



BIOLOGIC INTEGRITY: MEASURING AND MANAGING THE HIDDEN LEACHABLES RISK FROM PFS ADHESIVE

Here, Enrico Barichello, Syringe Product Manager at Stevanato Group, considers the often-overlooked influence of adhesive in the assembly of prefilled syringes and how the hidden risks can be managed and overcome.

The growing prevalence of biologic drug products witnessed in recent years has been matched by a parallel increase in demand for prefilled syringes (PFSs) as the delivery mechanism of choice.

These innovative systems offer numerous key benefits, providing a precise pre-measured dose of a particular medication within a ready-to-use secure container. Beyond this, PFSs offer the advantages of reducing the risk of dosage errors, avoiding the potential for contamination caused by repeatedly inserting and withdrawing a syringe into a vial, and enhancing patient convenience in self-administration or autoinjector applications.

However, when it comes to biologics and biosimilars, the benefits of PFSs can only be realised if specific factors around safety and efficacy are considered. Generally, drug products of this nature present challenges around integrity and stability due to their sensitive nature. For example, in injectable form, the liquid formulation can be susceptible to degradation or contamination through interaction with the critical components that make up the primary packaging of the PFS.

In light of this, pharma companies and their delivery partners naturally put significant focus on the various elements that present a threat to the container closure system and have the potential to compromise the purity of the drug product within. Among these elements, however, there is one that remains relatively unexplored and uncharacterised in terms of its influence on drug integrity – the adhesive used in the assembly for staked-needle syringes.

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CHALLENGES IN UNDERSTANDING SYRINGE GLUE LEACHABLES

With staked-needle PFSs, patient convenience and safety is increased as there is no requirement to attach a needle prior to delivery, which means time-consuming steps that could otherwise introduce human error are removed. To facilitate this, the adhesive plays a vital role in securing the needle to the glass in the cone of the syringe barrel. However, at the same time, the presence of the adhesive introduces a potential contamination risk, as it is an additional substance in direct contact with the drug product. In particular, it could result in leachable compounds migrating from the adhesive into the dose over time under normal storage conditions.

Adhesive leachables, such as acrylates, are problematic because they can potentially react with proteins and pose a risk to the integrity of the drug product. Given the sensitivity and complexity of biologic drug molecules, a comprehensive assessment of leachables is therefore essential to



Enrico Barichello
Syringe Product Manager
T: +39 049 931 8111
E: enrico.barichello@stevanatogroup.com

Stevanato Group
Via Molinella 17
35017 Piombino Dese
Padova
Italy

www.stevanatogroup.com

avoid undesirable interactions that could compromise drug quality or patient safety. This demands close control over the formulation, application and curing process of the needle adhesive, with a clear understanding of the interaction between the adhesive and the individual characteristics of the specific biologic formulation in question.

It might be assumed that such challenges can be overcome in large part through knowledge of the raw materials that constitute the adhesive, and suppliers are indeed likely to be able to provide preliminary extractable data relating to the ingredients used to form the adhesive compound. However, while this information should form part of the overall assessment, it does not account for the parameters associated with the final gluing and curing process, which, critically, can introduce new compounds that could impact the extractables profile and pose a risk to the purity of the drug product over time.

ADDRESSING SYRINGE-GLUE COMPATIBILITY

Pharma companies therefore face a situation where they must, in the interests of efficacy and patient safety, interrogate their choice of syringe platform in its market-ready state for the risk of extractables. Furthermore, the evaluation of syringe-glue compatibility should ideally be carried out early in the development process to avoid the possibility of subsequent complications and delays. In following this path, crucial questions emerge – What testing process should be followed? Does the chosen syringe platform allow for customisation to address any concerns that might be identified? Where should the process begin?

Stevanato Group undertook a project on behalf of one customer that provided important responses to these challenges based on a comprehensive assessment of the

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Figure 1: Both processes, industrial and bench top, employ a system using LED lights for the core task of curing the adhesive.

parameters involved in the gluing process. This work encompassed anticipation and management of potential issues that may arise in relation to leachables, including a tailored approach to resolving interaction-related concerns.

The project employed the design of experiments approach and method development in order to evaluate the influence of relevant variables and identify specific glue-derivative compounds that may interact with the drug product. This resulted in the creation of a series of experiments that accurately recreated the conditions being assessed and allowed for high-impact process parameters to be tested using varying values.

ENSURING PRECISE TESTING AND ANALYSIS

In any scientific approach to testing and analysis, precision is critical to the quality of the results. In this case, Stevanato Group’s in-house manufacturing equipment was used to develop a dedicated bench-top unit, upon which all experimental activities were conducted with meticulous attention to methodological detail. To ensure that the findings from the test correlated with authentic manufacturing processes, the bench-top unit was also calibrated in line with the real-world machinery used for needle assembly (Figure 1).

Both processes, industrial and bench top, employed a system using LED lights for the core task of curing the adhesive. This approach was designed to deliver improvements in the polymerisation process while also reducing the levels of energy consumption required.

A principal objective of the testing activities was the screening, detection and analysis of various potential extractables. As such, the Stevanato Group Technology Excellence Centers developed multiple techniques capable of quantifying the presence of glue-based compounds, such as acrylic acid, in the final cured adhesive. These techniques included high performance liquid chromatography and ion chromatography.

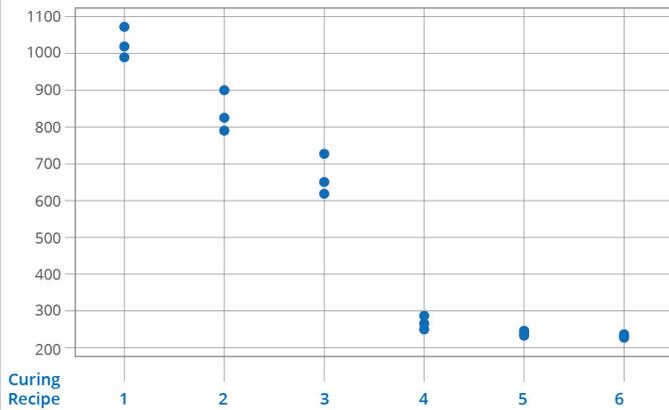
By optimising the parameters of the curing process through changes in curing impulse and energy, the tests allow the Technology Excellence Centers to determine the nature of the relationship between the curing method and any extractables observed. This provided the insight that is necessary for customising the adhesive curing method for a specific drug formulation, ultimately allowing adaptations to be made that minimise the risk of adverse interactions and ensure the highest level of drug product quality and patient safety.

CUSTOMISABLE APPROACH FOR OPTIMAL RESULTS

In both cases, the levels of extractables – measured in ng per syringe – varied with each of the different adhesive curing combinations (Figures 2 and 3). Generally, higher curing energy facilitates better polymerisation of the glue, resulting in lower values of extractables. However, it is noteworthy that this relationship does not apply universally to all extractables. Rather, there is the potential for certain extractables to display unique behaviours that would require specific adjustments to be made to the curing process parameters to maintain extractable levels within a desirable threshold.

INDIVIDUAL VALUE PLOT OF EXTRACTABLE 1

» Extractable 1 - NG/SYR



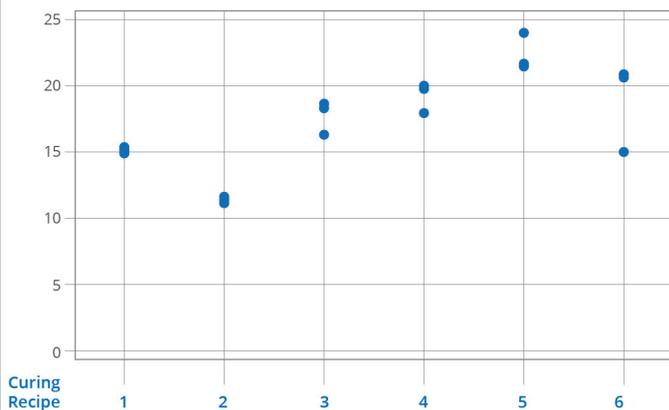
ONE DOT = POOL OF 5 SYRINGES | LOQ ABOUT 50 NG/SYR

Curing Recipe	Curing Impulse	Curing Energy
1	A	Low
2	B	Low
3	C	Low
4	A	High
5	B	High
6	C	High

Figure 2: Generally, higher curing energy facilitates better polymerisation of the glue, resulting in lower values of extractables.

INDIVIDUAL VALUE PLOT OF EXTRACTABLE 2

» Extractable 2 - NG/SYR



ONE DOT = ONE SYRINGES | LOQ ABOUT 2 NG/SYR

Curing Recipe	Curing Impulse	Curing Energy
1	A	Low
2	B	Low
3	C	Low
4	A	High
5	B	High
6	C	High

Figure 3: For certain extractables, higher curing energy does not result in lower values of extractables.

“A customised approach, based on specific drug formulation requirements, allows for the precise manipulation of curing impulse and energy to minimise the risk of adverse interactions and ensure the highest level of drug product quality and patient safety.”

These insights emphasise the complexity of the curing process and the diverse behaviours of extractables in relation to curing. This underlines the importance of taking a nuanced and tailored approach to the management of this risk, wherein a thorough evaluation of individual extractables is necessary to refine the adhesive process for optimal results. A customised approach, based on specific

drug formulation requirements, allows for the precise manipulation of curing impulse and energy to minimise the risk of adverse interactions and ensure the highest level of drug product quality and patient safety.

Stevanato Group can help drug manufacturers effectively address potential leachables issues through an approach that combines quality components with

customised support as part of an integrated offering. The foundation for this approach is provided by the Alba® and Nexa® syringe platforms. Both platforms have been designed to incorporate properties that mitigate the risk from extractables. Alba® syringes have been optimised specifically for applications involving high-value sensitive injectables, thanks to the addition of a specific internal coating (Figure 4).

When employing these products, pharma customers will know that every aspect of the individual components that form the complete system has been developed with consideration not only for injectable performance, but also for supporting the stability and integrity of the drug product. This, of course, includes the adhesive used in the needle assembly.



Figure 4: Alba® syringes – Stevanato Group's breakthrough solution for biologics.

But, as the study results have shown, drug products cannot be expected to demonstrate universal properties when it comes to containment. The risk of leachables from adhesives will vary depending on the specific formulation in question. This means that a level of customisation is essential to arrive at an adhesive curing process that minimises the risk of compromising a given drug's integrity by the presence of extractables.

The testing methodology described here provides the basis for analysing this risk for an individual API, employing the skills and knowledge of Stevanato Group's in-house engineering team. This analysis opens the door to iterative development work, where the parameters of the adhesive curing process can be modified to address extractable levels. Thanks to the close integration between product teams, engineering teams and materials suppliers, as well as the ability to draw on previous experience of this process, Stevanato

Group has the capabilities assist customers in arriving quickly at a compatible solution for protecting their high-value drug products.

CONCLUSION

While it might not be an aspect of containment that attracts significant attention, consideration of leachables in syringe adhesive can be of paramount

importance when it comes to PFS applications involving biologic drug products. The evidence from testing conducted by Stevanato Group shows that it has the potential to influence the levels of extractables in ways that might not be well understood, as well as in ways that will be specific to a given drug. It is only through a clear understanding of the interaction between adhesive and drug, and a focused approach to customising the curing process, that this relatively hidden risk can be managed and mitigated, avoiding any compromise to drug quality and patient safety.

ABOUT THE COMPANY

Founded in 1949, Stevanato Group is a leading global provider of drug containment, drug delivery and diagnostic solutions to the pharmaceutical, biotechnology and life sciences industries. Stevanato Group delivers an integrated, end-to-end portfolio of products, processes and services that addresses customer needs across the entire drug lifecycle at each of the development, clinical and commercial stages. Stevanato Group's core capabilities in scientific research and development, its commitment to technical innovation and its engineering excellence are central to its ability to offer value-added solutions to clients.

ABOUT THE AUTHOR

Enrico Barichello has a background in industrial engineering and a Master's degree in Management from the University of Padua (Italy), giving him a broad spectrum of skills in technical concepts and complex processes. Mr Barichello joined Stevanato Group in 2017 as a Product Management Specialist for the syringe platform. He defined and co-ordinated all the activities required to bring the products to market, bridging gaps between different company functions and aligning the involved teams. Since January 2021, he has been the product owner – responsible for the roadmap and execution – of the new innovative Alba® platform.

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A BREAKTHROUGH SOLUTION FOR YOUR GAMECHANGER BIOLOGICS



As pharmaceutical partners embrace the potential of biologics, we have developed our proven syringe platform, Alba[®], to enable the optimisation of your opportunity.

We know your challenges, including the increased viscosity and stability of biologics and the relative injection forces required for effective delivery. And we have responded.

The Alba[®] syringe meets the requirements of high-value and large volume biologics. Combining our cross-linked coating technology with dimensional, geometrical accuracy, and enhanced glide capability; this platform significantly reduces the release of sub-visible particles and inorganic extractables.

Easily integrated into automatic drug delivery devices, such as spring-based autoinjectors, and optimized for smooth self-administration, Alba[®] meets the needs of our pharma companies and their end users in equal measure.