Enabling a Healthier World

Lonza Biologics

White Paper

Straight to Market in an Autoinjector

A smart, data-driven approach to formulate biotherapeutics for PFS with confidence

Jean-Sebastien Steffen, PhD, Group Lead
Combination Products and Primary Packaging, Lonza

The global prefilled syringe (PFS) market was estimated as $7.22 billion in 2022 and is forecast to grow to $16.32 billion by 2030 [1]. The use of PFSs to administer biotherapeutics is beginning to gain traction because they offer a range of stability, efficacy, and patient safety benefits [2]. Lonza has developed a novel workflow to ensure confidence regarding functionality in PFS and autoinjectors.

Introduction

For biotherapeutics manufacturers prefilled syringes (PFSs) can provide flexibility in drug delivery options as they can be designed to accommodate a range of drug product (DP) viscosities, volumes, and administration routes. Their use can also reduce waste because PFSs can deliver an exact dose. This minimizes overfilling from a vial and reduces medication waste which can result in cost savings, as well as greater environmental sustainability.

For patients they can also provide many benefits such as accurate dosing. Since PFSs are manufactured with precise volumes, this can reduce the risk of dosing errors. Using a PFS also helps minimize contamination risks, as PFSs are filled in controlled cGMP environments and patients do not have to fill a syringe themselves from a vial which can reduce the potential for introducing contaminants during administration. Finally, they are convenient to use, and patients can self-administer their biotherapeutic without having to go to a hospital setting or have time-consuming IV infusions. This can help ensure compliance with regulatory standards and guidelines for drug administration, leading to safer and more consistent patient care.

Assessing a biotherapeutic for use in a PFS

Although PFSs offer numerous advantages, their implementation can also come with challenges such as packaging, storage, and compatibility with specific drug formulations. The decision to use a PFS should therefore be based on a careful assessment of the specific biotherapeutic formulation, the patient population it is aimed at and the healthcare setting it will be used in.

To evaluate the clinical application of a new biotherapeutic as quickly as possible, the drug substance (DS) will be formulated as a highly concentrated drug product (DP) in a vial presentation. However, as the biotherapeutic advances towards commercialization, most DPs require a presentation that can be easily administered by patients in a home setting. This can be achieved by filling the DP into a PFS assembled into an autoinjector. However, ensuring functionality of a PFS can be challenging or may even be impossible after the DP formulation has been locked down and approved by regulators. Using a PFS may not be suitable at this point because the high concentration of the DS in the DP formulation can cause greater viscosity [3] so that the autoinjector cannot easily expel the liquid DP. Additionally, if the target patient population suffers from dexterity issues, they may not have the strength to inject themselves, especially if the DP is too viscous.

There are currently few science based approaches to evaluate the risk of a DP not being suitable for PFS use prior to formulation lock. This is because in the initial stages of formulation development, most alternative formulations are only evaluated for stability. As DP production is low volume and limited quantities are available for evaluation, stability testing is usually prioritized. Additionally, the force required (injection force) to expel the liquid from the PFS is a multifactorial phenomenon and therefore requires a sizeable number of fully filled PFS samples for testing to generate meaningful results, which requires dozens of mLs of solution for each DP candidate.

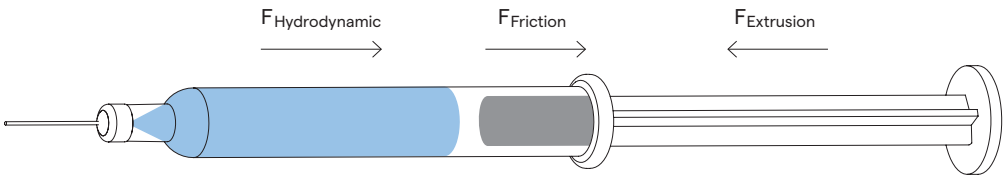
Considering that the clinical effectiveness of any biotherapeutic, as well as its stability/expected shelf life are uncertain at this development stage, scientists are forced to neglect a range of considerations. This often means they do not evaluate the syringeability (ability to expel the DP presentation from the syringe) and only deal with the consequences later, when it can be time consuming and expensive to rectify.

There is therefore a growing need to better manage this risk when developing new biotherapeutic products for use in a PFS. In this article we discuss how Lonza has developed a unique model to predict injection force designed to decorrelate factors linked to formulation development and the ones linked to container and delivery device selection. We will include technical considerations and case studies, as well as explaining how partnering with Lonza may help to overcome some of the challenges associated with selecting the optimum biotherapeutic presentation and PFS combination.

Challenges of developing a functional formulation for use in a PFS

Evaluating a DP formulation for use in a PFS with an autoinjector involves several challenges that scientists must address to ensure the product is functional (see Figure 1). In addition to protection against drug degradation and preserving drug stability over its shelf life, other key issues include assessing the injection force required to expel the liquid from a PFS. This depends on the formulation (viscosity) and the type of needle [4]. Typically, scientist base their assessment on an injection force model based on the Hagen-Poiseuille equation and crude approximations of the viscosity of the DP formulation and of the PFS geometry. The Hagen-Poiseuille equation calculates the resistance of a liquid flowing through a pipe, which in this case is the syringe barrel and the needle. However, crude approximations fail to provide reliable enough insights that can influence the development of the DP formulation. Such formulation development also cannot leverage injection force testing data, as these require significant quantities of DP that are not available in the early stages.

$$F_{Extrusion} = F_{Friction} + F_{Hydrodynamic}$$



$$F_{Hydrodynamic} = \frac{8 \cdot \pi \cdot \mu_{liquid} \cdot l_{needle} \cdot r^4_{barrel}}{r^4_{barrel}} \cdot Speed$$

Figure 1
Considerations for building a robust model to predict the injection force required to expel a biotherapeutic DP from a PFS.

Case Study 1: Assessing the standard injection force model

To define our baseline and better understand the limitations of the current practices, we wanted to determine the accuracy of the injection force model that is commonly used to predict injectability performance of a biotherapeutic DP from a PFS. We used the Hagen-Poiseuille equation with PFS barrel data (based on available manufacturer's specifications) and drug viscosity data from four different monoclonal antibody (mAb) formulations (designated A,B, C and D) at concentration ranging from 180 mg/m – 210 mg/mL to predict the injection force needed for expelling a liquid DP from a PFS. To compare the predictions with the actual force needed to expel a DP from a PFS, we filled syringes with mAbs A, B, C and D using our state-of-the art laboratory filling capability. Injection force was then measured for each filled syringe using Lonza's equipment and techniques that are used for late stage projects. The results (Figure 2) show there is a high variability in predicted force (shown in blue squares) and though the actual injection force measured is within the predicted range, the uncertainty of the standard model indicates it is not sufficiently accurate for use in practice to assess injectability performance.

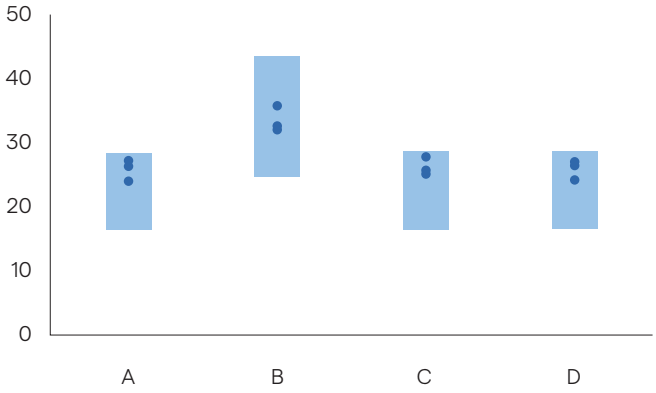


Figure 2
Standard model predicted (blue squares) versus actual (blue dots) injection force required (N) to expel four mAb formulations (A, B, C, D) concentrated at 180 mg/mL – 210 mg/mL.

Improving the injection force model for predicting injectability of a DP

The standard injection force model only takes into account limited data on formulation properties and syringe geometry, but by adding in accurate PFS property data (such as needle diameter and length) and precise rheological characterization of the liquid DP (see Figure 1), for example changes in viscosity caused by shear thinning, could improve the model.

Case Study 2: Generating accurate PFS property data to provide an improved predictive injection force model

For PFS property data, we had data from the PFS manufacturers but needed detailed characterization of the radius and length of needles in a PFS. Performing these types of measurement accurately is difficult and requires highly specialized, expensive equipment. To generate this data, in this study we used two thin-wall needle types (27G TW and 29G TW) that have been used in previous studies for injectability of biotherapeutics [4]. To perform accurate measurements, we leveraged the internal capability and expertise available in Lonza's analytical imaging laboratories and used their state-of-the-art proprietary systems to measure the needle diameter using imaging techniques and the needle length optically and by X-ray shadow imaging. Our results (Figure 3, next page) show that there is low variation in needle diameter. They also demonstrate (Figure 4, next page) that needle length is equivalent for 27G TW, and 29G TW needles and X-ray shadow images confirm that there is low variation in needle length (3s = 0.15mm). Therefore, using these highly-specialized optical and X-ray shadowing techniques to generate data for our model offers significant improvement over diameter and length measurements provided by the manufacturers.

Inner diameter of the needle

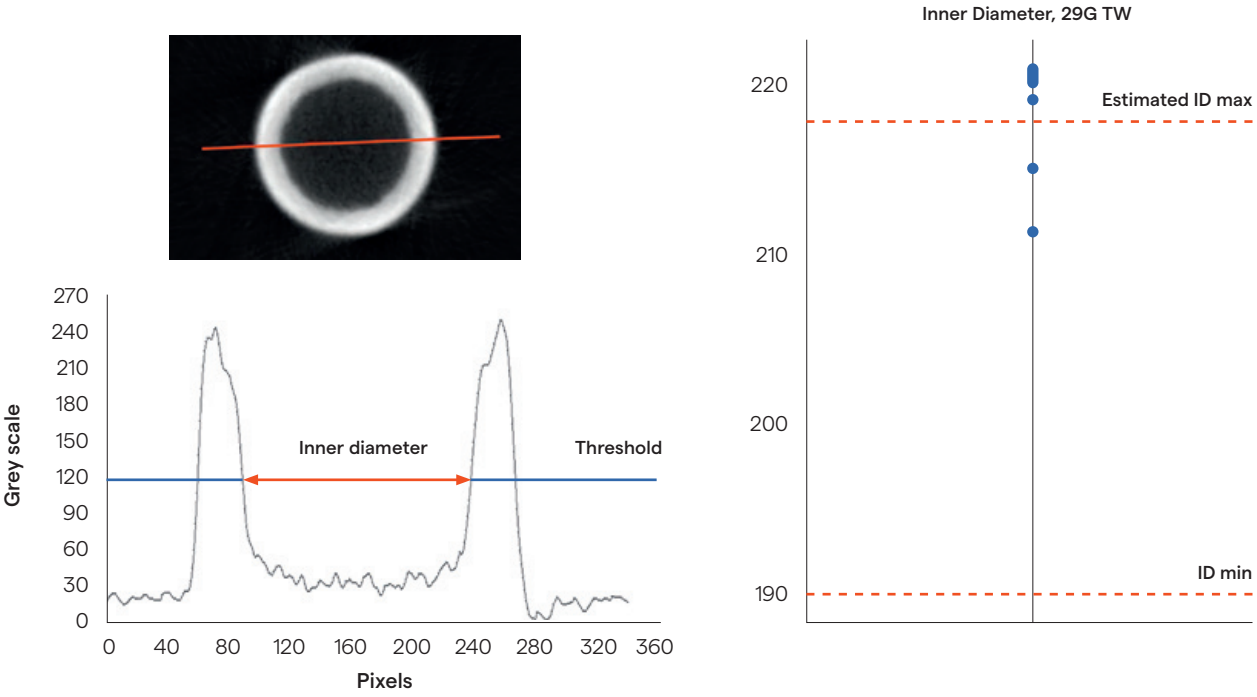


Figure 3
Diameter of needle (29 G TW) measured by optical imaging.

Length of the needle

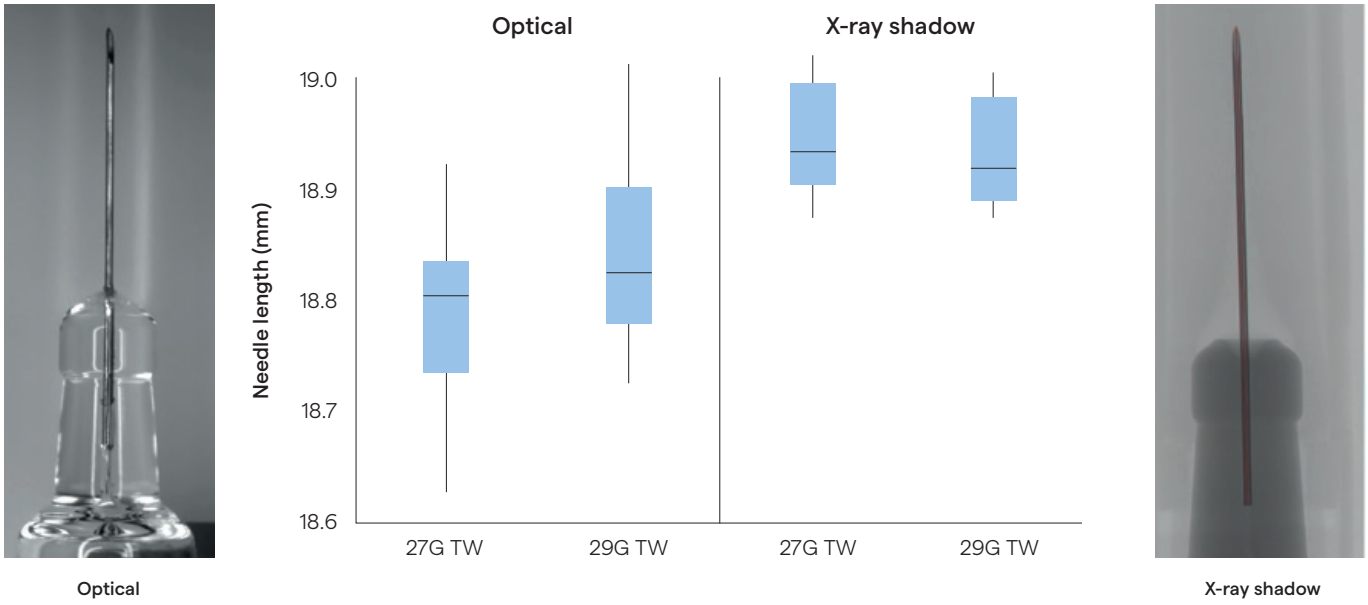


Figure 4
Length of 27 G TW and 29 G TW needles measured by optical imaging and X-ray shadow imaging.

Case Study 2: Continued

Using our needle diameter and length data we calculated the predictive force for mAb formulations A, B, C and D, used in our first injection force model and compared it with the actual measured forces. (Figure 5) Our results show that using detailed PFS characterization data instead of rough estimate from supplier's specification significantly reduces the variability of the model, bringing it to an acceptable level. However, the correlation between actual and measured force is variable across the mAb DS used. For example, measured injection force of mAb B, C and D are on the lower end of the predicted interval and the measured injection force for mAb B is even smaller than the lower end of the model.

This second model gives a more precise indication of the injectability of a formulation. However, it slightly overestimates the related risk. While it is effective in detecting formulations for which the injectability will not pose issues, it might lead to forego the PFS development of a promising formulation.

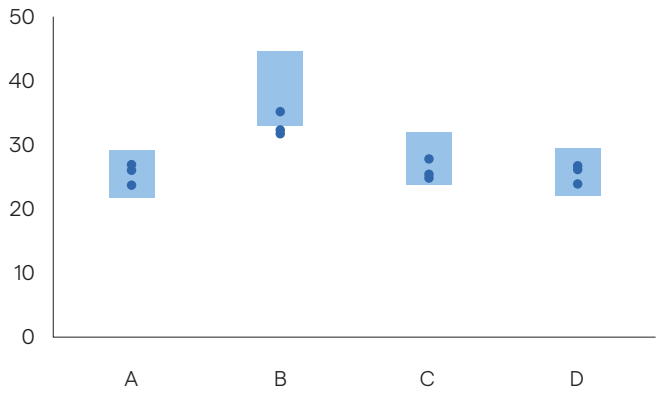


Figure 5
Improved model predicted (blue squares) calculated including the PFS data versus actual (blue dots) force required (N) to expel four mAb formulations (A, B, C, D) concentrated at 180 mg/mL – 210 mg/mL.

Case Study 3: Refining the predictive model to deliver a viscosity model

Since including Lonza proprietary measurement techniques and data on the PFS has improved the quality of our injection force model, we wanted to determine if we could refine our predictive model even further, by the addition of accurate characterization data on the liquid formulated DP (Figure 7). It is reported that concentrated biotherapeutics may show significantly reduced injection force because of shear-thinning (non-Newtonian) behavior [7], which makes the liquid less viscous and easier to inject. Therefore, we decided that we wanted to assess the rheology of the DP to determine how its viscosity changes linked to shear rate.

To determine how viscosity of the formulation is varying depending on the shear rate, we loaded mAbs A,B,C and D at the different concentrations, we used in Case Studies 1 and 2 in an automatic, high throughput Viscometer VROC® Initium One Plus System from RheoSense. In this system shear rate is controlled via flow rate and channel dimensions. Shear stress is calculated by measuring pressure changes (Δp) as the DS flows through the channel (Figure 6) and this also allows calculation of viscosity of the DS to generate viscosity-sheer rate curves.

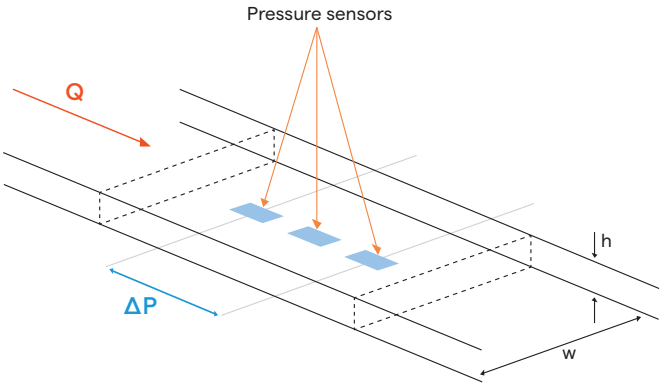


Figure 6
High throughput viscometer VROC® Initium System measuring Δp in a channel to calculate shear stress and viscosity.

Case Study 3: Continued

The viscosity-sheer rate data demonstrates that there is limited shear thinning below 4000 s-1 but above this range shear thinning is possible for formulations of mAbs A, B, C and D using a PFS with a 29G TW needle.

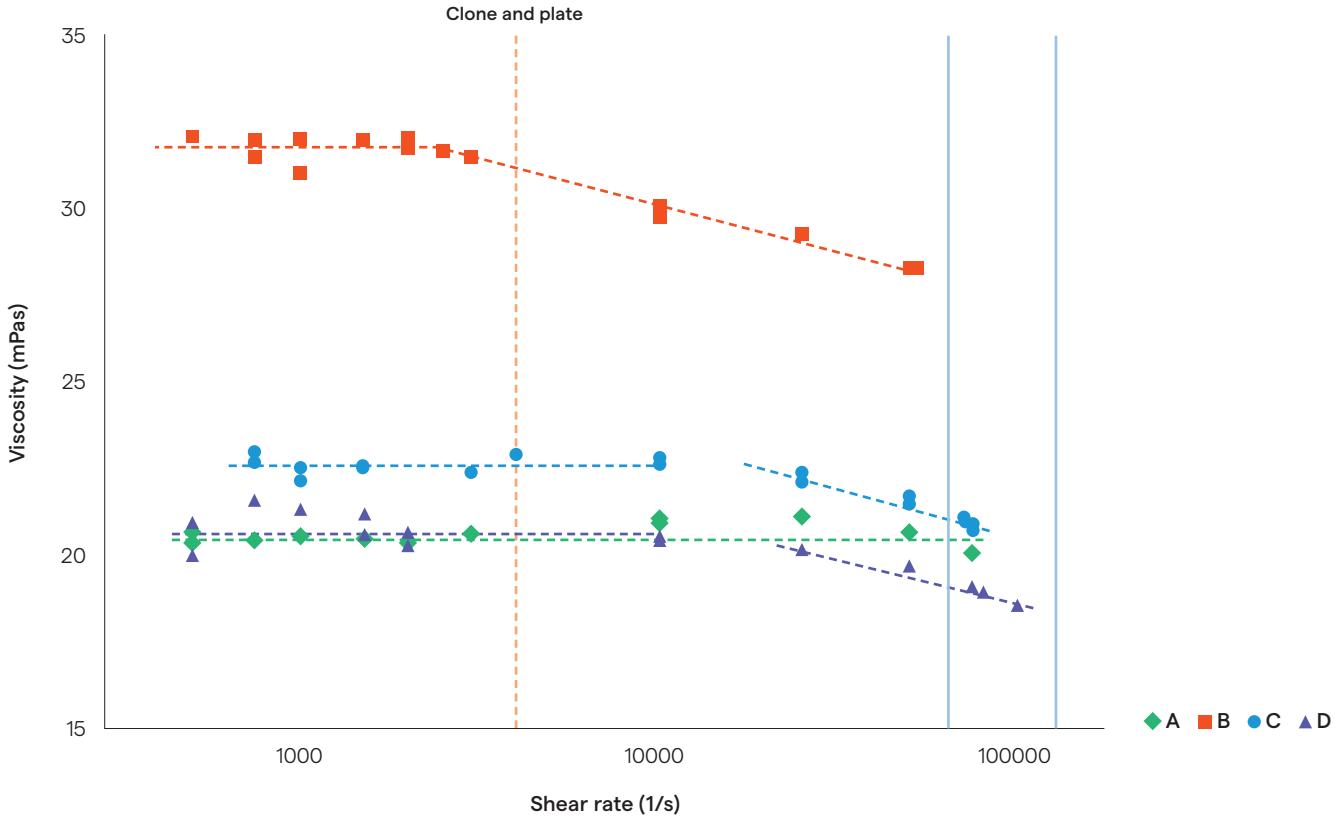


Figure 7
Shear rate and viscosity changes of formulations of mAbs A, B, C and D to demonstrate effects of shear thinning.

Using this experimental data, we have been able to make more accurate calculations of the hydrodynamic force in a PFS to generate predictive injection force data for formulations of mAbs A, B, C and D. We then compared the predictive and actual measured injection force. The results show that there is now a good correlation between predicted and actual injection force data for the four mAbs we tested, indicating that this model is suitable for use in practice to accurately predict injectability performance of biotherapeutics.

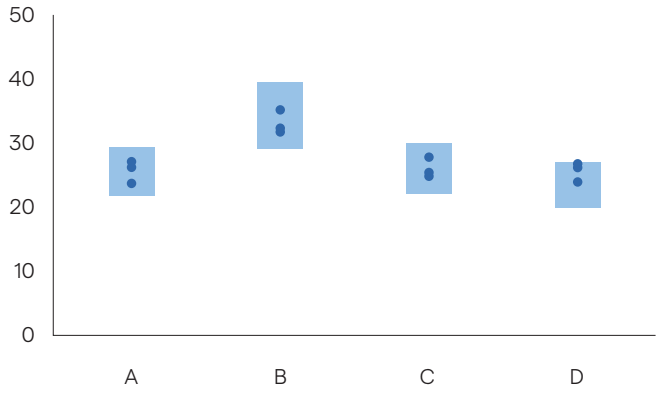


Figure 8
Improved model predicted (blue squares) calculated including the PFS and use condition data versus actual (blue dots) force required (N) to expel four mAb formulations (A, B, C, D) concentrated at 180 mg/mL – 210 mg/mL.

Conclusions

Accurately determining the injection force needed to expel a biotherapeutic from a PFS indicates how injectable the final formulation will be. As shown in this white paper, the current method of predicting injection force produces a model that is not sufficiently predictive. As an experienced Contract Development and Manufacturing Organization (CDMO), Lonza has used advanced testing capabilities to assess other factors that could impact injection force (needle length/diameter and viscosity changes with shear thinning). As detailed in this white paper, this has enabled us to produce a workflow process and improved injection force and viscosity models which can be used to accurately predict injectability performance of biotherapeutics in a PFS and autoinjector format.

Currently, we are offering this bespoke process and these injection force and viscosity models, (which are exclusive to Lonza) for clients that request these studies as part of their end-to-end drug development service. Leveraging this approach enables consideration and adjustment of the drug presentation earlier in formulation development. Additionally, it reduces the risk of selecting a PFS type with inappropriate properties, ensuring development of an optimum final concentration for injectability which has the potential to boost the prospects of the biotherapeutic becoming commercially successful.

References

[1] Prefilled Syringes Market Size, Share | Forecast Report by Fortune Business Insights (2023). Accessed August 8th, 2023. https://www.fortunebusinessinsights.com/industry-reports/prefilled-syringes-market-101946

[2] Bilski J. Prefilled Syringes Are the Preeminent Option. Outpatient Surgery Magazine, 2022. https://www.aorn.org/outpatient-surgery/article/prefilled-syringes-are-the-preeminent-option

[3] Palm T. et al. The importance of the concentration-temperature-viscosity relationship for the development of biologics. BioProcess Int, 2015;10. https://bioprocessintl.com/manufacturing/monoclonal-antibodies/importance-concentration-temperature-viscosity-relationship-development-biologics/

[4] Zhang, Q., Fassihi, M.A. and Fassihi, R. Delivery Considerations of Highly Viscous Polymeric Fluids Mimicking Concentrated Biopharmaceuticals: Assessment of Injectability via Measurement of Total Work Done "WT". AAPS PharmSciTech. 2018; 19:1520–1528. https://doi.org/10.1208/s12249-018-0963-x

[5] Krayukhina E., Fukuhara A., Uchiyama S. Assessment of the Injection Performance of a Tapered Needle for Use in Prefilled Biopharmaceutical Products. J Pharm Sci. 2020; 109, (1):515–523. https://doi.org/10.1016/j.xphs.2019.10.033

Learn more about Lonza's fully Integrated, phase-appropriate solutions

Contact us
Email: **jean-sebastien.steffen@lonza.com**
Web: **https://www.lonza.com/biologics/parenteral-drug-product**

Lonza Edition No. 11-2023