Pharmaversity®

How to choose the right vial: Influencing factors and solutions for liquid fills

SCHOTT PHARMA

Summary

In the development of injectable therapies – particularly biologics – the selection of primary packaging is a critical determinant of product success. Far from being a passive container, the vial plays an active role in maintaining drug stability, ensuring accurate dosing, and meeting regulatory requirements. Its influence spans formulation integrity, patient safety, and time-to-market.

This article provides a structured analysis of the key factors influencing vial selection for liquid fills. It outlines how variables such as filling volume, pH, temperature, leachable sensitivity, and drug registration status interact with container properties to affect drug performance. With the injectable pipeline becoming increasingly diverse and complex, early and informed packaging decisions are essential to mitigate risks such as protein adsorption, glass delamination, and chemical incompatibility.

Primary packaging: The critical link between drug innovation and patient safety

It cannot be highlighted enough that the primary packaging – the vial, cartridge, ampoule, or syringe – represents a highly relevant part of a drug product. The development of the most innovative, effective, and revolutionary drug is undermined if its functionality is compromised by the choice of a wrong container.

When considering the range of biologics and the upcoming injectable market pipeline, it becomes apparent that the right choice of primary packaging becomes more and more challenging. By nature, these are typically therapies that cannot be forced into one category. With the diversity of molecules and applications comes the diversity of requirements. For instance, more than 50 % of biologics need lyophilization, where challenges such as “fogging” might occur. For liquid drugs, sensitivity towards glass leachables can be an issue for delicate molecules, which is even more challenging when those drugs are in low-fill volumes. Some formulations contain proteins that tend to adsorb to the container’s surface, resulting in incorrect dosing or the need to overfill.

Primary packaging and drug delivery systems act as the essential interface between pharmaceuticals and patients.

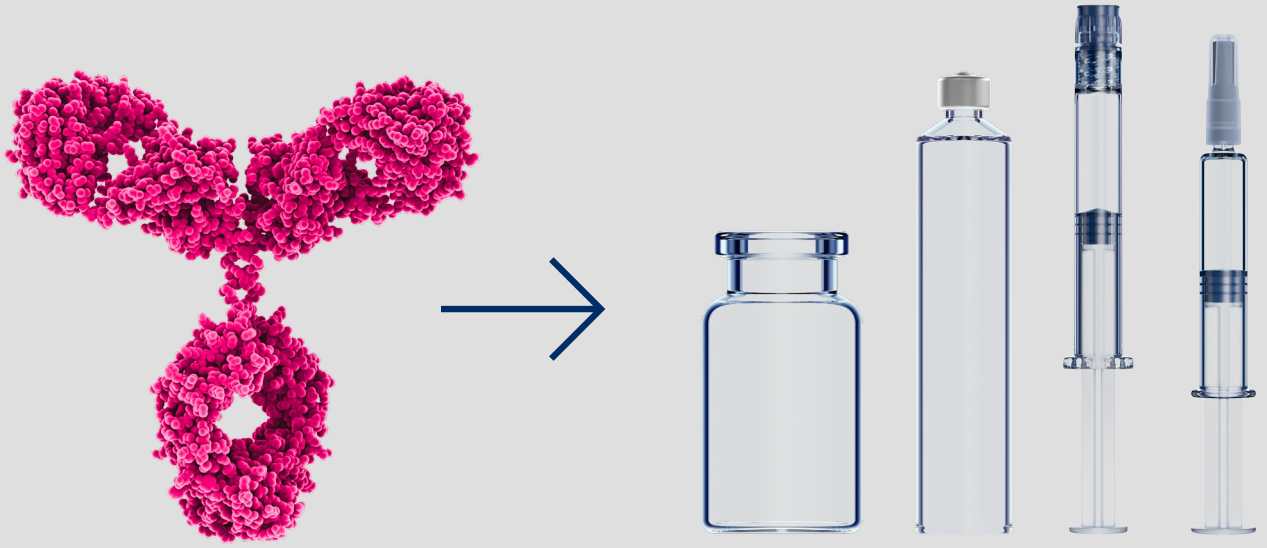
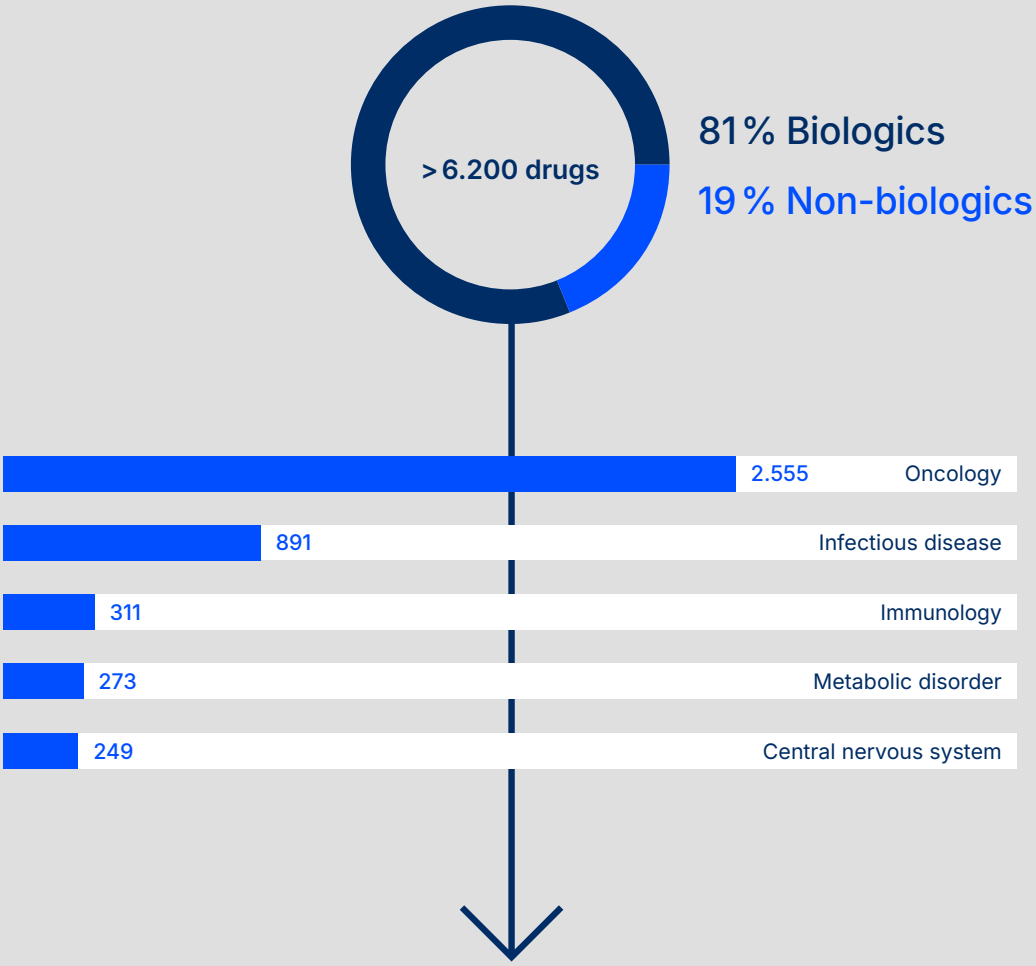


Figure 1: Primary packaging as bridge between drug and patient

A huge injectable drug pipeline with many therapy areas (top 5, 2024) ...



... leads to diversity of requirements for the primary packaging.

Leachables	Lyophilization	Efficiency
Adsorption	Freezing	Small batches
High pH	Low fill	Unique identification
Delamination	Fogging	Dosage accuracy

Source: Injectable drug pipeline: Clinical trails phase 1–3, pre-registration with develepment stage, Globaldata, April 3rd 2024
Figure 2: Injectable drug pipeline predicting a higher diversity of requirements

Vials: the default container for drug development

Thanks to their ease of use, syringes and cartridges are becoming the default choice for established drugs as part of their lifecycle management. When it comes to the development of new drugs, vials often remain the container of choice. There are two major reasons for this: Firstly, the use of a syringe means that more components or materials are in contact with the drug, which increases complexity thanks to the existence of a multitude of possible interactions (this is also partly true for cartridges).

As well as the silicone (Jones, Kaufmann, & Middaugh, 2005), there's the needle, cap, plunger, and, of course, the glass. When using a vial, only the glass is in constant, direct contact with the drug, and the influence of the rubber stopper is less prominent. In addition, vials offer a medium level of ease-of-use – typically closed with a stopper and a crimp, it allows easier and safer withdrawal than an ampoule, can also be used in combination with adapters and devices, but provides less convenience than a syringe.

Secondly, if a drug requires lyophilization (which is the case for more than 50 % of biologics), the vial is the best and most established container to handle this complex process.

Influencing factors for primary packaging selection

For liquid fills, there are five main influencing factors that should be considered when evaluating the correct primary packaging:

1) Filling volume
2) pH
3) Temperature
4) Leachable sensitivity
5) Drug status

1. Filling volume

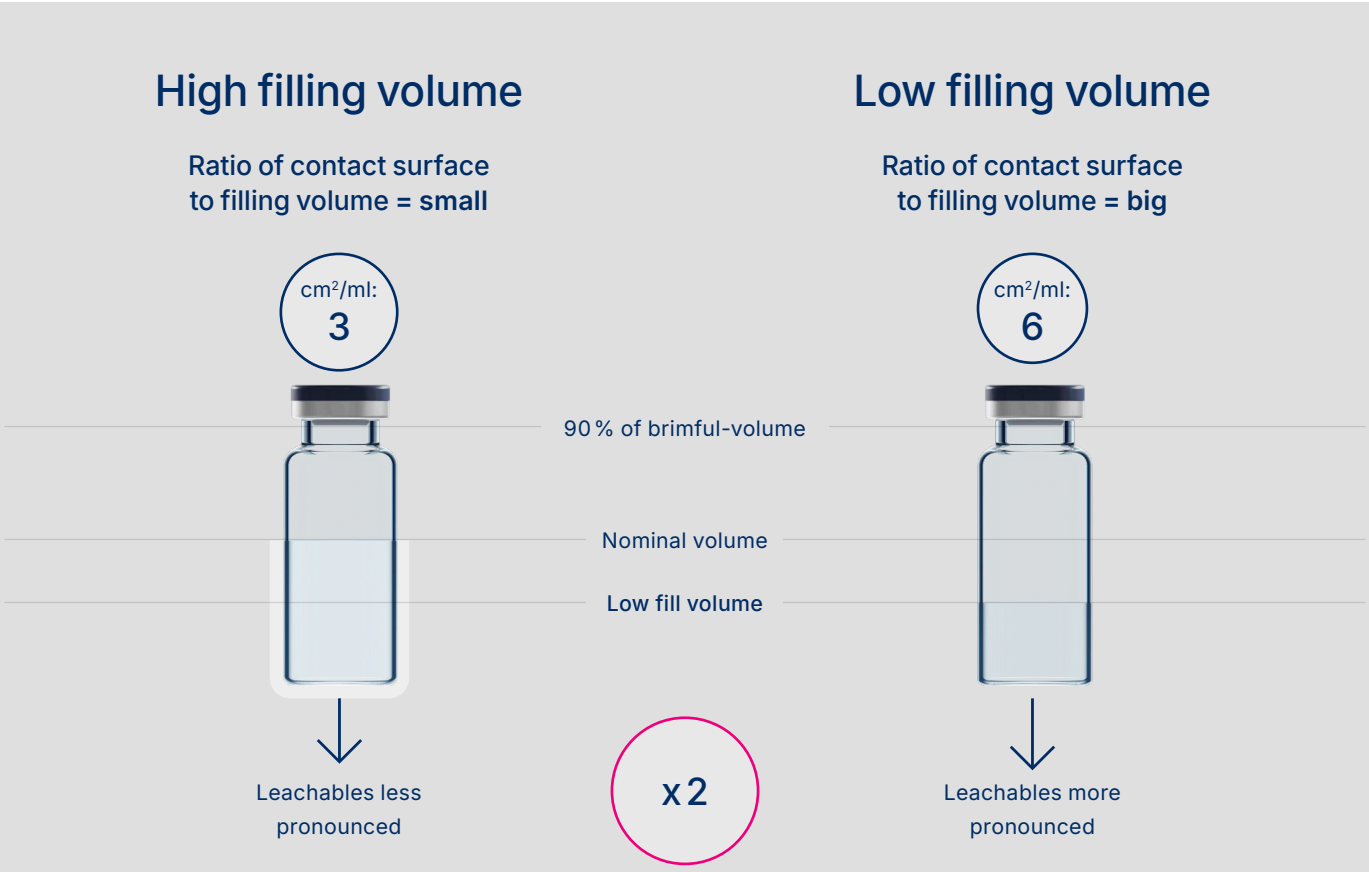
High-value drugs such as biologics are typically filled in vials below their nominal filling volume. As an example, a 2R vial has a nominal volume of 2 ml and a brimful volume of 4 ml. However, the observed filling volumes are often below 1 ml. The lower the filling volume, the higher the surface area in relation to that filling volume since the vial bottom increases the contact surface for low-filling volumes. The more the vial is filled, the more negligible the influence of the bottom (Hladik, Buscke, Frost, & Rothhaar, 2019).

In addition, there are two topics connected to filling volume. Firstly, when talking about high-value drugs, every droplet counts. Some molecules adsorb to the vial's surface in such a way that even mechanical impact (e.g. shaking) will not help. As a consequence, the concentration is lowered and it's not guaranteed that the drug will be administered to the patient in the right dosage.

Secondly, required filling volume is strongly connected to the hot-forming of the vial. During the forming process, the glass tube is heated, with the highest temperatures occurring at the bottom of the vial. As a result, evaporates re-condense on the closest cooler region of the vial's interior surface: the so-called heel zone. This is a zone near the bottom of the vial, just above the heel area. This area is less chemically durable, shows higher leaching, and is more susceptible to the processes that lead to delamination (Rupertus, Hladik, Rothhaar, & Scheumann, 2014).

The higher leachable level of a low-fill volume vial will have a much higher impact on low volumes. As a consequence, the leachables per filled ml are much more elevated for a 2R vial filled 0.5 ml compared to one filled with 2 ml filled.

Conclusion: Filling volume is not just something that needs to be considered during the filling process – it needs to be taken into consideration much earlier in the development process.



Assumption: a 2R vial filled with 3.6 ml (90 % of brimful acc. to USP 660 hydrolytic resistance measurement) vs. 0.5 ml
Figure 3: Leachables are more prominent for low-filled drugs due to the increased contact surface

2. pH

With regards to pH, a typical target range is pH 5-7 – more or less neutral and sometimes referred to as the “physiological pH” area. This has an important role when it comes to the experience of pain for the patient. Drugs that use buffers in the acidic range have been used when necessary, while there’s also been a recent trend for drugs with buffers in the alkaline range, sometimes up to pH 11.

Both extreme pH areas are a challenge for standard Borosilicate Glass vials (Rothhaar, Klause, & Hladik, 2016). In low pH, hydrogen ion attack takes place – a process that involves the ion exchange of positive hydrogen ions with network modifiers such as sodium. This results in a rise in pH, leading to a risk in the stability of the formulation.

When pH levels are high, hydroxide ion attack takes place. This attack is continuous and dissolutes the silicon-oxygen bonds of the glass network, releasing network modifier elements into the solution. These leachables may have an impact on the drug, resulting in denaturation of the protein, aggregation, or even deactivation. Of course, this is something that needs to be carefully evaluated.

Conclusion: pH is a crucial factor when it comes to the choice of primary packaging.

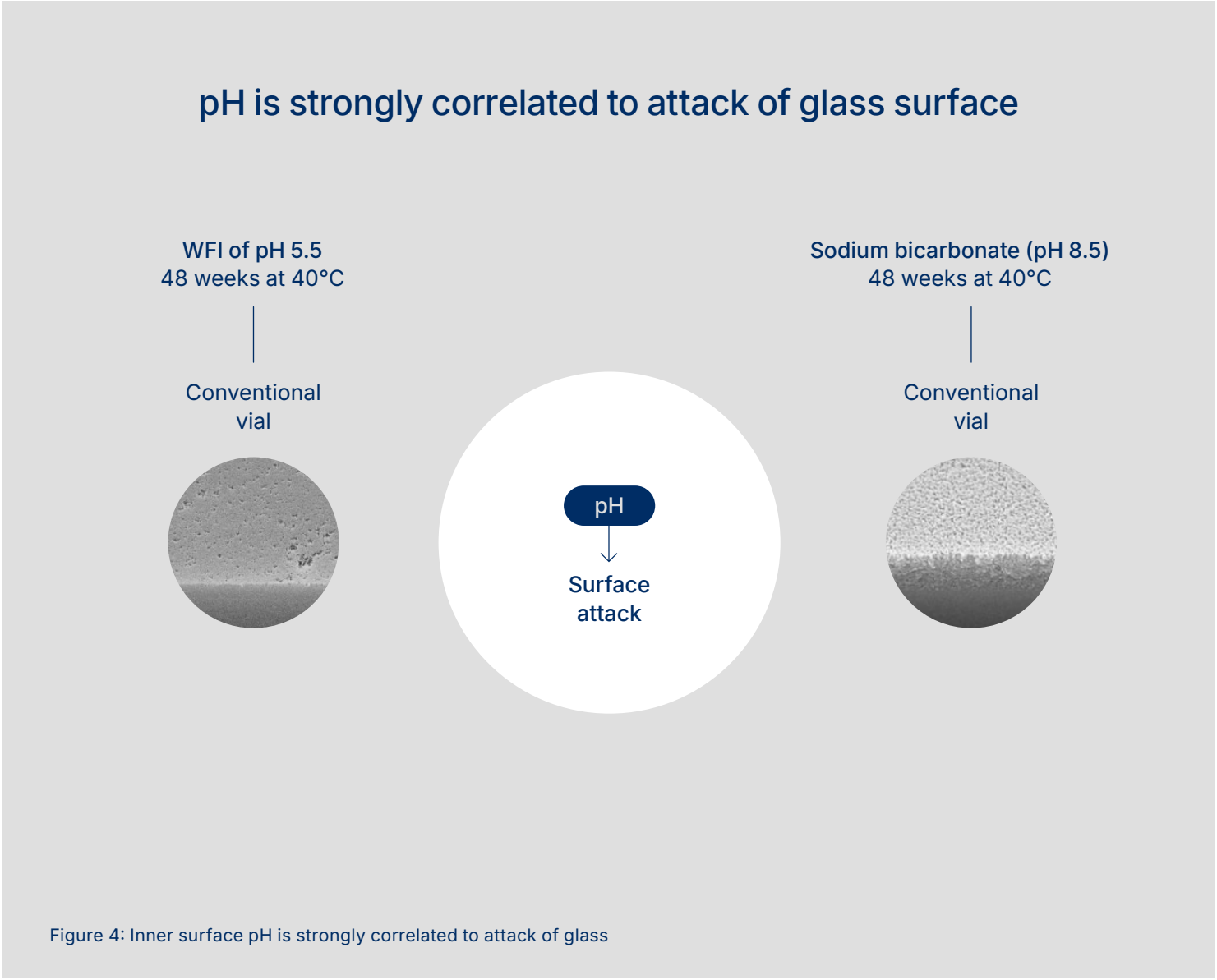


Figure 4: Inner surface pH is strongly correlated to attack of glass

3. Temperature

By its nature, temperature is an accelerator when it comes to chemical reactions. This is why terminal sterilization has such a high impact on drug-container interaction, which can result in glass leachables being extracted that can have an influence on the drug.

Storage temperature also plays a huge role. To evaluate drug shelf life, accelerated ageing is typically performed, in which the ambient temperature is increased to mimic a certain length of time. The relationship between storage period, temperature, and real-life storage time is well understood. Of course, when it comes to drug stability, ambient storage temperature is an important consideration.

Conclusion: Whether during the process of terminal sterilization or storage, temperature has a huge impact on drug-container interaction.

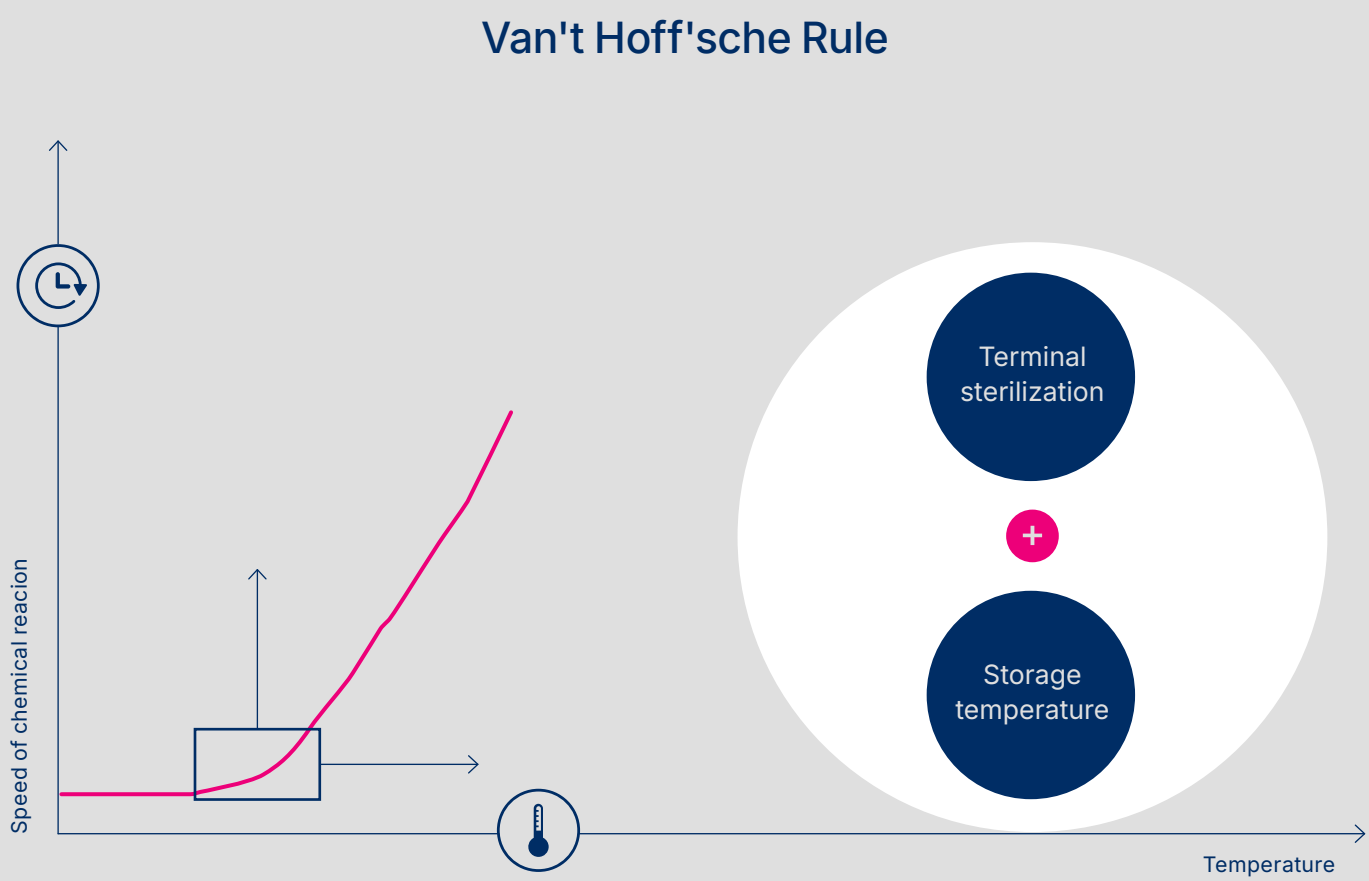


Figure 5: The temperature impact on the rate of chemical reaction

4. Leachable sensitivity

There is more to the topic of leachables than the impact for low-fill volumes, as some active pharmaceutical ingredients (APIs) are sensitive towards glass leachables in general, independent from the elevated impact due to low-fill. The truth about leachable sensitivity is complex and cannot be simplified.

What we can say is that increasing the complexity of the molecule increases the risk of sensitivity towards leachables. This can result in proteins denaturing, unfolding, and agglomerating, risking a loss of activity of the protein, making the drug ineffective.

Conclusion: It's vital to fully understand how your drug interacts with container leachables.

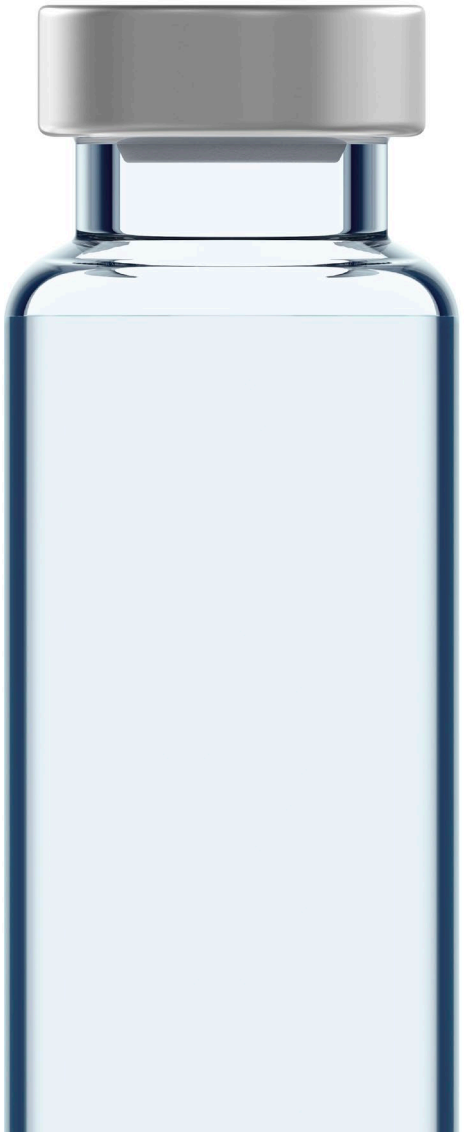
5. Drug status

Here, "drug status" refers to the registration of a product. While the shelf life and effectiveness of some commercial drugs may be improved by using a different container, the hurdles to changing the primary packaging and re-register the product would be huge. Such a move is only done if the product represents a real danger to patients' lives and there's been a warning by a regulatory agency. The good news is that certain aspects of the packaging can be improved without altering the registration.

Conclusion: Careful, early evaluation of the container is necessary to avoid a costly and time-consuming change of packaging for an already registered product.

Decision tree as first aid to select appropriate inner surface quality

Many different requirements need to be considered when choosing the correct primary packaging, with the interplay of factors leading to an limitless set of potential combinations. Different solutions exist to mitigate and avoid certain risk factors. Every therapy and molecule is unique, resulting in specific primary packaging requirements that need to be carefully evaluated and tested. As a first step, the "Vial decision tree for liquid fills" can help you select different inner surface quality options out of our EVERIC® vial family.



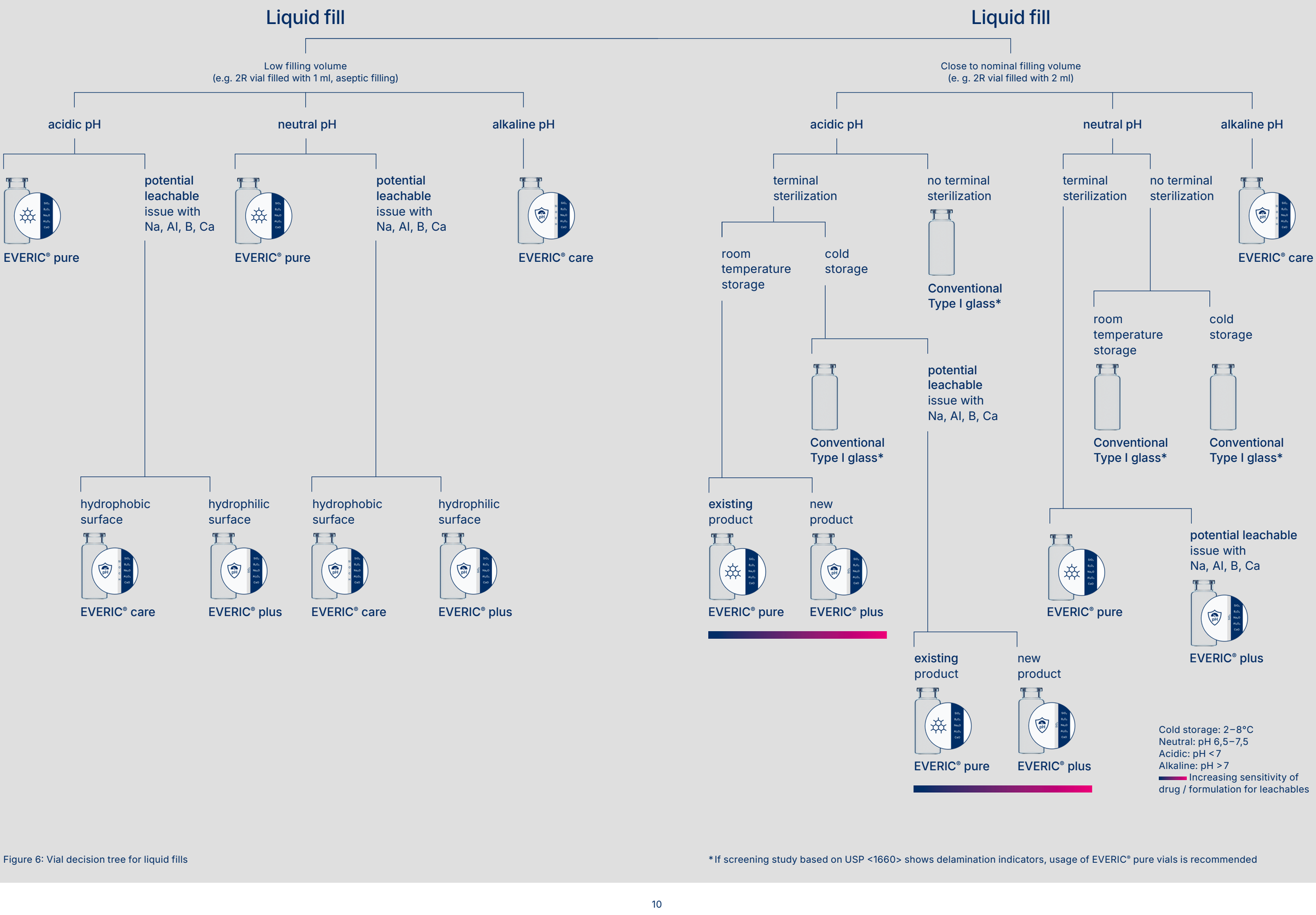


Figure 6: Vial decision tree for liquid fills

*If screening study based on USP <1660> shows delamination indicators, usage of EVERIC® pure vials is recommended

The alleged “standard”

Assuming a filling volume close to nominal, such as 2 ml in a 2R vial, a formulation in neutral pH with no use of terminal sterilization and storage by fridge temperatures, it might be thought that a standard, conventional Type I glass inner surface is suitable. However, even for that “standard” combination of factors, it is emphatically recommended that screening studies are carried out according to USP <1660> (USP 1660, 2015). This recommendation chapter of the US pharmacopeia helps to rule out an elevated risk for delamination, and was published as a direct consequence of recalls due to glass delamination that took place in the 2010er years.

At that time, it was found that the origin for delamination lies in a zone just above the heel of the vial. During the vial production process, the glass tube is heated, which results in evaporates that re-condense on the nearest cooler region of the vial’s interior surface: the heel zone. This area is less chemically durable and more susceptible to the processes that lead to delamination.

If a risk according to USP <1660> becomes apparent (Bicker, Haines, & Rothhaar, 2020; Haines, Scheumann, & Rothhaar, 2013), a vial that helps to mitigate this risk such as EVERIC® pure is recommended. However, even if the outcome shows no risk for delamination, it is still advisable to choose a controlled Type I glass inner surface for high-value drugs such as biologics and their diluents.

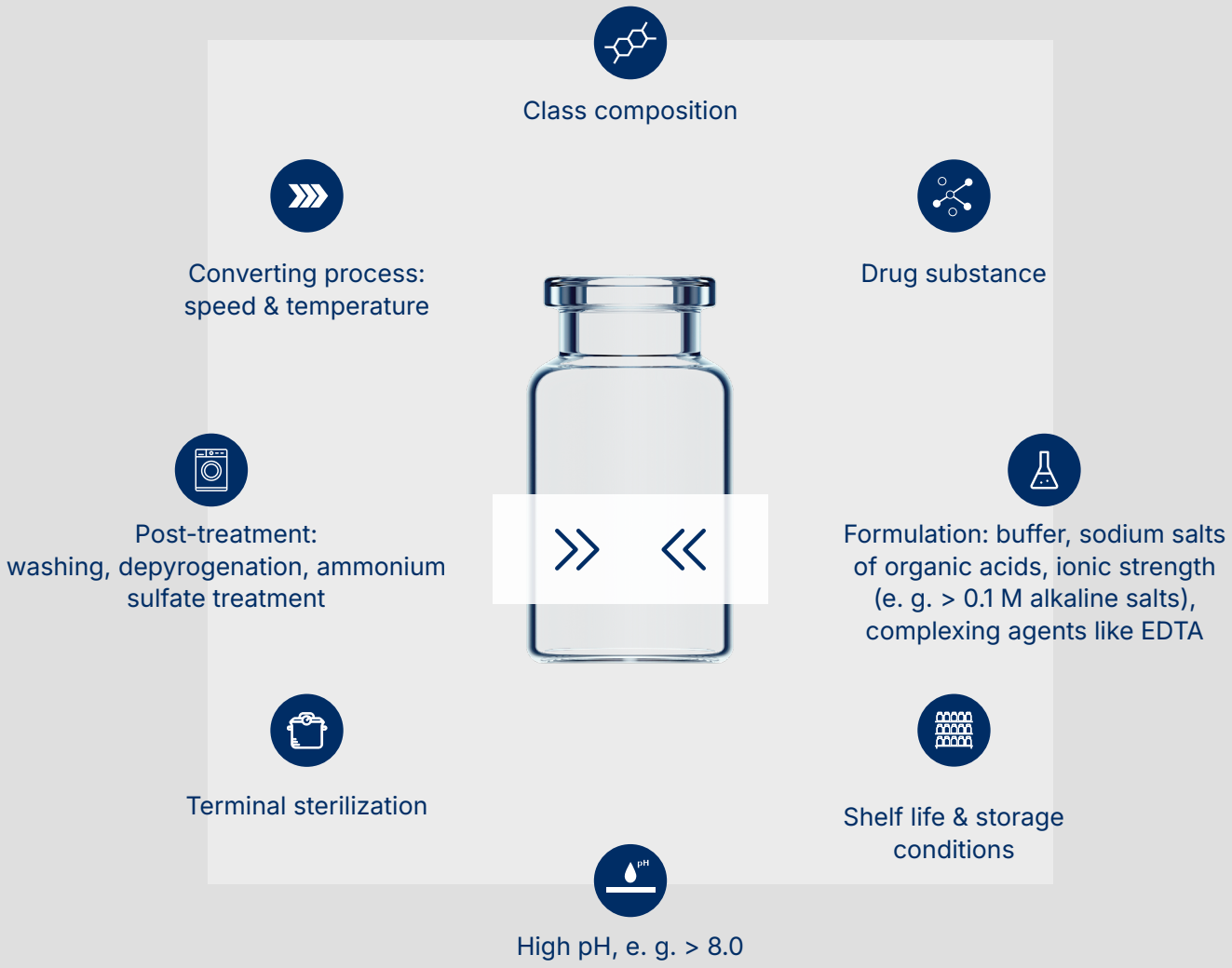


Figure 7: Risk for glass delamination according to USP <1660>

EVERIC® pure – a safe platform

As well as controlling delamination, the inner surface of EVERIC® pure offers a low leachable level, which is especially beneficial for low-fill volumes. The key to this low leachable level is a patented manufacturing technology that ensures a homogenous inner surface.

EVERIC® pure is increasingly used as a platform for drug development activities. Choosing EVERIC® pure as your default container solution at this stage offers the most significant reduction of risk, which is vital for patient safety, cost, and time to market. There's an increased likelihood that a formulation remains stable, meaning there's less risk to the stability of a protein or for the pH shift of a diluent.

Since the interplay of different factors cannot be predicted at the beginning of the vial selection process, EVERIC® pure offers a safe platform that provides a broader range of formulation options. This avoids additional re-formulation cycles if one formulation fails, resulting in a faster time-to-market.

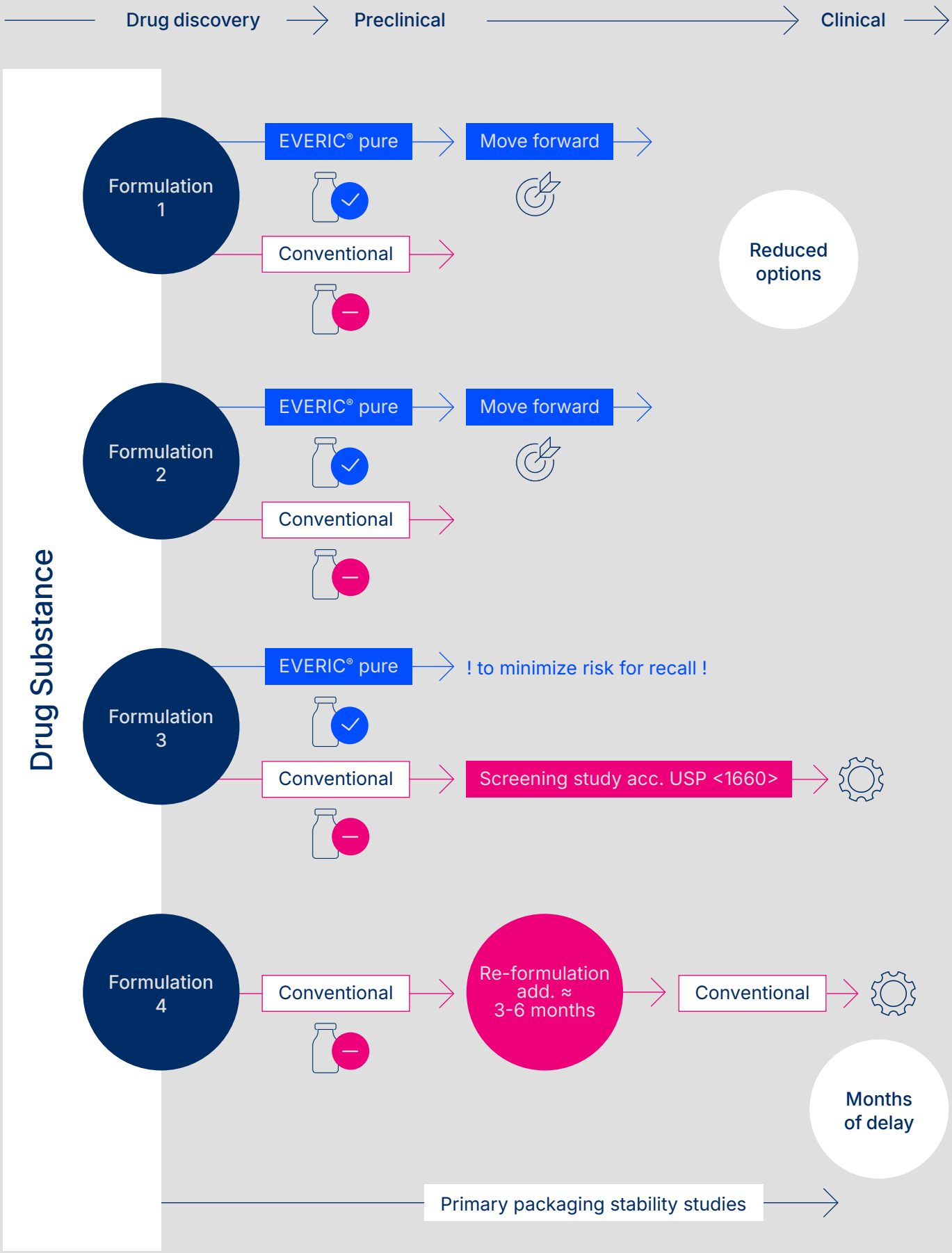
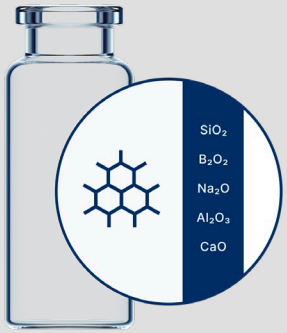


Figure 8: EVERIC® pure increases formulation options and reduces the risk of delays due to re-formulation

Even if the worst case occurs and glass delamination or risk indications are found in already commercialized products, EVERIC® pure offers a solution. Since it's made using pure Borosilicate Glass, it is possible to switch existing drug products from a standard Borosilicate Glass vial to EVERIC® pure.

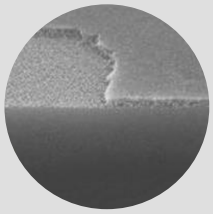
- Delamination under full control
- Reduced leachable levels
- Decreased pH shift & conductivity
- No re-registration



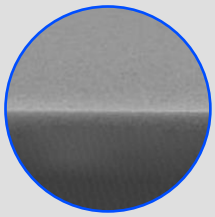
EVERIC® pure
Homogeneous inner surface

Delamination under full control

Phosphate buffer pH 7
24 weeks at 40 °C



Conventional vial



EVERIC® pure

Low leachables for low fill volumes

2R vials, Na in purified water afer for 24 weeks at 40 °C

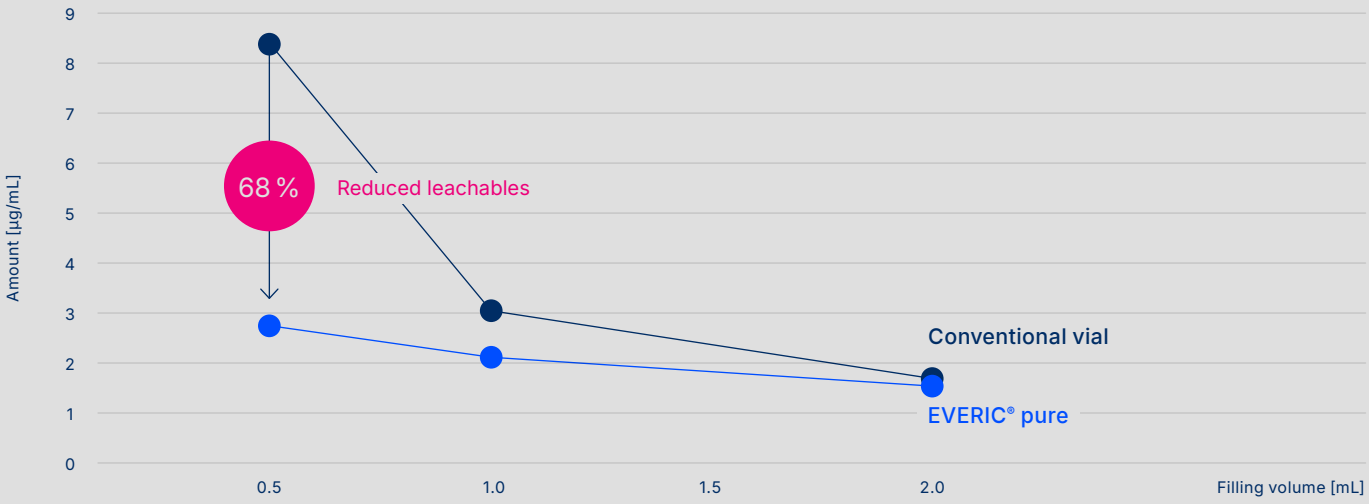


Figure 9: EVERIC® pure – delamination under full control and low leachable levels

EVERIC® plus – reduced adsorption and protection for leachable-sensitive drugs

Even an optimized Type I glass such as EVERIC® pure may not offer enough protection when it comes to applications sensitive to leachables. From a chemical resistance perspective, pure quartz glass (SiO_2) would offer the best performance. However, this requires very high melting temperatures to produce the glass tube and forming would be very challenging. Dimensional accuracy would be compromised and it's unjustifiable from an economic standpoint.

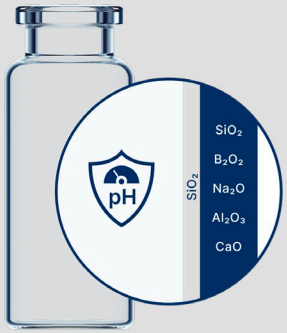
An alternative solution is EVERIC® plus, which features Borosilicate Type I Glass coated with an inner SiO_2 layer. This is applied using a plasma impulse chemical vapor deposition (PICVD) process, which involves microwave-induced plasma with HMDSO (hexamethyldisiloxane) used as precursor gas and oxygen used to activate the inner surface.

The result is covalently bonded SiO_2 coating that acts as a stable barrier to leachables.

This could be relevant to formulations with very large and complex molecules that may be sensitive towards glass leachables, such as sodium, aluminum, boron, and calcium. Potential interactions could lead to protein denaturation, compromising the drug's activity.

In cases where fluctuations in pH need to be kept to a minimum, such as for diluents which are typically being terminally sterilized, EVERIC® plus helps to keep the equilibrium. It has also been proven that its hydrophilic inner surface can help to avoid the adsorption of proteins, which can put drug effectiveness at risk.

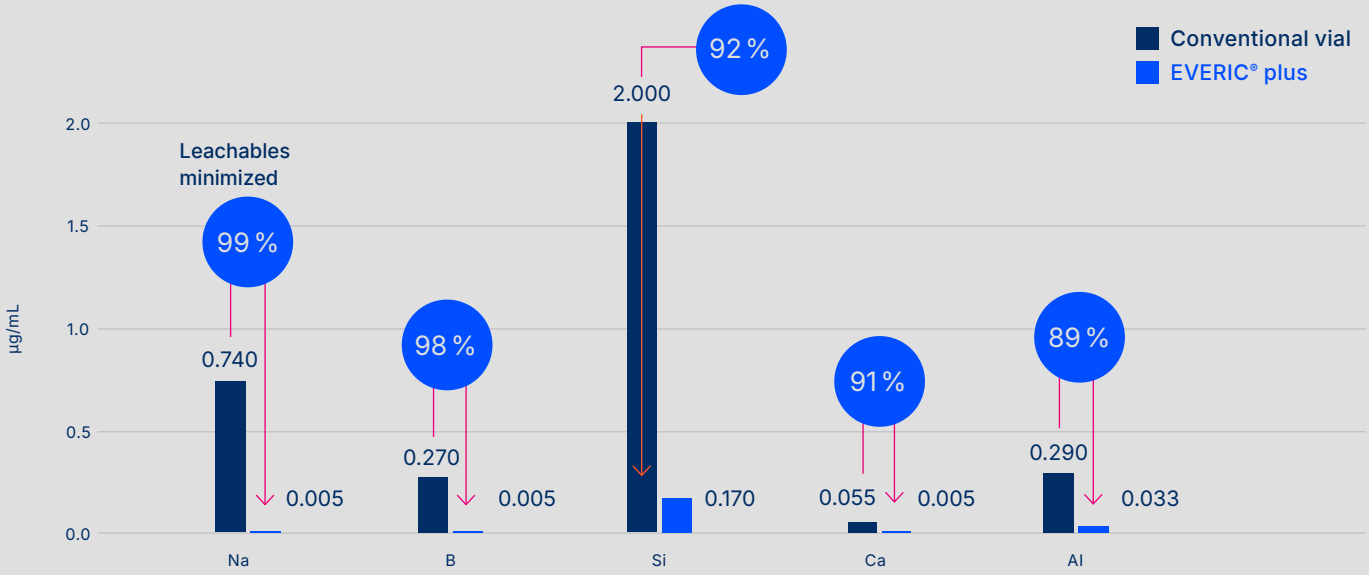
- Ion barrier
- Low to medium pH
- Reduced adsorption



EVERIC® plus
SiO_2 inner coating

Ion barrier

10R vials, purified water, autoclaved, measurement of leached ions by ICP-MS (IPS-OES for Si)



Reduced adsorption

Nicotinic acetylcholine receptor, concentration: 150 µg/ml, A. Schrattenholz: Drug loss through adsorption of a nicotonic acetylcholine receptor

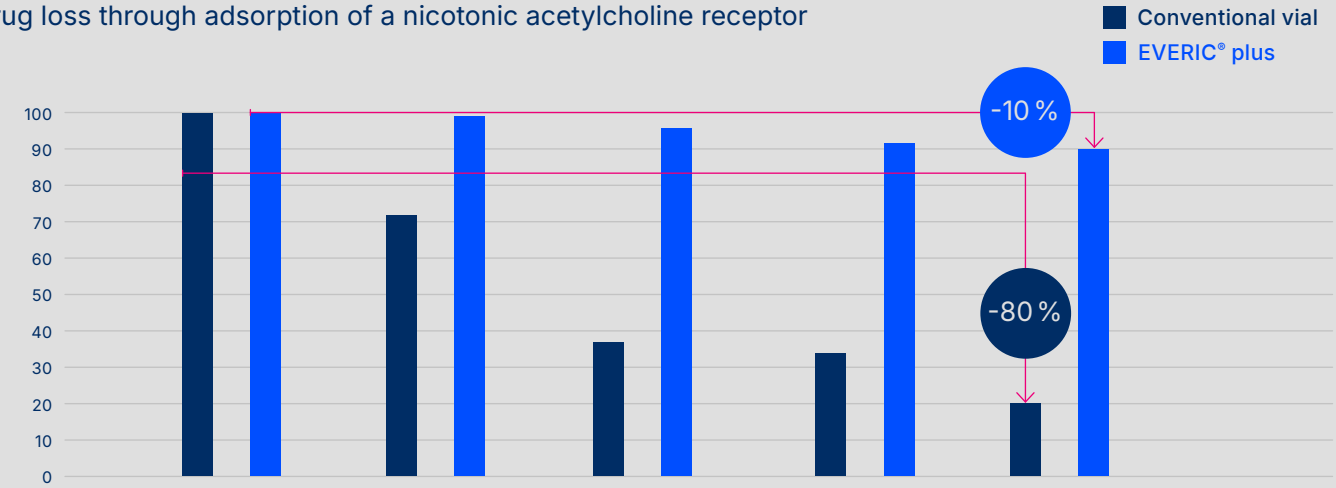


Figure 10: EVERIC® plus – ion barrier and reduced adsorption

EVERIC® care – improved residual emptying and leachable protection even in high pH

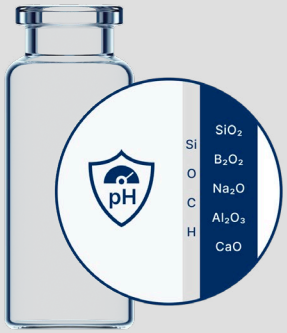
Although EVERIC® plus offers high levels of leachable protection, it reaches its limit when it comes to high pH. At high pH levels, hydroxide ion attack takes place, continuously attacking and dissoluting the silicon-oxygen bonds of the glass network.

EVERIC® care offers a solution in the form of an inner Si-O-C-H coating applied using Plasma Impulse Chemical Vapor Deposition (PICVD) technology. This results in a hydrophobic surface that is in contact with the drug, providing a stable leachable barrier even in high pH conditions. In addition, its hydrophobicity improves residual emptying, which can be particularly beneficial for low-filled volumes.

Primary-packaging selection – a decision based on multiple factors

A multitude of factors influences the interaction between a drug and its container, resulting in a limitless set of potential combinations. The uniqueness of every medication requires an individual evaluation of its primary packaging. With an increasingly diverse and complex range of molecules comes an increasingly diverse set of requirements. For liquid applications, the Vial decision tree for liquid fills, is a good first step in evaluating solutions to mitigate and avoid certain risk factors. However, a thorough, individually adapted analysis and test set-up is necessary to find a suitable primary packaging.

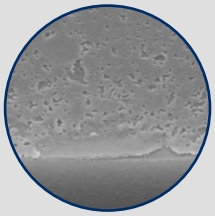
- Ion barrier
- Even in high pH
- Reduced adsorption



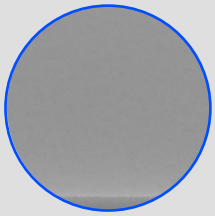
EVERIC® care

Stable coating

Sodium bicarbonate (pH 8.5) after 48 weeks at 40 °C



EVERIC® plus



EVERIC® care

Ion barrier in high pH

Glass elements in sodium bicarbonate (pH 8.5) after 12 and 48 weeks at 40 °C

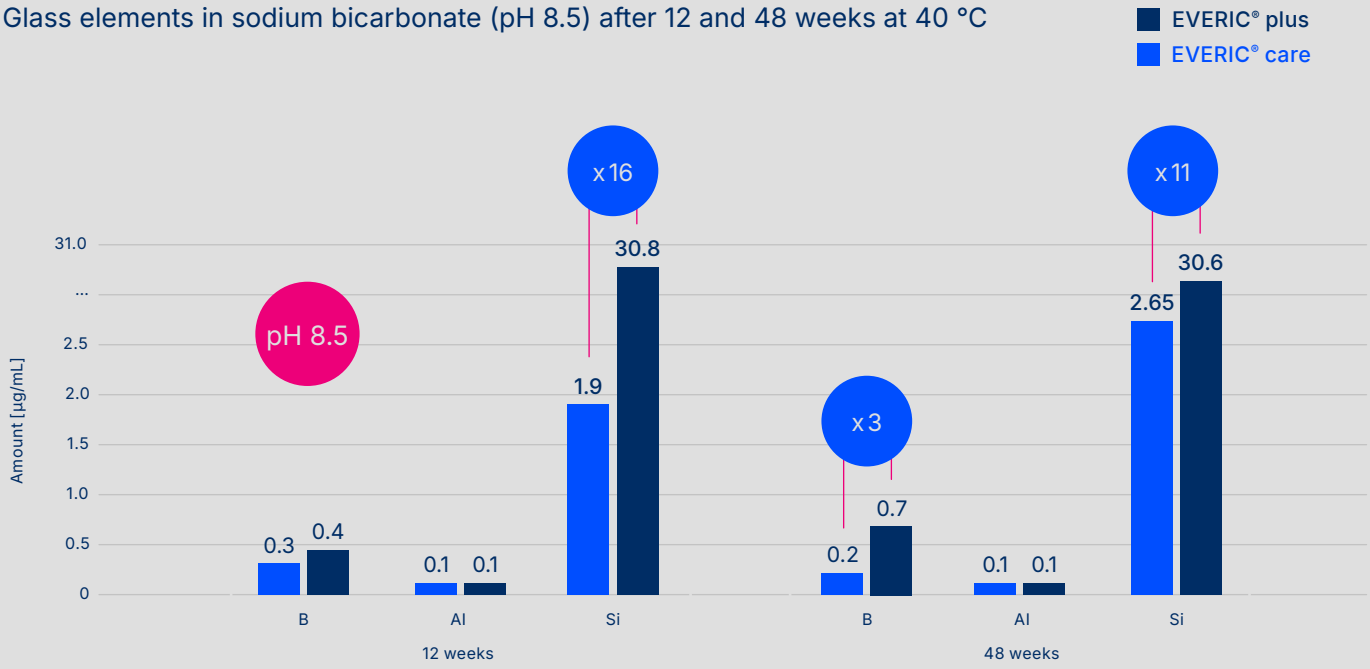


Figure 11: EVERIC® care – stable coating and ion barrier in high pH

Diana Löber

Diana Löber (Global Product Manager Specialty Vials & adaptiQ®) started her career in the medical device industry prior she joined SCHOTT in summer 2018. With now more than 10 years experience in the area of product management, as global product manager for vials, she is responsible for the product strategy, including the identification of new market opportunities, implementation of lifecycle measures and the development and launch of innovative products.

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