



OMPI NEXA SYRINGES: THE IDEAL SOLUTION FOR THE MOST DEMANDING DRUGS

Here, Alessandro Morandotti, Technical & Quality Assurance Front-End Manager, and Rob Swift, Product Manager, both of Ompi, introduce the Ompi Nexa Syringe, and describe in detail how its design fulfills the challenging quality requirements for prefillable syringes used for the storage and delivery of biological molecules.

The origin of biotechnology and therapeutic biotech products can be traced to the discovery of DNA in 1953. Since that time, extensive research has explored the role of specific DNA segments or chains in biologic processes and diseases.

The key dates are in 1972-1973 when scientists at Stanford University carried out the production and replication of recombinant DNA. The basis of this technology is to introduce a segment of DNA from one organism into the DNA of another host organism. One important application of this technology is to use simple organisms or cells to produce human protein that has therapeutic use as a drug. The first therapeutic product based on recombinant DNA technology was insulin, which the US FDA approved in 1982. Since then, human growth hormone and numerous additional drug products followed these new discoveries.

One of the characteristics of the biotech drugs is the size and geometric complexity of the molecules. These specific aspects have as a consequence the relative instability of the product compared with traditional small-molecule drugs. As a result, the primary packaging materials used to store and administer therapeutic protein products play an important role. Therefore, bio-pharmaceutical manufacturers may require special properties for the packaging materials and for the interactions of the container system surfaces with the drug product formulation.

In many cases, bio-pharmaceutical companies utilise lyophilisation – freeze drying – to ensure the long-term stability of protein products. However, ongoing developments in formulation science are allowing more products to be introduced as liquids for patient convenience and advantage. When this is possible, drug product presentations in prefillable syringes or auto-injectors often are the preferred marketing choice.

THE OMPI NEXA SOLUTION

Today it is common to refer to the syringes used for storing biotech drug as “Biotech Syringes”. The idea of identifying these goods is to highlight that behind these syringes there are specially developed manufacturing processes based on the key requirements for the syringes dedicated to biotech drug products. Thanks to the experience from working on different development projects involving drug products, Ompi decided to put together the different identified solutions and to offer a new syringe called Ompi Nexa Syringe (see Figure 1).

This special glass primary packaging can be considered the ideal pharmaceutical packaging solution for biotech drugs. Its key elements are:

- increased compatibility between drug and container
- minimum risk of false rejects of filled syringes
- improved auto-injector compatibility
- superior gliding performance.

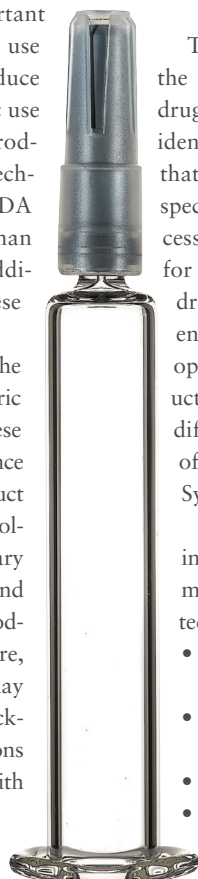


Figure 1: The Ompi Nexa Syringe.



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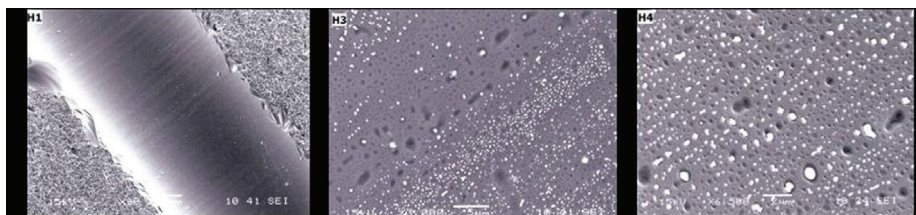


Figure 2: SEM images of showing different Tungsten residuals species.

In addition to the abovementioned features, Ompi is also able to assure regulatory support and a more proactive quality management.

INCREASED COMPATIBILITY BETWEEN DRUG & CONTAINER

In 10-15% of cases, drug formulations have a high to very high sensitivity to one or more of the components of a primary container. During shelf life, interaction between the drug product solution and silicone lubricant on the inner wall of the syringe can result in silicone droplets – typically in the 2-5 μm range. There have been some reports of protein aggregation linked with interaction with silicone.

To overcome such issues with silicone, the numerous experiments have led to an optimised siliconisation process in terms of both silicone distribution and droplet size. Each of these parameters may be factors in silicone particle generation.

Similar issues can be generated also by interactions between the drug product and with the leachable elements of the container system.

The Ompi Nexa Syringe has been developed to optimise the following attributes:

- A) Low tungsten through a new specific forming process
- B) Low leachables from the adhesive by using an improved needle assembling process
- C) Low particles thanks to an innovative washing process of the syringe barrel.

A) Low tungsten through a new specific forming process

Tungsten is introduced into the syringe during the forming process from the pin used to create the internal channel on the barrel tip. This material is used because of the good combination between resistance to high temperatures and mechanical properties. Tungsten residuals appear in different species (Figure 2).

The tungsten metal begins to oxidise to tungsten oxide at about 400°C. Near 800°C this oxide starts to sublime and during the process these vapours are deposited to the glass surface. The contribution of the tungsten residuals is due to the mechanical contact and the high temperature of the pins.

The factors influencing the tungsten residuals include temperature and mechanical contact.

Following these principles, Ompi introduced a new forming system to reduce the temperature of pins and to create a sort of protecting layer reducing the interaction as well. The Ompi Nexa Syringe with the optimised forming steps can offer an extracted residual of W mean <250 ppb (Tested according to Ompi internal method ICP-OES).

B) Low extractable from adhesive through improved needle assembling process

Originally, the process for validation of needle assembly developed at Ompi has been centered on the mechanical properties of the assembled syringes (needle pull-out force). However, thanks to a specific customer request to have ultra-low adhesive extractables, different improvements have been put in place meeting this new requirement. These improvements were achieved through a strong collaboration with the customer to develop not only a modified production process but also an adaptation of analytical methods. Up to now, there are no standardised laboratory methods for these specific tests.

The photo-polymerisation theory states that to reach the best adhesive performances (UV curing adhesive) in terms of adhesion and cohesion, the highest UV energy must be applied at the beginning of the polymerisation process. In fact, the polymerisation reaction can be divided into three steps:

1. a constant normalised rate of classical radical chain (see Figure 3, Region 1)
2. a dramatic increase in polymerisation rate (auto acceleration) due to the Trommsdorff effect (Figure 3, Region 2)
3. a rapid decrease in the polymerisation rate as a result of radical isolation: vitrification (Region 3 of Figure 3).

Significant amounts of unreacted functional groups are available in networks cured at low temperatures as a result of vitrification. For this reason, it is crucial to reach the highest possible conversion before the beginning of vitrification. Considering these principles, Ompi has redesigned the needle assembly process and developed a testing method focused on reducing the level trimethylolpropanetrimethacrylate (TMTPMA) – a specific chemical marker for incomplete polymerisation of the adhesive. With the new optimised adhesive curing process, the level of extractable of TMTPMA is typically below the detection limit (<0.05 μg per syringe).

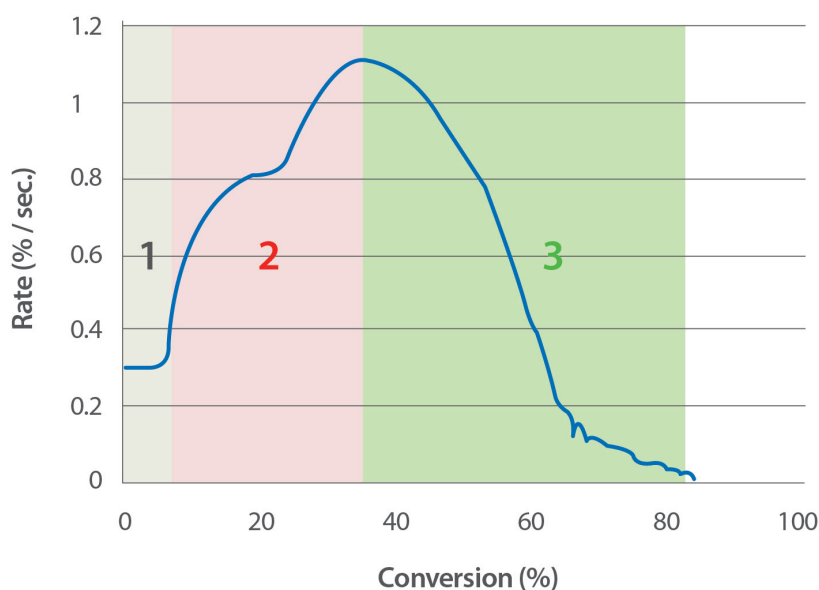


Figure 3: Graph profiling the rate of polymerisation during the UV photocuring process.

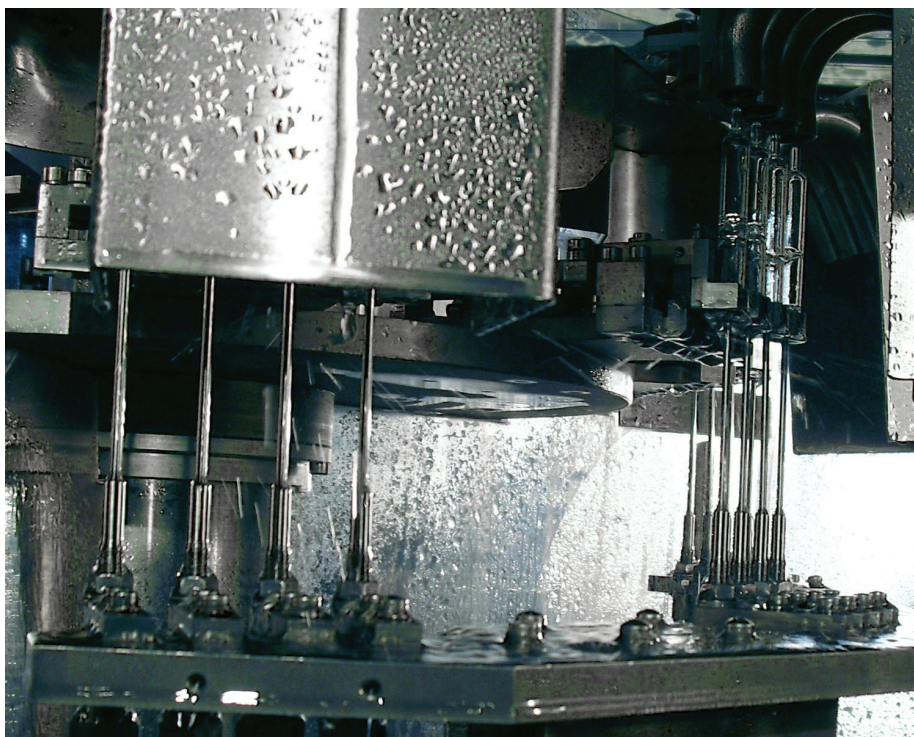


Figure 4: Ompi's high-pressure syringe barrel washing machine whose introduction means that Ompi Nexa Syringes can offer ultra-low particle levels.

C) Low Particles thanks to an innovative washing process

As particulate-related issues could potentially lead to injection failure in syringe products, particulates have become an increasingly critical concern in the pharmaceutical industry. Most of the particles are already present in the raw material (glass tubing) rather than a consequence of the converting process.

As standard practice, the glass tubes are received from the suppliers and then they are introduced into the forming process leaving them as they are. During the production of the glass cane at the supplier site the process is designed to offer raw materials respecting dimensional, chemical and quality attributes.

Specifically for particles, many efforts are put in place for minimising the issue even though the presence of particles due to the cane manufacturing process cannot be avoided. The issue is becoming even more relevant when the size limit for the particles is reduced. In this case, the raw material itself cannot meet this requirement and additional steps in the process are needed to eliminate the particles inherent in the tubing production process.

For this reason the forming process has been improved by developing a high-pressure washing machine (Figure 4) washing each single syringe barrel after forming in order to eliminate the parti-

cles already present on the raw material and also any that may be generated during syringe barrel forming.

As a result of the introduction of this process improvement, Ompi Nexa Syringes can offer very low particle levels.

MINIMISING RISK OF FALSE REJECTION OF FILLED SYRINGES

The manufacturing process for the Ompi Nexa Syringes is not only designed to have a good compatibility with the drug but also to assure the best cosmetic quality. Cosmetic quality can be considered as a secondary element. However, all the syringes must be inspected after filling and, considering that the inspection is linked to critical attributes such as small foreign particles and container closure integrity issues, inspection is based on very tight acceptance criteria. Therefore, it is possible that filled syringes may be rejected due to a cosmetic defect of the glass syringe barrel even though there is no impact on drug product quality. Such "false" rejections due to the secondary defects have a direct impact on the manufacturing costs creating losses and additional expenses and reducing the output of the manufacturing process.

The new Ompi Nexa Syringes are produced according to a specific manufacturing process in which glass-to-glass and glass-to-metal contact have been dramatically

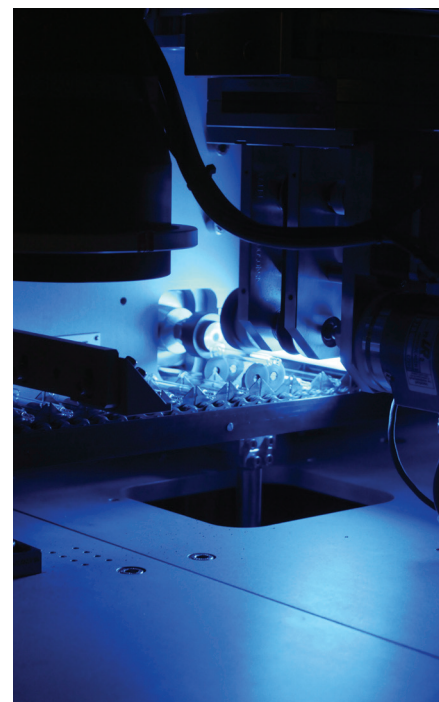


Figure 5: Automatic camera inspection systems monitor quality along the entire manufacturing process.

reduced. These are key factors to produce the desired Ompi Nexa quality.

In addition, to certify the quality of Ompi Nexa Syringes, specific automatic camera inspection systems monitor the quality of the product all along the manufacturing process (Figure 5). The results are stored and analysed before releasing the syringe batch. As results of the gentle handling process and the new camera inspection systems, we have been able to reduce the cosmetic defect rate significantly and offer a superior quality.

INCREASED AUTO-INJECTOR COMPATIBILITY

As a general consideration when we are speaking about drug products in prefilled syringes, we are always thinking about auto-injector devices as an option. It does not mean that all syringes are used in combination with auto-injectors but in the last years, there is an evident trend of increased demand for auto-injectors, because they:

- hide the needle from the user which can help to overcome needle phobia
- generally include safety features to prevent needle-stick injuries
- simplify the injection process which may benefit users with limited dexterity
- could enhance patient compliance through ease of use and lower perceived pain
- may offer a marketing advantage over

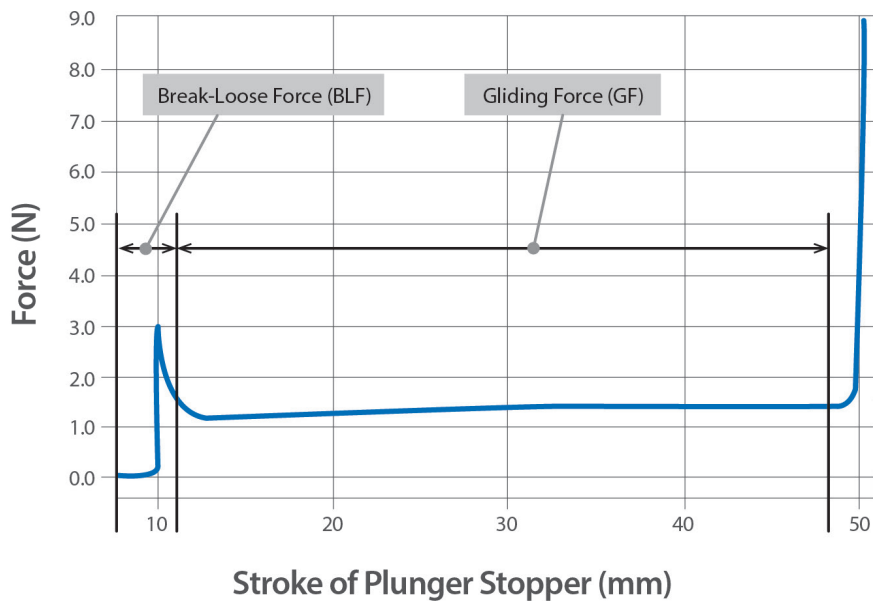


Figure 6: Graph profiling the force required to depress the plunger (break-loose, then gliding force) down the syringe barrel.

competitive products in the same therapeutic area

- can support drug product lifecycle management.

Looking at this list of benefits it seems obvious that auto-injectors are an attractive option for patients and caregivers as well as for biopharma companies. However, incorporating a prefilled syringe into an auto-injector introduces some challenging new requirements for the dimensional and functional attributes of the syringe.

Assembly and operation of the auto-injector may require tighter dimensional tolerances of the syringe flange, body and shoulder. Ompi Nexa Syringes are able to meet these new requirements thanks to manufacturing processes with minimal glass-to-glass contact, a precision forming process and sophisticated dimensional camera inspection systems.

Assembly and operation of the auto-injector may also exert new or different mechanical forces on the syringe when compared with manual injections. As such, syringes for auto-injectors may need to have greater strength. To achieve this, the prevention of surface flaws is a key factor. In Ompi Nexa Syringes, this is accomplished through the dramatic reduction of glass-to-glass contact and verified for each syringe barrel by the cosmetic camera inspection system of the Ompi Nexa production process.

SUPERIOR GLIDING PERFORMANCE

Glide force measurement of empty syringes is a way to characterise the effect of syringe and plunger friction on the overall force required to administer the dose. Typically, this requirement is

defined as two distinct forces:

- Break-loose force: the initial force needed to start the injection stroke
- Gliding force: the continuous force needed to sustain motion during the injection stroke.

Figure 6 shows a series of glide force measurements where the force applied to the plunger is plotted on the vertical axis. The horizontal axis shows the distance the plunger has moved along the injection stroke. At the right side of the figure, the force rises rapidly at end of the stroke when the plunger contacts the inner surface of the syringe shoulder. A similar test procedure typically is performed using filled syringes to measure the break-loose and extrusion to deliver the drug product.

The uniform and homogenous distribution of the Ompi Nexa siliconisation process results in consistent and predictable gliding force behaviour required for demanding biotech and auto-injector applications.

CONCLUSIONS

The Ompi Nexa Syringe can be considered the optimised packaging solution designed around key attributes linked to the drug product storage and administration.

Thanks to the increased compatibility between drug and primary container and the reduced level of false rejections due to quality level, Ompi Nexa Syringes are improving the timeline for stability studies and reducing costs during the fill-finish operations. Regarding the combination with auto-injectors or safety devices, the design of the syringes has been optimised to offer improved performance and reduce risk of failure. Last but not least, the optimised siliconisation process offers a superior gliding performance that is key, especially for auto-injector platform solutions.



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Increased
compatibility
between drug
and container

Better silicone oil
distribution and low
level of tungsten

Improved
auto-injectors
compatibility

Restricted tolerances
on syringe's flange
and shoulders

Superior gliding
performance

Optimized silicone oil
distribution inside
the barrel

Minimum risk
of false reject
of filled syringes

Advanced cosmetic
inspection technology

