable and convenient method of drug administration. Furthermore, the ease at which patients can self-administer many types of injectable drugs makes prefilled syringes ideal to accelerate the transferral of healthcare treatment out of hospitals and into the home.

Over the past decade, one of the key emerging challenges in the pharmaceutical market for prefilled syringes has been compliance with needlestick prevention laws. The US was the first country to mandate the use of safety-engineered medical devices within healthcare facilities to protect healthcare workers, with the adoption of the Federal Needlestick Prevention Act in 2000 and subsequent amendments to the Bloodborne Pathogens Standard (BPS). Since then, the US Occupational Safety and Health Administration (OSHA) has moved to enforce the BPS aggressively with around one in every

five inspected healthcare facilities issued with citations for non-compliance between 2002 and 2007. OSHA has further stipulated that prefilled syringes should include a safety device when used within healthcare facilities even in pandemic situations.

Other international markets including the European Union, Canada and Australia are also taking steps towards the use of safety products, including prefilled syringes, which can help protect healthcare workers from harm.

Because there is currently no prefilled syringe with integrated safety features, pharmaceutical companies marketing drugs in a prefilled format have two main options to comply with laws seeking to protect healthcare workers from needlestick injuries (see Figure 2).

The first and arguably most common option, particularly for drugs supplied with an attached needle and administered via subcutaneous injection, is to fill a standard ready-to-fill syringe as normal then attach an ancillary safety product over the barrel prior to packaging and shipment. To protect those at risk of harm from needlestick injuries, these ancillary safety products typically slide an external plastic sheath over the entire prefilled syringe upon activation of the safety feature.

The primary advantage of these ancillary products is that they serve as a secondary drug container, thus minimising additional pharmaceutical requirements for biocompatibility and stability testing. However, pharmaceutical companies must not only purchase these ancillary safety products, but also invest in the automated assembly systems which attach them onto a prefilled syringe. As these safety products are much larger in size than a standard prefilled syringe, they can significantly increase pharmaceutical costs related to packaging, shipping and storage.

Stephen Allan
Vice-President of Marketing and Communications
T: +1 717 938 9323
E: stephen.allan@unilife.com

Unilife Medical Solutions, Inc
633 Lowther Road
Lewisberry, PA 17339
USA
T: +1 717 938 9323
F: +1 717 938 9364
E: info@unilife.com

www.unilife.com

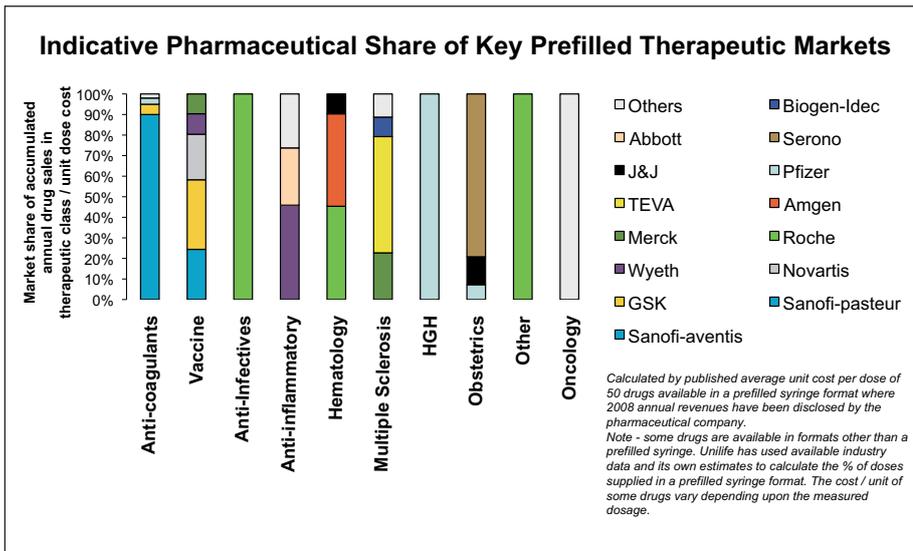


Figure 1: Indicative Pharmaceutical Share of Key Prefilled Therapeutic Markets

Compared with the use of standard prefilled syringes, operators may also be required to undertake additional steps or procedures to activate the safety mechanism. For example, one ancillary safety device supplied with a prefilled low-molecular-weight heparin product in the US requires operators to remove the non-sterile needle from the body prior to activation. The operator is then required to activate the safety mechanism manually after the completion of dose delivery to protect themselves and others from the risk of needlestick injury. Should this additional action not be undertaken, the risk of harm remains. Furthermore, it is recommended that the operator point the needle down towards the ground when activating the safety mechanism with this product to minimise the infection risk associated with aerosol (splatter).

The second option for pharmaceutical companies is to place the onus for compliance upon the healthcare facility. Prefilled syringes are

commonly supplied without a needle for drugs and vaccines that are administered via intramuscular (IM) injection. In addition to selecting a needle, healthcare workers are also required to select, attach and activate the needlestick prevention device manually. Typically, these operator-attachable safety products require the operator to remove the needle from the body after dose delivery before electing to slide a plastic guard over the needle to render it safe. This leaves open the possibility that the needlestick prevention device may not be attached or activated at all.

THE UNILIFE PHILOSOPHY

Traditionally, medical device manufacturers have sought to develop technology-driven solutions designed to address a particular market need such as the prevention of needlestick injuries. Like trying to force a square peg into a round hole, the consequences of such an

approach can be the development of products which do not fully address the operational, safety, usability or functionality requirements of all target stakeholders.

Unilife Medical Solutions was founded on a different philosophy. Unilife strives to design, develop and manufacture innovative safety medical devices via a market-driven approach to product commercialisation. The Company seeks to look beyond a single issue such as needlestick prevention to develop “products of choice” that can help address the specific needs of all relevant industry stakeholders. In this way, Unilife seeks to provide the ‘round peg’ which is perfect for the ‘round hole’ of each target market.

Unilife considers that the market for prefilled syringes will be increasingly driven by pharmaceutical companies, healthcare workers and self-injecting patients for products which can deliver the following core outcomes:

- Serves as a primary drug container with safety features being integrated within the barrel
- Can be inserted into fill-finish systems used for standard ready-to-fill syringes
- Utilises materials in the fluid path which are compatible with the contained drug
- Safety mechanism is passive, requiring little or no operator activation upon dose delivery
- Activation of the safety mechanism does not create additional hazards or infection risks
- Needle is covered permanently after activation, with minimal opportunity for re-exposure
- Operators require minimal training for use compared with conventional products
- Allows safe and convenient disposal, and does not increase sharps waste volumes

THE UNIFILL™ SYRINGE

Unilife has worked with its major pharmaceutical partner over several years to develop a ready-to-fill product which is well positioned to attain best-in-class status within the pharmaceutical market for prefilled syringes.

The Unifill™ syringe is the first known ready-to-fill syringe with safety features that are fully contained within the glass barrel.

As a primary drug container, the Unifill™ syringe is designed to be supplied to pharmaceutical manufacturers in three sub-assembly parts (glass barrel, rubber seal and plunger) for insertion into fill-finish systems currently used for standard ready-to-fill syringes. Secondary assembly, packaging and logistical issues relating to the attachment of ancillary safety devices can thus be eliminated, with the Unifill™ syringe similar in size to a standard prefilled syringe.

Unifill syringes are designed for insertion into current fill-finish systems used for equivalent

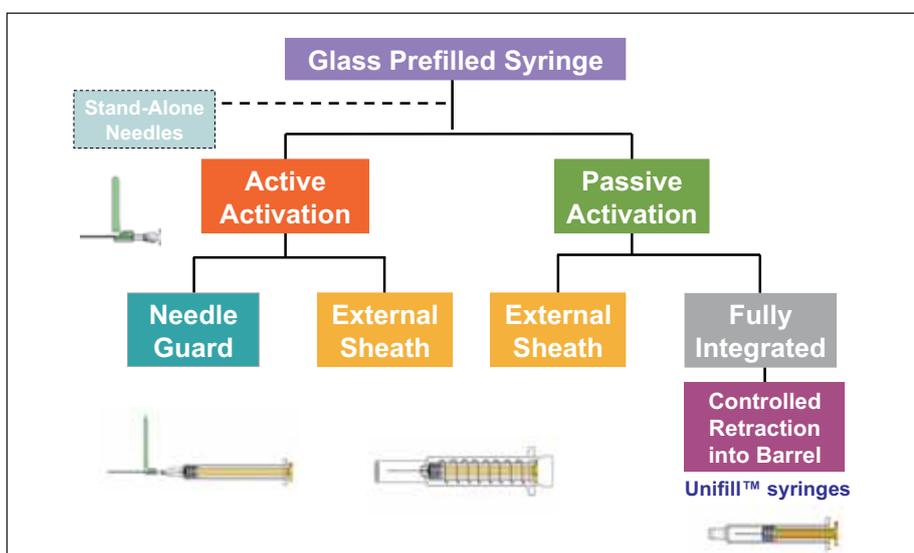


Figure 2: Classification of safety options for prefilled syringes



Figure 3: Unifill syringes are designed for insertion into current fill-finish systems used for equivalent standard ready-to-fill syringes.



Figure 4: Unifill syringes have passive, operator-controlled needle retraction from the body into the barrel.



Figure 5: Unifill is ISO 13485 certified with FDA registered manufacturing facilities in Pennsylvania, US.

standard ready-to-fill syringes. They are supplied in a standard tray (nest) system (see figure 3).

To assist with pharmaceutical drug validation processes, the Unifill™ syringe contains components in the fluid path which utilise a number of materials commonly used with standard vials and ready-to-fill syringes. Unifill is also building relationships with a number of trusted names within the prefilled syringe market to enhance material choices for pharmaceutical customers.

To strengthen its supply chain further, Unifill has designed the glass barrel of its Unifill™ syringe so that it utilises glass cartridges which are shaped at only one end. This differs from the more challenging manufacturing process used for traditional ready-to-fill syringes, whereby the glass barrel must be shaped at both ends (needle and the finger flanges).

Being a fully integrated medical device, the Unifill™ plunger contains the proprietary safety mechanism which is activated automatically (passively) upon full dose delivery (see figure 4). The operator is able to control the speed of needle retraction directly from the body into the barrel of the syringe simply by relieving thumb or finger pressure on the plunger. Upon full retraction of the needle into the barrel, the plunger is automatically locked to prevent needle re-exposure or product tampering.

The unique combination of passive activation of the safety mechanism and the ability for operators to control the speed of needle retraction into the barrel can virtually eliminate potential infection risks associated with needlestick injuries or aerosol. Further to accommodate healthcare procedures which seek to minimise contaminated medical waste disposal volumes, operators may also snap off the end of the plunger rod after use as it has not been in contact with the fluid path.

The Unifill™ syringe delivers the same core outcome to all target stakeholders—a device nearly identical in size, shape and similar steps of use to standard prefilled syringes. The integration of fully passive safety features, however, takes this device class into a new generation of convenience, passive functionality and safety.

With the Unifill™ syringe, it is possible for pharmaceutical manufacturers to utilise current fill-finish processes with minimal changes, contain packaging and logistical costs; comply with needlestick prevention laws; and expand levels of product differentiation in competitive therapeutic markets. Healthcare workers and patients who self-administer prescription medication who are using the Unifill™ syringe also require minimal training compared with other safety prefilled syringes, yet can be fully protected against infection from needlestick injuries or splatter.

THE UNIFILL™ SELECT

Unifill filed patent applications in the US last year for a new ready-to-fill syringe product to be marketed as the Unifill™ Select. This new pipeline product is designed to complement the Unifill™ syringe, and is targeted at addressing the requirements of pharmaceutical companies that manufacture injectable drugs and vaccines indicated for administration via IM injection.

Unifill™ Select syringes will allow healthcare workers to attach needles of up to 1 ½ inches in length and inject the dose into the patient as per routine procedures for IM administration. Unifill is not aware of any ancillary safety product currently used by pharmaceutical companies which can accommodate needles of 1 ½ inches in length.

Upon full dose delivery, the needle retraction mechanism is activated automatically with the operator being able to control the speed of needle withdrawal directly from the body into the barrel.

Pharmaceutical companies may elect to supply the Unifill™ Select to healthcare facilities in a compact and convenient kit format which is ready for injection by healthcare workers.

Like its companion product the Unifill™ syringe, the Unifill™ Select would also be designed for insertion into the fill-finish systems currently utilised by pharmaceutical companies manufactured for use with standard ready-to-fill syringes.

BUILDING A WORLD-CLASS BUSINESS

Unifill is a fast-growing company and an emerging industry leader committed to building a team with the technical expertise to make it a preferred and trusted partner for pharmaceutical customers. The US based company is ISO 13485 certified and employs more than 100 people at its FDA-registered facilities in Pennsylvania. To support its continued global expansion, the company is redomiciling from Australia to the US and is now finalising its application to list on NASDAQ as Unifill Corporation (figure 5).

As a demonstration of the calibre of the industry leaders now joining Unifill, the management team includes the former SVP of Operations for Bayer AG, the former head of medical devices for the World Health Organization and other senior professionals from companies including Safety Syringes Inc, Teva and CR Bard.

Given its plans to manufacture more than 400 million units per year beyond 2014, Unifill has also outsourced the development of its automated assembly systems to Mikron. Following the completion of proof-of-principle activities which successfully manufactured the Unifill™ syringe on proven assembly systems, Mikron has commenced development of the first commercial assembly line for the Unifill™ syringe with scheduled completion during the second half of 2010.

The first commercial line will have an annual capacity of 60 million Unifill™ syringes, and is to be installed in Unifill's new 165,000 square foot global headquarters and manufacturing facility currently being developed in York, Pennsylvania. High-volume assembly lines with a capacity of 150 million Unifill™ syringes will also be developed to support additional pharmaceutical demand.

Unifill has retained the right to negotiate with other pharmaceutical companies seeking to use its Unifill™ syringe in areas outside of those secured by its major pharmaceutical partner.

Unifill welcomes enquiries regarding its Unifill™ range of ready-to-fill syringes via its website at www.unifill.com or at its booth (A34) at Pharmapack, Paris between February 1 and 2, 2010.



Introducing the Unifill™ Syringe

Outside the box *innovation*

Inside the syringe *safety*

Compatible

Integrated

Retractable

Intuitive

Safe

*Booth A34 - Pharmapack
Paris, France - February 1 & 2, 2010*

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ADVANCED INNOVATIONS ON A NEW GENERATION OF PLASTIC PREFILLED SYRINGES

Aguettant has developed and launched a new polypropylene prefilled syringe designed to improve safety and quality of care whilst maintaining acceptable cost levels. Danielle Labreche, Director, Business Development & Innovation at Aguettant, and Guillaume Bonnefond, Plastic Engineer & PFS Project Manager, explain the benefits of the new syringe and provide details of its patented design features.

To date prefilled syringes have been designed and commercialised globally on the market, in various shapes, sizes and materials.

Plastic syringes bring a true benefit over glass. Plastic provides improved robustness against breakability and better ergonomics (lightweight), while delivering for many products an adequate stability performance level regarding water/gas permeability as well as extractibles/leachables.

“NESTED PREFILLABLE SYRINGES, AND THE ASSOCIATED MANUFACTURING EQUIPMENT, STILL REMAIN COST PROHIBITIVE FOR MOST INEXPENSIVE EMERGENCY AND CRITICAL DRUGS”

In the industry, standard empty plastic syringes (made of cyclo-olefin polymer (COP) or cyclo-olefin co-polymer (COC)) are available in a ready-to-fill format, arranged in nests, pre-siliconised and pre-sterilised. Glass, sterile, ready-to-fill syringes are also available in the same nest format.

It is true that the main advantage of the “nest” manufacturing process over the “bulk” process rests in its flexibility for development or multiple format productions, independently of the volumes produced. However, these nested prefillable syringes (glass and plastic), and the associated manufacturing equipment, still remain cost prohibitive for most inexpensive emergency and critical drugs. At the same time though,

prefilled syringes are highly anticipated by healthcare professionals in the hospital and homecare markets.

Having this in mind, Aguettant took the challenge to design a new generation of polypropylene prefilled syringes, intending to improve safety and quality of care at an acceptable cost for the market.

It took five years of product and industrial development and more than €5 million invested to bring this new syringe to life. Aguettant PFS (see Figure 1) was finally launched at the international fair for Anaesthesia and Critical Care (SFAR) held on September 28, 2009 in Paris.

Aguettant PFS is produced bulk-wise, it is terminally sterilised with steam in a peelable blister pack. This syringe delivers true design innovations of which two are patented worldwide:

- 1 A SIMPLE AND SECURE OPENING SYSTEM**
- 2 IMPROVEMENT OF THE STOPPER STERILISATION EFFICIENCY**

A SIMPLE AND SECURE OPENING SYSTEM

The syringe is sealed at its end by a frangible obturator which is injection molded in one embodiment with the barrel of the syringe (see Figure 2a). The frangible obturator itself is covered by a protective cap (Figure 2b).



Danielle Labreche
Director, Business Development & Innovation
T: +33 4 78 61 47 97
E: Danielle.labreche@aguettant.fr

Guillaume Bonnefond
Plastic Engineer/
PFS Project Manager

Laboratoires Aguettant
1 rue Alexander Fleming
69007 Lyon
France
T: +33 4 78 61 51 41
F: +33 4 78 61 09 35

www.aguettant.com

A simple rotation of the protective cap breaks the frangible obturator and opens the tip of the syringe. After opening and removal of the protective cap (see Figure 3 on page 10), the Luer Lock male connector at the end of the syringe allows a secured connection with any transfer set, catheter or any other compatible female port for needle-free administration or reconstitution.

This concept offers several advantages:

- **Closure integrity:** the integrity of the syringe at the tip end is guaranteed by design since the obturator is molded in one embodiment with the barrel.
- **Reduction of leachables:** the plunger stopper and the barrel of the syringe are the only two components in contact with the product; the protective cap is not. The risk of interactions between the container and the solution is therefore reduced.
- **Sterility of the connector:** as for the sterility of the solution, the sterility of the external surface of the syringe is guaranteed through terminal sterilisation process. The Luer connector is not in contact with the cap and the sterilisation efficiency is therefore enhanced (the sterilisation agent can easily pass through large openings in the cap frame and circulate in the critical Luer Lock area)
- **Convenience and security of use:** the opening system is simple and fast without any risk of manual contact with the Luer Lock connector thus precluding risk of user contamination of this critical area. These points have a special importance in emergency situations. A tamper evident system is also provided by this opening system.



Figure 1: The recently launched Aguettant PFS

IMPROVEMENT OF THE STOPPER STERILISATION EFFICIENCY

The second innovative concept relating to its prefilled syringe that Aguettant has patented improves the sterilisation efficiency by moist heat of a specific area of the syringe: the annular chambers created between the barrel and the stopper sealing lips that ensures closure integrity at the plunger end (see Figure 4 on page 10).

The plastic barrel of the syringe, which is injection molded, is provided with two channels leading to the open end of the syringe. When the stopper is inserted into the

syringe after filling, it is placed below these two channels (Figure 4a)

During the sterilisation process, the plunger is pushed back as the temperature and pressure increases, until a backstop annular bead that prevents the plunger from being ejected of the syringe (Figure 4b).

At this step the channels in the syringe barrel create a passage for the vapour penetration between the lips of the stopper (Figure 4c).

During cooling as the temperature and pressure decrease in the syringe, the stopper goes back below the channels ensuring a perfect sterile barrier (Figure 4d).



Figure 2: a) Molded tip with frangible obturator; b) with protective cap (shown in blue) fitted

“EPHEDRINE IS THE FIRST OF MANY MOLECULES EXPECTED TO BE MARKETED BY AGUETTANT, IN THIS MOST COST-EFFECTIVE READY-TO-USE PREFILLED SYRINGE.”

This concept improves sterilisation efficiency in a critical area which may be important for heat-sensitive drug products for which the stability would detrimentally be affected by an excessive sterilisation time.

LOOKING AHEAD

Since 1903, Aguettant’s main challenge has been to make it easier and safer for healthcare professionals to attend their patients and provide comfort, confidence and better quality of care. Motivated by this responsibility, Aguettant developed this new generation of plastic prefilled syringes.

Ephedrine is the first of many molecules expected to be marketed by Aguettant, in this most cost-effective ready-to-use prefilled syringe.

To date, Laboratoire Aguettant has to its credit 14 patents on innovative delivery system devices. At Pharmapack 2010 in Paris on February 1, the company launches a range of delivery systems under a new brand: “AGUETTANT SYSTEM”.

AGUETTANT SYSTEM represents a guarantee of quality design and innovative technology by Aguettant.

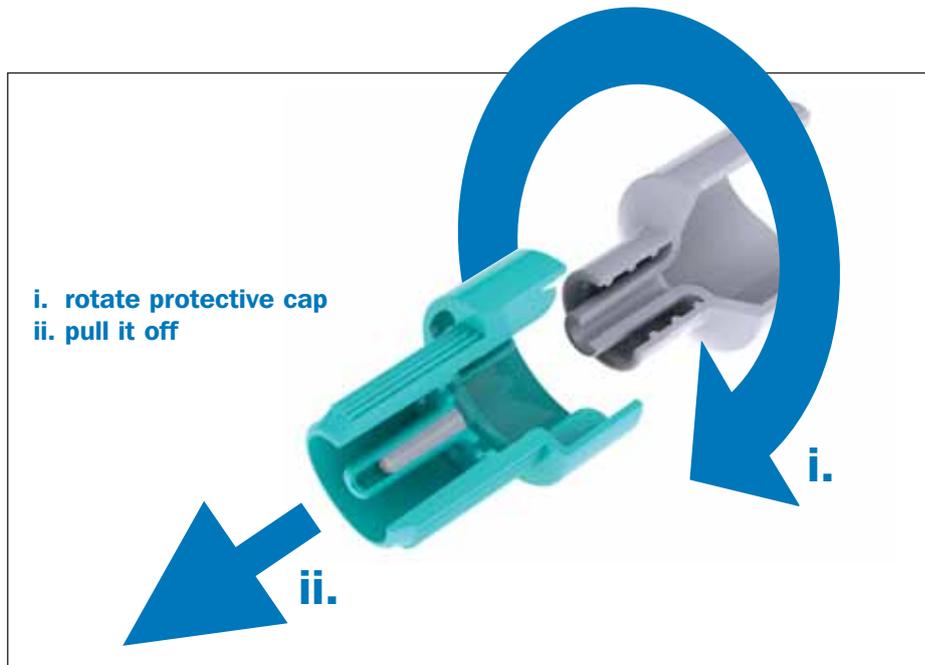


Figure 3: Opening the syringe

This new brand is comprised of:

- the recently launched ready-to-use Aguettant PFS
- the multidose self-injector pen
- the self-flushing perfusion bag
- the Mapset®, a reconstitution device for powder drugs

- €81 million turnover for 2009 in 70 countries
- 400 products registered
- 14 patents on innovative delivery system devices for injectables
- 5% of turnover dedicated to R&D

ABOUT AGUETTANT

As an independent laboratory, Aguettant has the flexibility and reactivity that are critical to seize opportunities for alliances, partnerships and licensing of its patents and technologies.

The company has:

- 550 employees worldwide

In France Aguettant is:

- a partner to 3000 clinics and hospitals and 1200 professionals outside of hospitals.
- third-ranked supplier (in units) of hospitals and clinics.
- leader* in the sectors of :
 - anaesthesia/ intensive care
 - injectable morphine
 - irrigation and rinsing
 - small-volume infusion
 - injectable trace elements

* in number of units sold. Source: IMS 2008

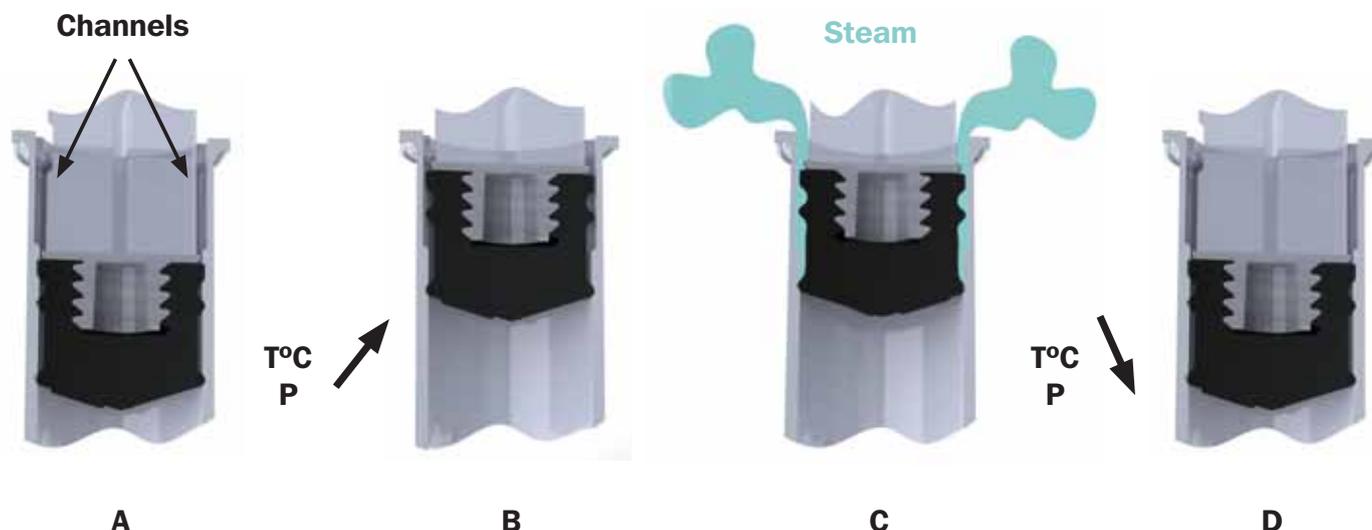
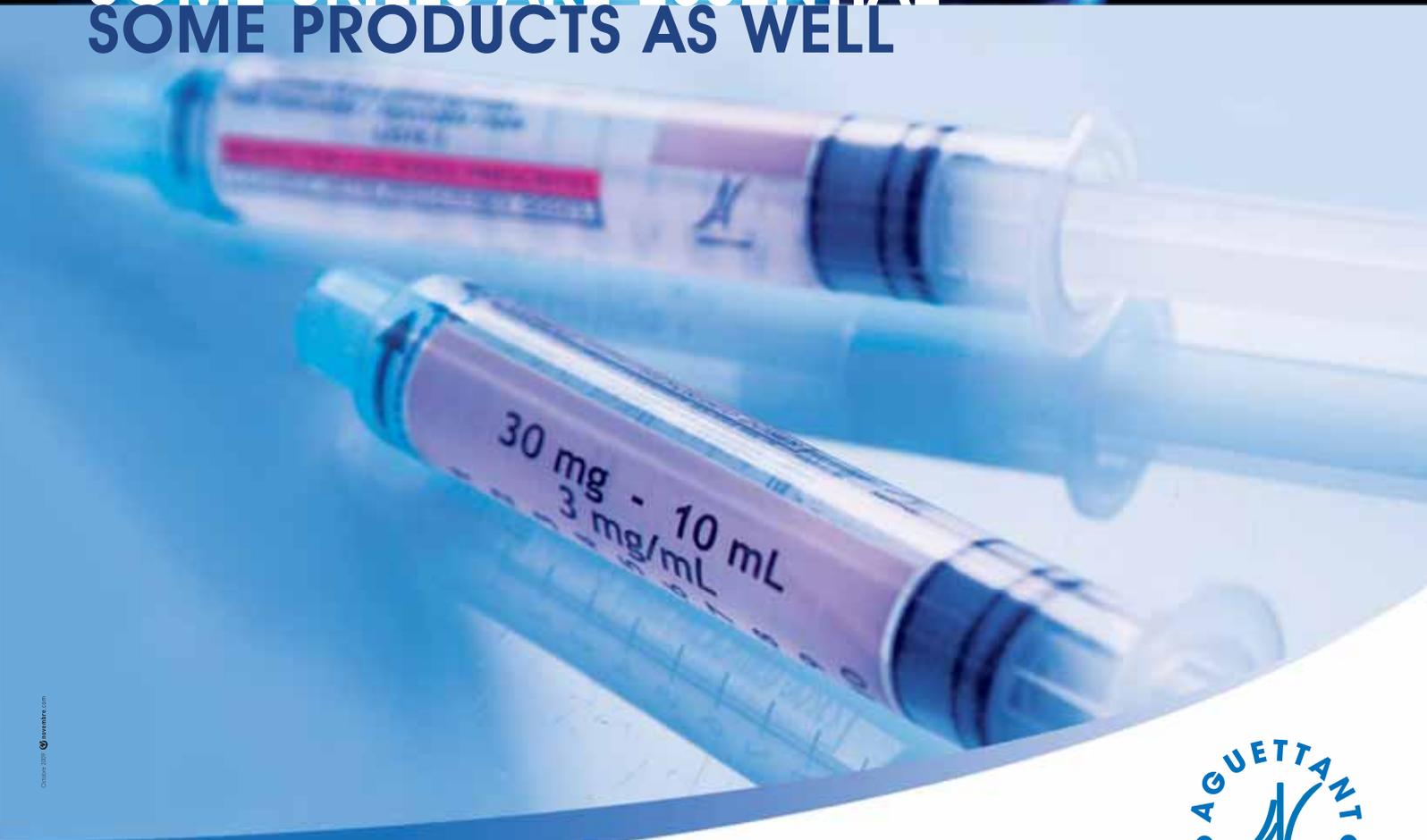


Figure 4: Process of stopper terminal sterilisation by moist heat



**SOME SKILLS ARE ESSENTIAL
SOME PRODUCTS AS WELL**



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Ypsomed is the largest independent developer and manufacturer of custom-made injection systems for self administration. Our pens range from simple disposable pens to reusable pens with variable dosing and spring-assisted injection. We also manufacture unique click-on needles and safety pen needles which are compatible with our own and all other widely-available pens.

We are constantly expanding our platform portfolio to cover new therapy and patient needs, including disposable auto-injector platforms for the treatment of autoimmune diseases and other indications. A broad-based technology platform and over 300 patent families mean Ypsomed can meet virtually all partner needs in the growing market for self-injection systems.

All products are developed and manufactured in Switzerland, where internal capabilities include R&D, tool-making, injection moulding, clean-room production and assembly facilities. Ypsomed provides not only marketing and technological expertise but also production expertise according to the latest regulatory requirements, for both low and high-volume production. Ypsomed manufactures in FDA-registered facilities, is inspected regularly by its customers and regulatory authorities, and supplies devices approved for all leading markets including the US, Europe and Japan.

Ypsomed has well-established partnerships of many years with numerous leading pharmaceutical and biotech manufacturers such as Sanofi-Aventis, Pfizer, Roche/Genentech, Merck-Serono and Lilly.



Ypsomed AG

Brunnmattstrasse 6, 3401 Burgdorf

Switzerland

Tel. +41 34 424 41 11

Fax +41 34 424 41 22

www.ypsomed.com

Contact:

Ian Thompson, Head of Business Development

info@ypsomed.com

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Pre-Filled Syringes Americas, 12-14 April, Philadelphia

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ENCODING AND READING OF CODES ON GLASS CONTAINERS FOR PHARMACEUTICAL AND DIAGNOSTIC PRODUCTS

First publication in *Pharm. Ind.* 71, No. 10, 1770-1774 (2009) and *Pharm. Ind.* 71, No. 11, 1945-1948 (2009); ECV Editio Cantor Verlag, Aulendorf (Germany)

Authors:

Simone Voldrich¹, Robert Hormes¹, Sabine Lehnicke², André Witzmann³, Ulla Trink³, Oliver Berger⁴, Volker Wedershoven⁴, Sergej Toedtli⁵

¹ SCHOTT forma vitrum ag, St. Josefenstr. 20, 9001 St. Gallen, Switzerland, ² SCHOTT AG, Hattenbergstr. 10, 55122 Mainz, Germany,

³ SCHOTT-Rohrglas GmbH, Erich-Schott-Strasse 14, 95666 Mitterteich, Germany, ⁴ Seidenader Vision GmbH, Lilienthalstr. 8, 85570 Markt

Schwaben, Germany, ⁵ VESDO AG, Roosstrasse 23, 8832 Wollerau, Switzerland. An undisclosed major pharmaceutical company was also involved with this project.

In light of ever increasing demands for documentation and monitoring, advanced methods for product identification are of great interest to the pharmaceutical industry, especially with regard to guaranteeing patient safety and preventing mix-up. In the case of disposable syringes, the following requirements can be formulated.

Patient safety

The European Federation of Pharmaceutical Industries and Associations (EFPIA) recommends an identification solution in the form of a data matrix barcode.¹ Consequently, new measures for guaranteeing patient safety were presented by the European Commission in December 2008.² Specific marking of the primary packaging should guarantee that it can be tracked and traced. By placing an individual code on each separate syringe, the pharmaceutical product can be tracked to 100% over the entire process chain.

Each glass container shall bear such individual identification which can be read during syringe manufacture, filling and packaging. Using a database, the data can be compared and retraced. This enables the medication to be tracked and traced from consumer back to manufacturer, in conjunction, for example, with the endeavors to introduce an electronic pedigree system (e-pedigree).

Avoidance of mix-up

There is also a demand for improved identification systems in the context of avoidance of mix-ups within the process chain of filling and packaging.

Pharmaceutical active ingredients and diagnostic presentations are available in many dos-

ages. Parenteral medications, for example solutions for injection, are distributed worldwide in prefilled glass syringes (disposable syringes) in up to 16 different dosages.

Today, coloured rings on the barrels of the glass syringes facilitate quick identification of the different dosages.

On account of the coloured rings already in use, further colour-coding options cannot be pursued since the range of colours is limited and depends on the energy input in the stress-relieving furnace (gas or electric heating). Furthermore, the effects which arise from heating during the sterilisation and baked-on siliconisation process cause the colours of the rings on the glass to change. Mechanical colour identification must therefore incorporate increased colour variance in order to guarantee clear assignment of the colours. With 16 colours such a method reaches its limits. Hence, the development of a novel method was the aim.

Requirements for the quality of machine-readable product coding

The optimal solution is to apply an individual, machine-readable code to each manufactured syringe. In line with the present state of technology, the data matrix barcode is perfectly suited to such an application. Very stringent requirements are placed on the fact that the code must be of a consistently high quality, in order to guarantee a high level of readability over the entire process.

Standards ISO/IEC 15415 and 16022 are used as the basis for evaluating the quality of the

data matrix barcode, although they in fact apply to flat, printed paper which has been printed with ink, for example.

In this project the translucent codes have been engraved by a laser technique on the transparent curved glass surface. Project-specific guidelines for quality assessment, similar to the said standards, therefore had to be developed.

Evaluation of different marking systems

The following criteria were to be considered when evaluating different systems for marking single glass containers and selecting the most appropriate method:

- no influence whatsoever from the product (drug formulation)
- readability and durability of the code
- mechanical stability of the glass unchanged after coding

Christa Fritschi
Director Marketing
T: +41 71 274 1602
F: +41 71 274 4244
E: christa.fritschi@schott.com

SCHOTT forma vitrum ag
St. Josefen-Strasse 20
P. O. Box
9001 St. Gallen
Switzerland
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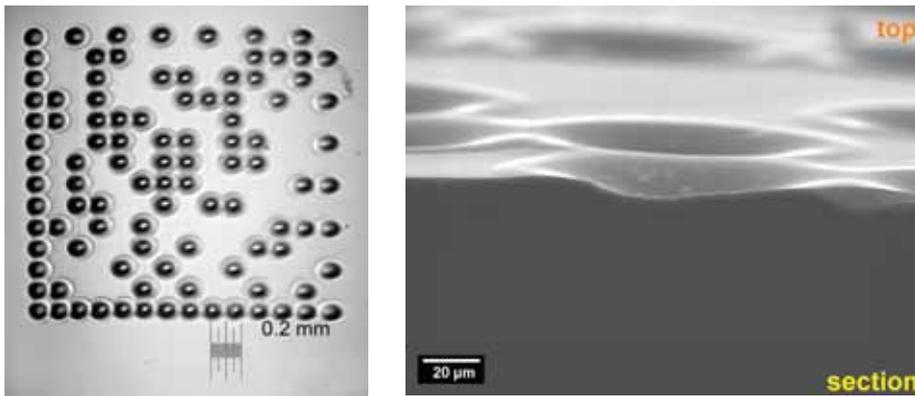


Figure 1: Left – Matrix code produced by CO₂ laser on heated glass guarantees there are no cracks. Right – SEM/BSE of the cross-section of a code enlarged 700-fold. The intact glass matrix is clearly identifiable.

A value benefit analysis was performed to ultimately select the preferred solution. The many variables to be considered were weighted according to their importance. An extensive evaluation process produced a shortlist containing several possible solutions, such as various laser, inkjet and pigment-transfer methods.

One possibility for identification was the ablation of a single layer or multiple coloured layers using a laser. High-contrast codes could be produced with such a method, but it would entail additional production stages. A further identification system for selection was the firing of cold glass with a CO₂ laser (wavelength 10.3 μm), although cracks appeared as a result.

The development of cracks is prevented by heating the glass to the transformation temperature. The selected method with CO₂ laser irradiation on hot glass thus guarantees that no cracks are generated during encoding (see Figure 1).

This laser method, further developed on the basis of a procedure for identifying special glass tubes for technical and pharmaceutical applications^{4,5}, was fully integrated into the process of syringe manufacture. The data matrix barcode is engraved thereby onto the hot glass barrel. Such a method has certain challenges: to apply a durable, easily readable code as well as to protect the glass matrix from microcracks during laser engraving.

METHODS

Content, structure and quality of the code

The coding is applied to empty glass syringes below the finger flange (see Figure 2), guaranteeing unimpeded transillumination when reading the code.

The content of the square code – unique to each glass syringe – involves a sequence

Figure 2: Position of data matrix code below the finger flange.

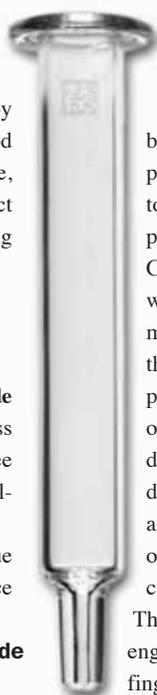
of 16 symbols containing packaging data (glass type, syringe format, labeling site, production line, date of manufacture, batch number) and a serial number. The Data Matrix ECC 200 measuring 14x14 with a perimeter length of 2 mm was chosen as the barcode symbology.

Laser coding process

SCHOTT FIOLAX® clear glass tubing was used in this project as the starting material for the syringes to be filled. It is made of borosilicate glass of hydrolytic class I, with a transformation temperature of 565°C.³ An already established laser method^{4,5} was further developed within the syringe forming process and the coding device integrated into the existing manufacturing equipment. This entails the commercially available rotary indexing machine for syringe manufacture.

To optimise the laser process in terms of readability of the code, the long-wave CO₂ laser (wavelength 10.6 μm) was programmed to 20% of laser output power. The glass matrix to be marked was heated with burners and the achieved temperature recorded and controlled during the laser process using a pyrometer.

The scan head guarantees that the laser beam is accurately focussed at the desired position on the syringe barrel. In addition to the exact position, it also specifies the pattern of the data matrix barcode. The CO₂ laser head also produces laser pulses which are directed at the glass material by means of scan optics. The pulse length of the CO₂ laser is between 50 and 70 μs and produces temperatures locally of >2,000°C on the surface of the glass. Spots with a diameter of approximately 100 μm are produced on the hot glass by the laser firing, and result solely from the thermal effect on the surface of the glass. This process can be detected indirectly (see Figure 3). The entire data matrix barcode of 2x2 mm is engraved on the cylindrical section below the finger flange (Figures 2 & 3).



If the transition temperature of the glass is not achieved during the laser process, the syringe is rejected immediately thereafter. This is to ensure that only crack-free, coded material is conveyed further.

In order to relax the thermal tension of the glass barrel induced by the manufacturing process, the syringes are ultimately conveyed through the tensile stress relieving furnace. The temperature in the furnace corresponds to the transition temperature of the glass.

The geometric, cosmetic and qualitative properties of the coded syringe are then subjected to visual inspection and several quality control tests.

Optical reading of the code

The 14x14 data matrix barcode is optically read from the surface of the glass syringe. Thus it is possible to produce a variable number of images of the syringe surface. A special image processing system was designed for multiple imaging, comprising illumination, camera and synchronisation to the handling of the syringe barrel.

The images were taken using LED flashlight. The code was backlit (transmitted light method) and the camera delivered a black and white image to the image processing software. Maximum reflection causes the cavities produced by the laser process to appear as white spots on a black background. This is a result of the effect of the lens on local deformations (Figure 5 on page 16).



Figure 3: The process of applying the matrix code. A light can be seen at the point of impact of the laser.

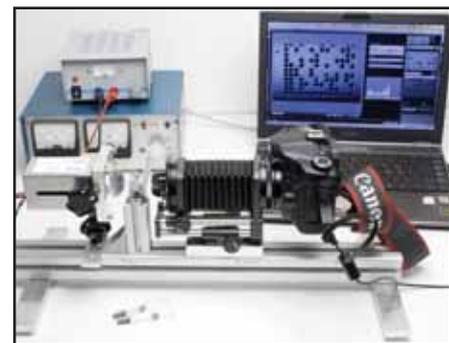


Figure 4: The testing station

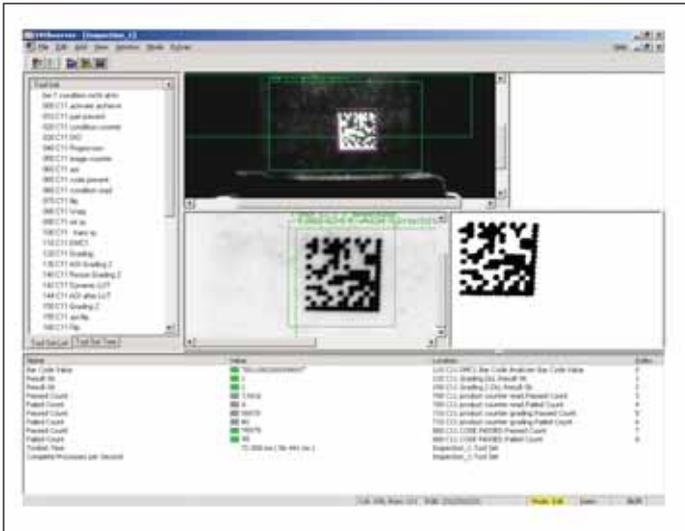


Figure 5: Screenshot of SVObserver with analysis of the code.

The total processing time of the reading phase, including data transfer, is between 20 and 200 milliseconds per syringe, from the point of localisation of the code on the glass. Software (SVObserver, Seidenader) then reads and analyses the 14x14 data matrix barcode. Special filters and additional tools are used to optimise the evaluation of the code.

Based on the scanned image data, the data matrix barcode is decoded and the data saved as well as the quality of the code checked. The glass barrels are then sorted according to quality criteria and released into the filling process. The data saved from the scanned code are transferred via a qualified interface to a superordinate ERP system (PI server).

The clear correlation between data set and medication takes place at the time of filling the solution for injection into the glass syringe.

During the entire production chain of the preparation on the filling and packaging line, the glass barrel undergoes two scanning and assessment steps. The first scanning step ensues

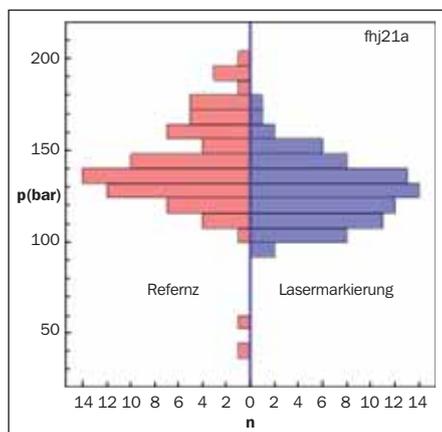


Figure 6: Double histogram of burst pressure testing.

prior to siliconisation and sterilisation of the glass syringes. At the end of the filling line the syringes are scanned a second time.

Quality controls

With a view to technological development, tests were carried out to check the quality of the coded glass syringes as well as the code itself.

The syringes were exposed to thermal stress: resistance to high temperatures was tested for 30 minutes at 230°C, and resist-

ance to low temperatures for a week at -20°C and -40°C.

The syringe and code were exposed to mechanical loads: the glass syringe barrels were subjected to hydrostatic burst testing (constant pressure at a rate of 10 bar/sec until rupture) and the resulting fractographic tests analysed (SCHOTT Research). Distilled water was used as the pressure medium.

In order to expose the data matrix barcode to high frictional loads, the parameters were selected in such a way that limit samples emerge. The code was subjected to a friction test using a crockmeter (Mathis) with an abrasive of

semi-friable aluminum oxide and silicon carbide with a grain size of P2500 with 50 strokes.

The code was examined on the surface and, after cutting the syringe across the coded area, the cross section analysed for microcracks. A polarised light microscope (PLM) and scanning electron microscope (SEM) with a magnification of up to 625x were used for these tests.

RESULTS

The integration of the coding process into the production line was successful and produced high-quality patterns which later could be successfully read, both before and after the pharmaceutical filling process.

Aside from SCHOTT FIOALAX® clear, two other types of glass were coded successfully, including SCHOTT BORO-8330™.

Reading of the code

To ensure that the code is visible on the syringe barrel, images are taken of the whole circumference of the syringe (see figure 5). To this aim the syringe is rotated while being conveyed by the apparatus past the camera station. Multiple images are produced in the visual field of the camera. Depending on the synchronisation of the rotation, distance and imaging, a variable number of images can be produced to cover the entire circumference of the syringe barrel.

High expectations were placed on the performance capabilities of the reading systems.

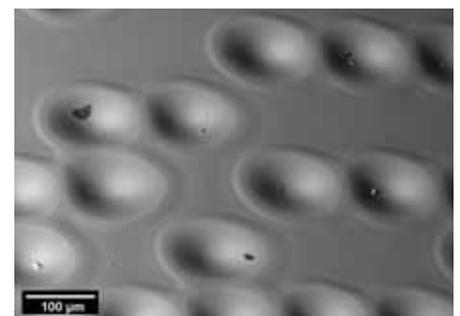


Figure 7: Left – total view of code enlarged 62.5-fold using polarised light microscope, non-analysed transmitted light (PLM/LPNA). Right – 200-fold enlargement of code using SEM/BSE.

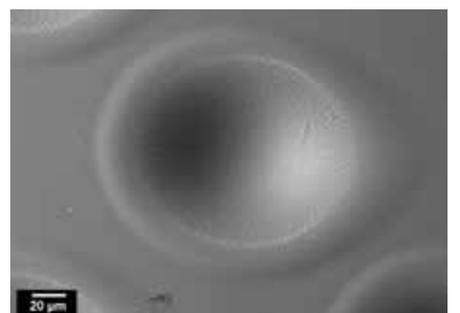
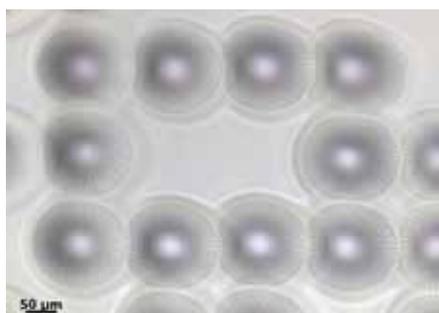


Figure 8: Left – section of code enlarged 250-fold using PLM/LPNA. Right – a code element enlarged 500-fold using SEM/BSE.

The coded syringe barrels were required to pass the test run to 99.9% before entering the packaging line.

To guarantee the prevention of mix-up, syringes of a second batch were deliberately intermixed. These samples differed only by their coded batch number.

The test run was successful. The run lasted 62 minutes, and 17,019 syringes were analysed. Of these, 1,474 items were rejected. This means all of the intermixed syringes were clearly identified. In 40 syringes the code had become contaminated, but was readable once cleaned.

Thus, avoidance of mix-ups is guaranteed and the proof of concept substantiated.

Quality controls

At a thermal load of 230°C, the readability of the samples was satisfactory. The low-temperature resistance testing at 20°C and 40°C did not reveal any damage to the glass resulting from the laser process.

During burst pressure testing, ruptures attributable to the laser marking were not detected. Defects causing breakage therefore were not produced under the applied parameters. No significant differences could be identified at these points between the laser-marked and non-

marked syringes (reference). That is, the laser-marking process does not cause any defects in the support points (see Figure 6).

When measuring the data matrix code quality of samples submitted to abrasion tests 90% were readable but 10% of the samples did not fulfill the quality requirements as defined in ISO 16022.

The samples subjected to optical testing revealed no cracks (see Figures 7-8). The quality testing reveals that the coded glass syringes were free of cracks, the mechanical stability of the glass barrels guaranteed and the quality of the coding sufficient.

CONCLUSIONS & PERSPECTIVES

It can be concluded that avoidance of mix-ups was guaranteed and the proof of concept substantiated. The glass barrels also passed all quality inspections. In particular, the glass matrix revealed no microcracks or mechanical damage due to the laser process. The described technology can be used for other types of glass pharmaceutical containers such as ampoules, vials and cartridges, in addition to syringes. Hence we have a promising, industrially proven process for the identification of glass containers.

The newly developed process described here for encoding and reading a data matrix barcode on glass pharmaceutical containers fulfills all the criteria for tracking and tracing, as well as prevention of cross-contamination. In order to be able also to apply this code in the prevention of counterfeits, a random number rather than a serial number should be used as the code. Such technology can also be used commercially to prevent drug counterfeiting.

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FINE TUNING OF PROCESS PARAMETERS FOR IMPROVING BIOCOMPATIBILITY OF PREFILLABLE SYRINGES

The complete automation of a processing line permits the continuous improvement of production while increasing the process knowledgebase. Here, **Andrea Sardella**, R&D Engineer at Nuova Ompi, underlines two areas in which, by investigating and tuning process parameters, relevant improvements have been achieved regarding biocompatibility.

Pre-attached needles are fixed in syringes by means of UV-activated adhesives specifically formulated for this application. Comprehension of the process, understanding the mechanisms and mastering its variables allows important improvements in terms of extractables. Alternative glue compositions have been tested as potential replacements for very demanding drug formulations.

Siliconisation seems to remain one of the processes required to allow good performance in the effective delivery of injectables. Many studies and projects have been set up to eliminate or at least reduce it and, nowadays, there are some alternatives on the market.

Prefilled syringes are one of the most challenging applications, where silicone is a key factor in combination with glass barrel, rubbers stoppers to obtain effective and accurate drug delivery. Combining packaging is a mandatory requirement for all the companies involved in development of primary packaging compliant to regulatory guidelines and GMP framework.

Working with pharmaceutical partners, Ompi has industrialised and improved a process allowing reduction of siliconisation spread minimising the presence of silicone particles in glass syringes.

Focus:

- Adhesive chemistry
- UV activation (photo-initiators)
- Materials compatibility (glass/steel)
- Dimensional compatibility
- FDA studies on Protein agglomeration due to silicon particles
- Reduction of silicon content by optimizing the spraying technology
- Controlled silicone distribution along the internal surface
- OMPI capability, optimised process

MEASUREMENTS OF POLYMERISATION DEGREE VS CURING DOSE

To develop a correct UV-curing recipe, Ompi started from the glue supplier specification (0.04 J/cm²) to achieve the nominal physical properties in terms of adhesion. The curing chemical kinematics was investigated by FT-IR Spectroscopy to measure the temporal evolution of carbons bonding in the acrylic group to verify whether the nominal dosing was sufficient to polymerize the glue completely (see Figure 1).

By this method we determined the complete settings of the relevant bonding at a value that differs by nearly a two orders of magnitude from the nominal value indicated by the glue supplier.

Evidently for the glue supplier “complete polymerisation” means the minimum energy required to achieve the nominal mechanical properties of the glue, not the energy required to polymerise it completely.

We decided to integrate the FT-IR results with UV-VIS Absorbance Spectroscopy (see Figure 2), which is more specific in monitoring the surface curing and provides a more accurate time evolution.

The measurements with UV-VIS indicates an even higher curing dose needed to polymerise the glue (3 J/cm²). The final slow tail in the absorption evolution is mostly due to the UVC part of the spectrum and so is mostly related to the surface of the glue (UVC has a depth of penetration of 10µm), probably this effect is due to the inhibitory effect of atmospheric oxygen.

It is important to notice that FTIR absorption and UV-VIS reflection data have an asymptotic



Andrea Sardella
R&D Engineer
T: +39 049 931 8111
E: andrea.sardella@stevanatogroup.com

Nuova Ompi
Via Molinella, 17
Piombino Dese
(PD) 35017 – Italy
T: +39 0499 31 8111
F: +39 0499 36 6151
E: nuovaompi@stevanatogroup.com

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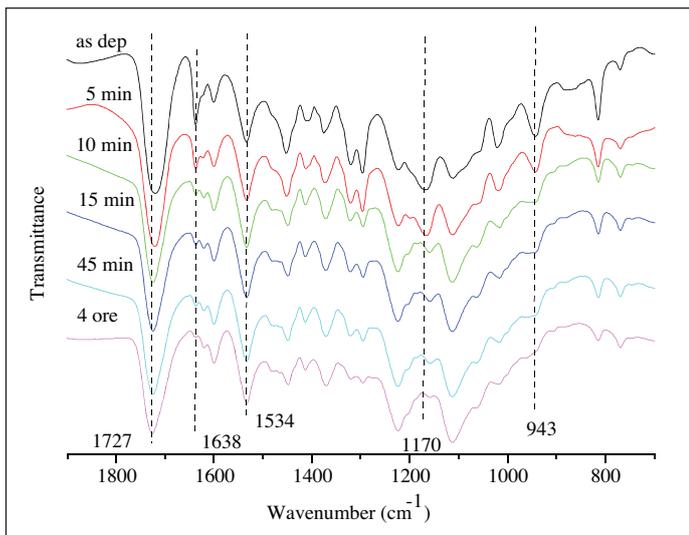


Figure 1: FT-IR transmittance

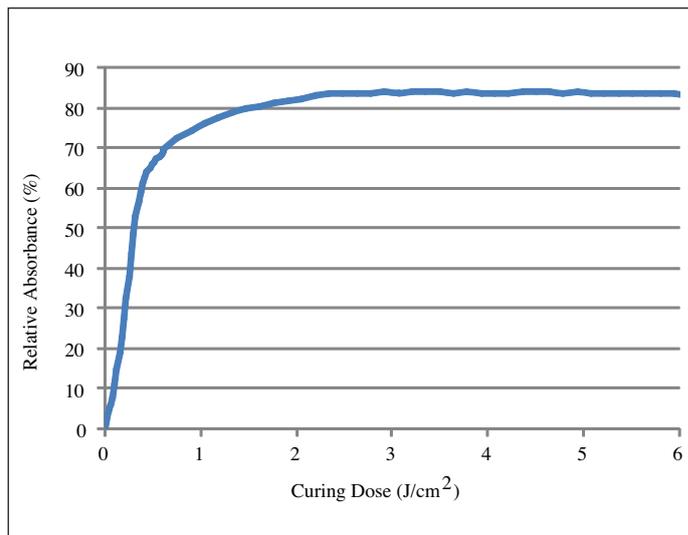


Figure 2: UV-VIS Absorbance evolution

behaviour so it is inaccurate to extrapolate the final degree of polymerisation from it.

To provide an independent determination of the polymerisation degree we directly correlated the curing dose to the maximum pull-off force (Figure 3) extending the investigation at higher dosing to check for any potential over-curing shrinkage that could be detrimental to the adhesion.

From the result it is evident that the maximum pull-off force continues to increase even after UV-curing at 3 J/cm² and up to 7 J/cm², and there is no evidence of degradation due to over-curing even when doubling the energy. To emphasise any potential glue instability due to improper curing we ran an accelerated aging test without finding any evidence of reduced force.

Achieving the requirements in terms of adhesion does not necessarily guaranty an adequate extractable level; standard requirements focus on adhesion between glass and needle but not on glue cohesion.

As we have seen there is no absolute indicator of complete glue polymerisation and we do not have a direct measurement to determine how the cohesion is influenced by the curing dose.

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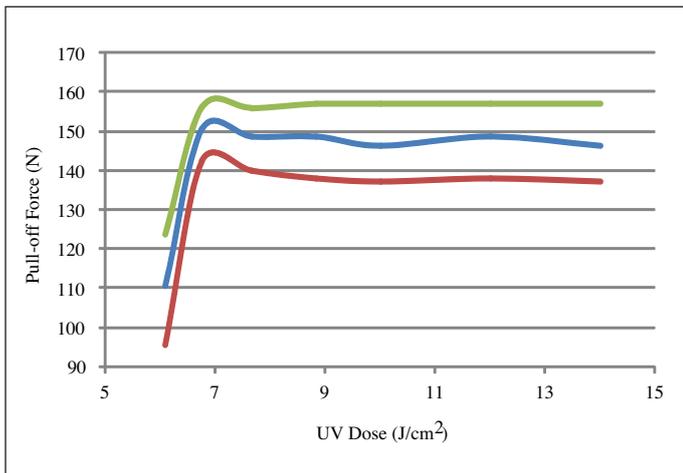


Figure 3: Pull-off force vs curing dose

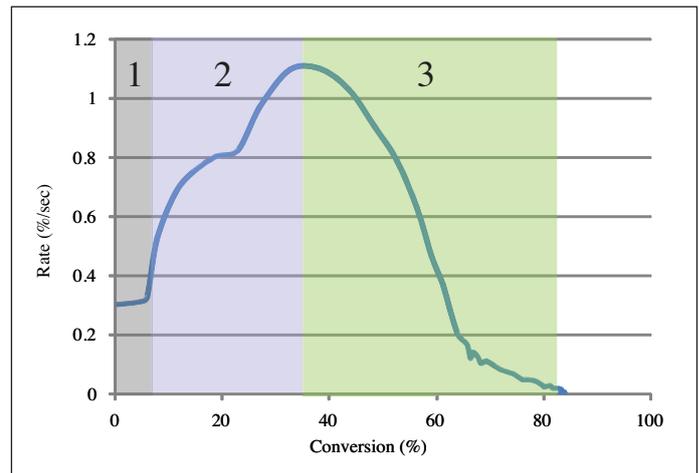


Figure 4: Conversion rate profile showing induction phase (1), auto-acceleration phase (2), and auto-deceleration phase (3).

KINETICS EQUATIONS

To improve our process knowledge we started from the polymerisation kinetic equations.

The free-radical bulk polymerisation of dimethacrylates is a complex process and exhibits a number of unexpected behaviours with respect to the reaction kinetics. For the sake of simplicity we identify three reaction phases (see Figure 4):

- Induction phase (1)
- Auto-acceleration phase (2)
- Auto deceleration phase (3)

The induction phase is a classical diffusion-controlled balance between photo-initiated free-radical concentration and single polymer chain termination rate.

The auto-acceleration phase is due to the gelation in the initial stage of the network formation as growing chains sharply increase in molecular weight and thus, viscosity.

As the viscosity increases during the formation, the mobility of the initiating photo-induced radical species in the network is restricted. Throughout this stage of the reaction, chain

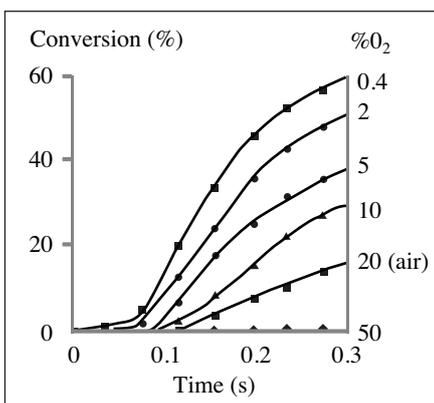


Figure 5: Oxygen inhibition³

termination is diffusion controlled and the termination constant is continually decreased. The decreasing termination rate leads to an increase in the number of macromolecular radicals. Because propagation is not as strongly diffusion controlled in this regime, the rate of polymerisation increases as the radical concentration increases due to photo-excitation from the external UV source.

Auto-deceleration or vitrification, on the other hand, begins in the third phase of the reaction as the rate of reaction reaches its maximum. The onset of vitrification occurs when the propagation of the network becomes equal to the polymerisation termination rate. This phase of the reaction continues until the reaction is essentially stopped.

The auto-deceleration causes the rate to decrease much more rapidly than can be accounted for by depletion of reactive groups. This event severely restricts the rate of polymerisation.

IMPROVED CURING METHOD

It is crucial to reach the highest possible conversion rate before vitrification begins.

The kinetic equations of free-radical polymerisation predict an increase in conversion rate with increasing light intensity, also the initial induction phase can be reduced by increasing light intensity, so it is fundamental how the curing energy is delivered.

The same curing dose but with higher intensity gives a higher conversion degree.

The auto-acceleration phase is due to reduced mobility of free radicals around the increasingly viscous polymeric network. Temperature increase inhibits the acceleration phase reducing the effects of high-intensity UV.²

Temperature increase, moreover, induces strain stress in the substrate and on the glue

itself so a multi-curing strategy with high intensity, short exposure pulses is more effective and less aggressive.

SURFACE POLYMERISATION: INFLUENCE ON EXTRACTABLES

The simplified scenario above is not adequate to model the surface polymerisation because it lacks to consider the role of oxygen. Oxygen is a well-known strong inhibitor of radical-induced polymerisation due to its high reactivity towards radicals (see Figure 5). By scavenging the initiator radicals, oxygen reduces the rate of polymerisation near the surface. UVC has a higher free-radical yield (by two orders of magnitude) and a short penetration depth (10µm), so UVC is important for fast oxygen consumption at the surface, increasing cohesion and sealing the surface to reduce potential extractables.

To test our conclusions, we have run extractables tests with and without the use of UVC to seal the glue surface, obtaining a reduction of nearly 50% in the extractables profile (see Figure 6).

UVC can be applied only with direct sight of the glue because Type I glass absorbs UVC quite strongly. It has therefore been necessary to develop a dedicated optical system to deliver a high-intensity UVC focused spot to the inside annular region.

BIOCOMPATIBLE SILICONISATION

The demand for enhanced biocompatibility requires advanced solutions to provide barrels characterised by two aspects in "conflict":

- Extrusion speed at minimum (high lubrication)
- Reduced overall silicone oil quantity

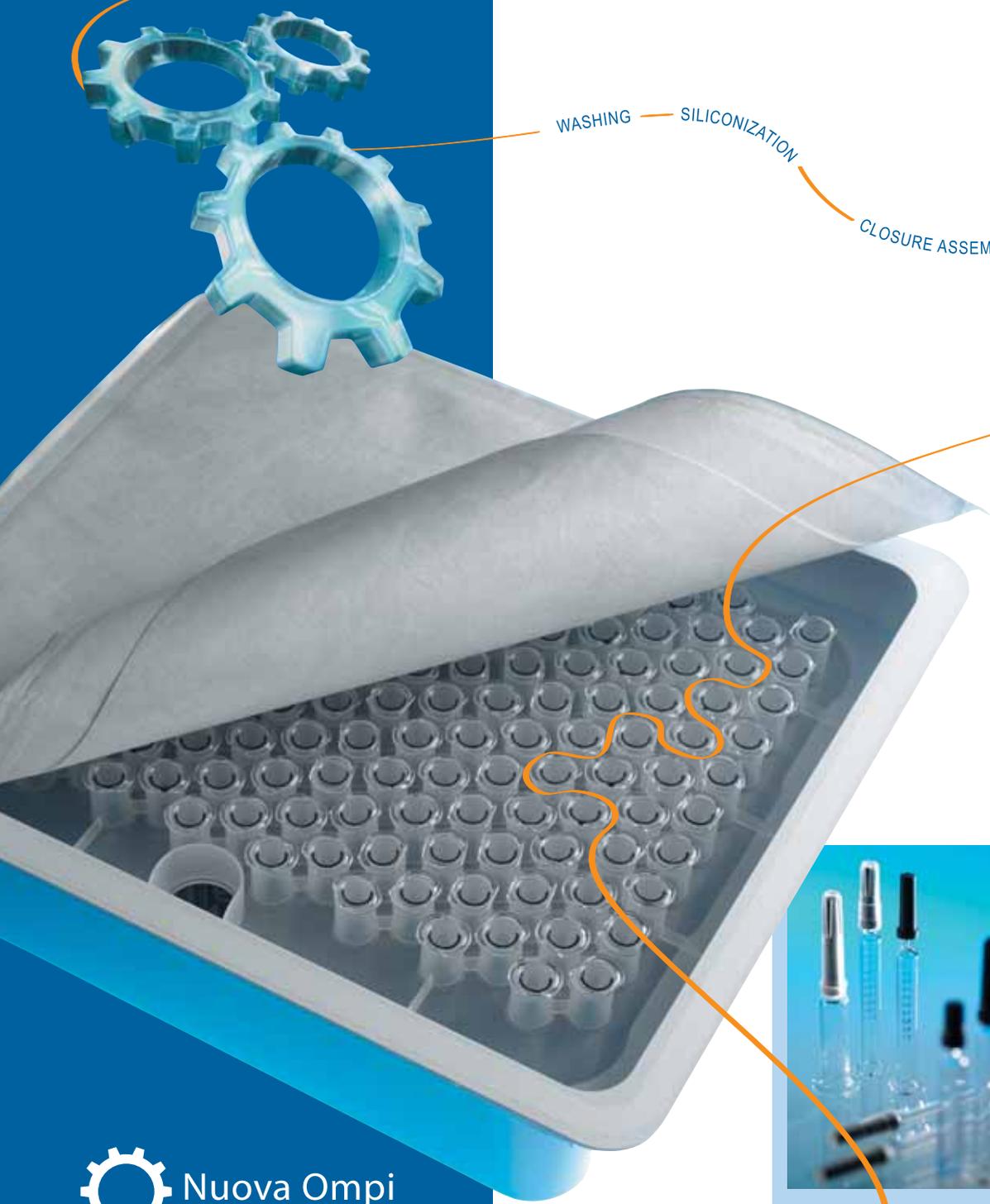
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READY TO FILL - THE EZ WAY

Despite the superior performances of the “diving nozzles” system currently used, an extended process evaluation was put in place to investigate the following points:

- Capability to produce samples with different patterns of silicone distribution
- Produce different droplet sizes and evaluate silicone aggregation
- Compare the microscopic detection method used at Ompi with one established by a customer

The full automation of our refillable syringe production lines provides several parameters that can be fine-tuned in order to set the optimal silicon oil deposition profile.

The amount of silicon is regulated through the micro-dosing pumps. The movement of the nozzle is configurable in terms of: speed of movement down-up and up-down; maximum height reachable by the nozzle inside the barrel; start and stop height of the air activation and silicone pumps activation.

The air atomisation pressure is also programmable: the amount of silicone dosed in each cycle is exploded inside the barrel through air turbulence that can be adjusted by the compressed air pressure.

Figure 7: Dynamic silicosisation timing

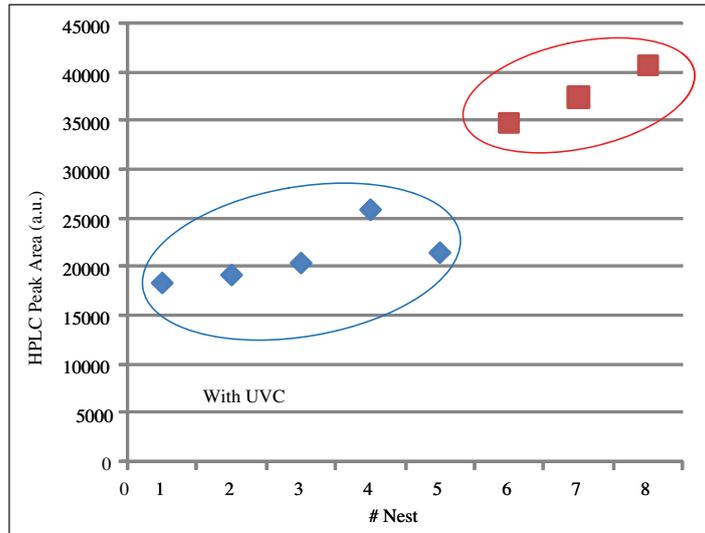
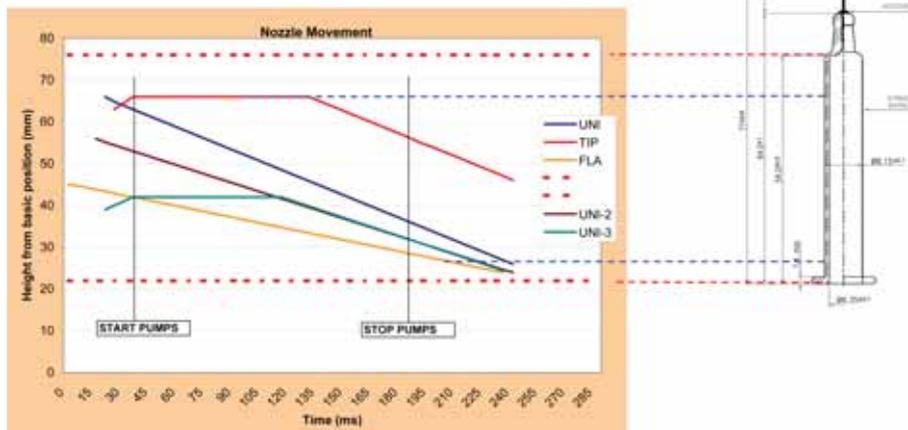


Figure 6: Extractable profile area vs UVC curing applied

EXPERIMENTAL TESTS

The standard operating set-up uses a static configuration satisfactory for most production. We investigated the potential improvement achievable with a dynamic set-up (Figure 7), in which also the timing of the different silicosisation parameters is changed, and tested it in the laboratory.

Anticipating the air activation with respect to the beginning of the up-down movement, the onset of the turbulence inside the barrel enhances silicone atomisation. The con-

trol of atomisation air pressure is directly correlated to the control of droplet size.

So increasing the air pressure and anticipating the air activation improved atomization, decreased the size of silicone droplets, and reduced the quantity of silicone oil used for achieving the same gliding force.

Different silicone activation/deactivation timing provides the ability to define a controlled deposition profile, while slowing the down-up movement gives a better control of the silicone distribution. Varying with nozzle speed and activation/deactivation silicone time, it is possible to produce any customer-defined

profile (Figure 8).

The distribution profiles and droplet size results measured by optical microscope have been confirmed by the use of the Gradience Instruments system. Further correlation tests made at a customer’s site demonstrated that the optimisation of distribution and droplet size has a direct effect of reduction of sub-visible particles in our prefilled syringes.

CONCLUSIONS

An in-depth investigation and fine tuning of the process parameters has increased our knowledgebase and identified improvements to our production process through optimisation of existing equipment, optimising the production yield and the quality reached in order to satisfy the stringent requirements of the biotech market.

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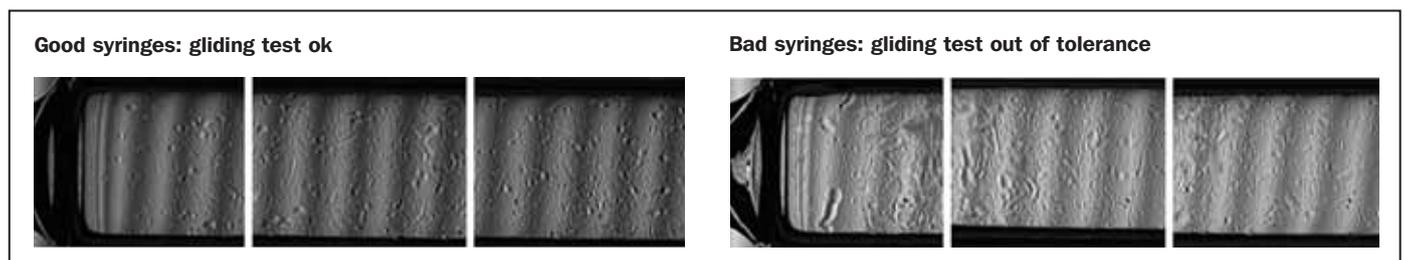


Figure 8: Distribution profiles with different droplet sizes



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For more information contact: Andrea James +44 (0)1483 730071
email: andrea.james@management-forum.co.uk
website: <http://www.management-forum.co.uk/medical>



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