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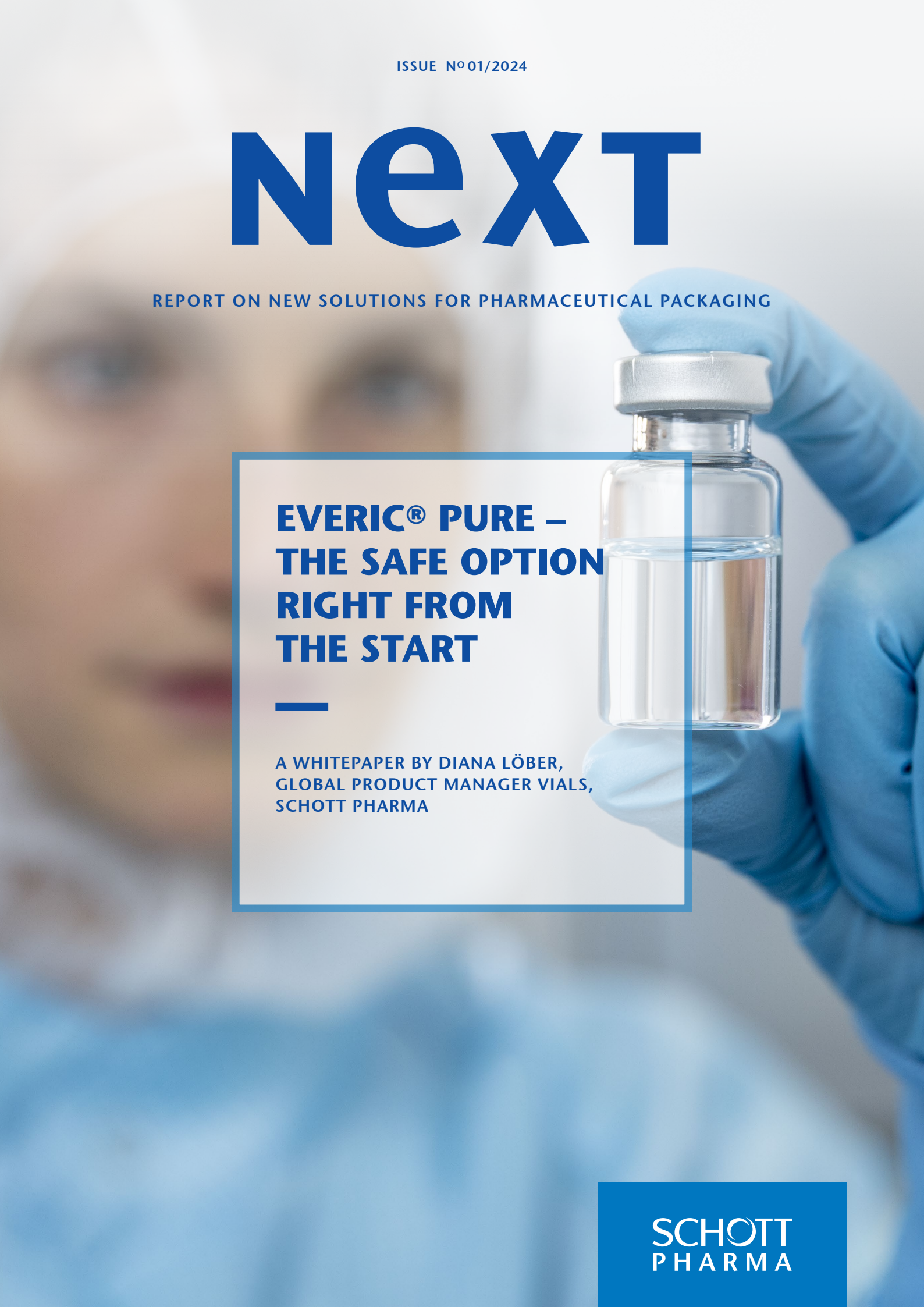
REPORT ON NEW SOLUTIONS FOR PHARMACEUTICAL PACKAGING



EVERIC® PURE – THE SAFE OPTION RIGHT FROM THE START

A WHITEPAPER BY DIANA LÖBER,
GLOBAL PRODUCT MANAGER VIALS,
SCHOTT PHARMA

SCHOTT PHARMA

EVERIC® PURE – THE SAFE OPTION RIGHT FROM THE START

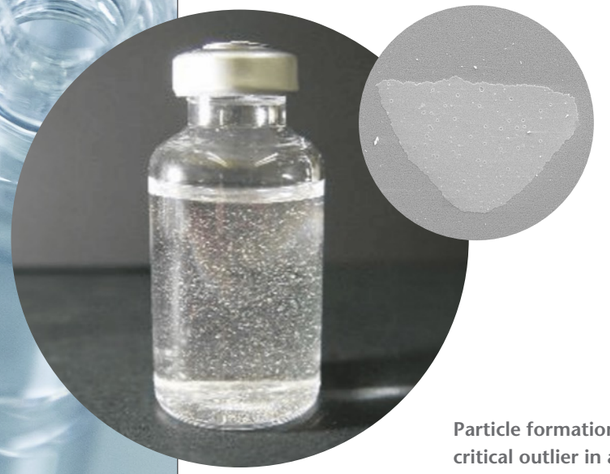
A DRUG CONTAINMENT PLATFORM TO STREAMLINE DRUG DEVELOPMENT

A whitepaper by Diana Löber,
Global Product Manager Vials,
SCHOTT Pharma AG & CO KGaA

WRONG CONTAINER CHOICE – A THREAT TO PATIENT SAFETY AND TIME-TO-MARKET

A common situation is that pharma companies select a certain primary packaging container and in first short term studies, everything is fine … Later, issues could occur during development or after launch – maybe even years after the launch. These issues could be the presence of glass particles due to delamination or a shift in pH because of elevated leachables. From a patient safety perspective, this is disastrous, with a threat of blocked blood vessels, adverse reactions, or unavailability due to market recall respectively drug shortage.

One example is a case from 2010. The drug had been on the market for roughly ten years before suddenly, certain vials showed the presence of particles. A big recall followed, and all containers were retrieved from the market. Glass particles were found in only 0.03 % of the analyzed vials. This demonstrates that appearance of glass delamination is driven by production outliers, which makes it very difficult to address.



Particle formation of critical outlier in a conventional vial batch

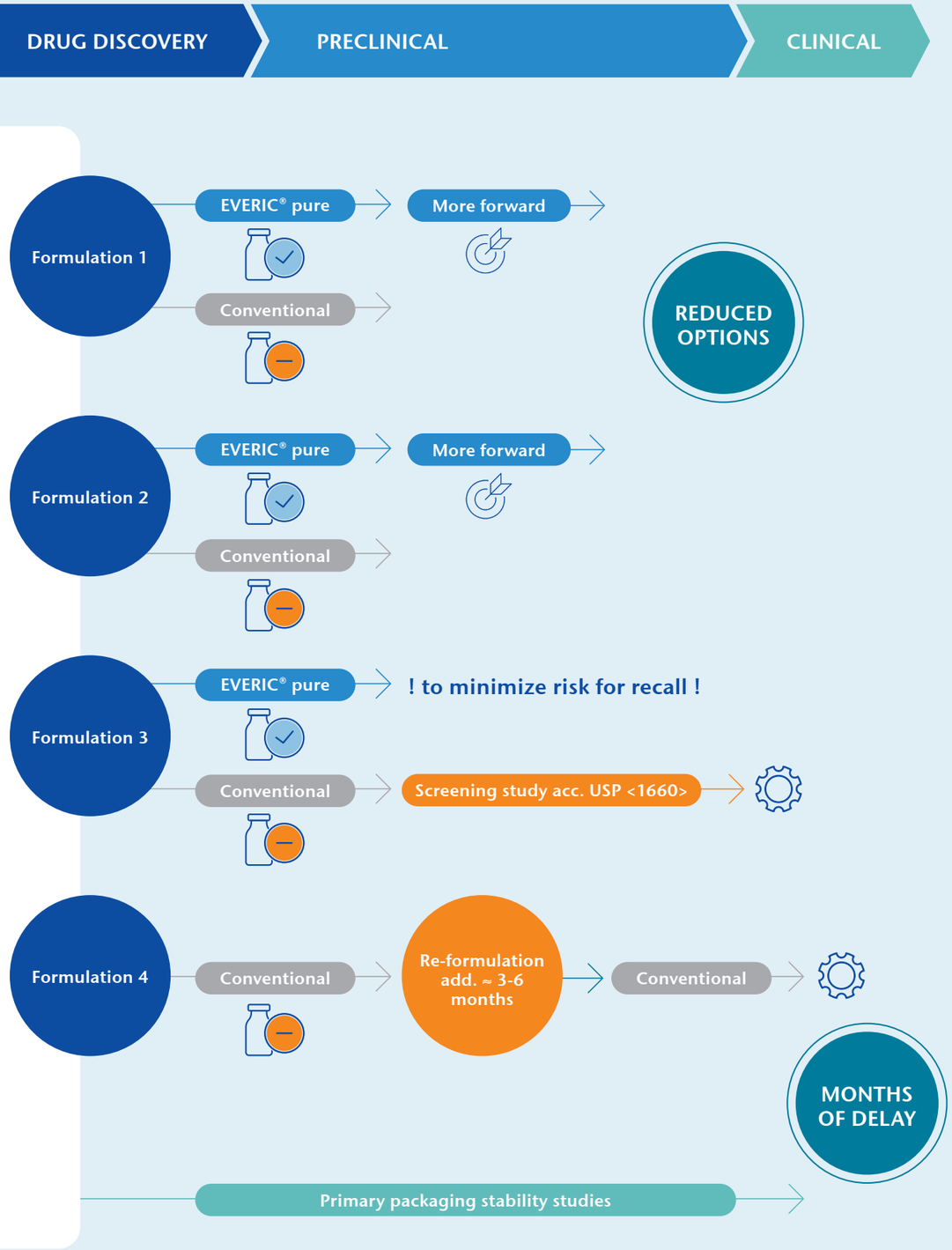
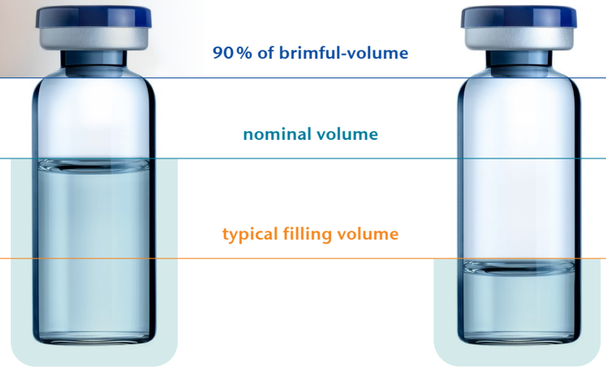


FIGURE 1: Primary packaging stability studies



Pharma companies can also face unpleasant surprises in the early stages of development when specific formulations are not stable in conventional vials. This can lead to a restriction in packaging options or even product re-formulations that can take many months, resulting in lost time and money.

CONTROLLING THE CONTAINER'S INNER SURFACE

As the most relevant contact surface for the drug formulation, a conventional vial container's inner surface may not be chemically stable enough for long term storage through the desired shelf-life. The only chemical durability test pharmacopeia require for Type I glass is for surface hydrolytic resistance, which is insufficient to determine a container's suitability for long term drug storage.

The hydrolytic resistance test assesses a glass container's chemical stability by measuring its resistance to releasing soluble ions into water.

The procedure begins with the determination of 90 % of its brimful capacity, its maximum useful storage volume. The containers are repeatedly rinsed to replicate the washing process on bulk filling lines before filling with purified water to 90 % of its brimful volume. After the containers are autoclaved, solutions from the containers are pooled for titration or flame spectrometry measurements for the amount of released alkali. This means that one "very good" and one "bad" container would end up with an average good result.

A QUESTION OF PROCESS CONTROL

Achieving a consistently high surface quality is a matter of process control. Theoretically, every vial should have the same inner surface quality if the process is stable. Reality proves different, though: outliers exist that can lead to costly recalls if the criticality is not correctly assessed, and follow-up measures taken. With millions invested in development, drug stability can be put at risk because of the wrong container choice.

The inhomogeneity of the inner surface of these outliers originates from a zone just above the heel of the vial. During the vial production process, the glass tube is heated, which causes evaporates to condense on the nearest cooler region of the vial's interior surface: the aforementioned heel zone. This area is less chemically durable and more susceptible to the processes that lead to delamination.

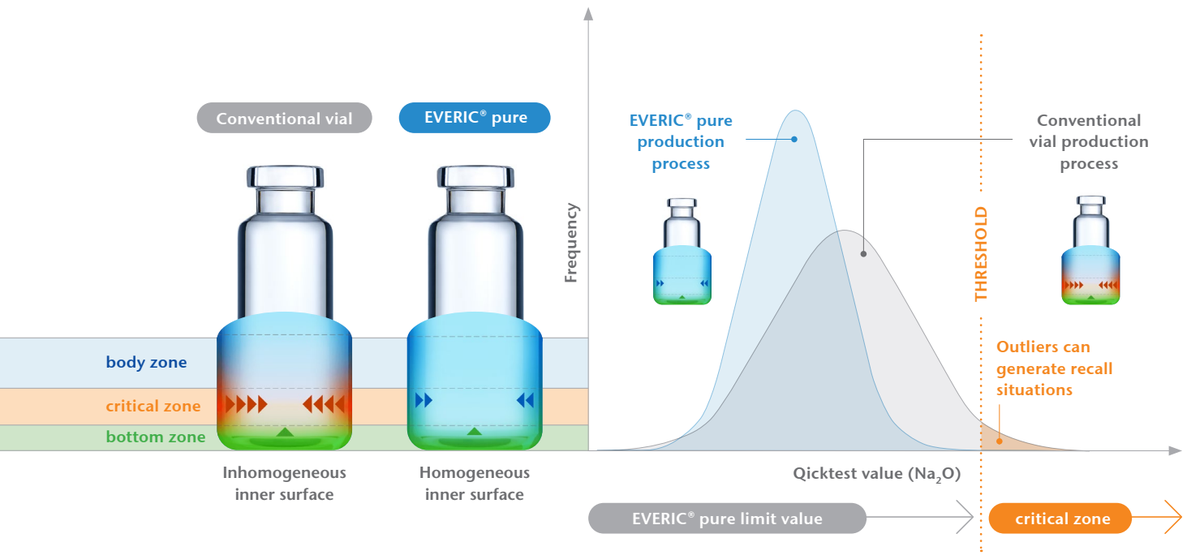
THE SOLUTION TO A CONTROLLED, HOMOGENEOUS INNER SURFACE

In combination with a leachable-improved glass tubing (Controlled Hydrolytic Resistance), SCHOTT Pharma has established a patented process that avoids these condensates and leads to a homogenous inner surface in conjunction with a dedicated release test (Quicktest). Imagine having a vial with a bad heel zone – if filled to 90 % of its maximum capacity, the effect is diluted and will normally pass the standard pharmacopeia surface hydrolytic resistance test. It might be a vial with a very bad heel zone but a good remaining quality of the rest of the inner surface – it cannot be identified as a "bad" vial, and the severity will not be detected.

The release test involves mimicking a glass attack by autoclaving and then filling with purified water. In the usual test for hydrolytic resistance, the vial is filled to 90 % of its maximum capacity. For the **EVERIC® pure** release test, each format is filled so that only the relevant heel zone is covered to determine the effect of that area.

The amount of released sodium is measured and compared with a certified limit value for each format. It is even possible to produce vials that are within the limit for the hydrolytic resistance of pharmacopeia but outside the specified Quicktest limit value. These are the critical outliers, or “bad vials”, that can occur during conventional vial production.

FIGURE 2:
Conventional vial vs. EVERIC® pure



How the Quick-test works

01

Glass attack
Autoclaving empty head first

02

Leaching
Autoclaving filled with H_2O

03

Determination of Sodium via AAS*
Certified release citeria for Sodium (Na) – limit value defined per format

*AAS = Atomic Absorption Spectroscopy

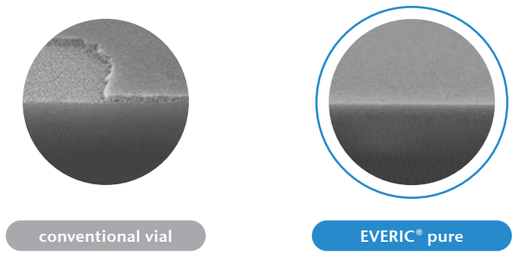
SAFEGUARD THE INTEGRITY OF VALUABLE DRUGS

A homogeneous inner surface results in two factors that increase drug stability: no delamination and a lower leachable level.

NO DELAMINATION

The microscopic images below show that a detachment of flakes took place in a conventional vial filled with a phosphate buffer at pH7 after storage for 24 weeks at 40 °C. In contrast, the **EVERIC® pure** vial under the same conditions shows no sign of glass attack. This has also been seen with different buffers at different pH levels, but phosphate represents one of the more critical buffer systems.

DETACHED FLAKES IN CONVENTIONAL VIAL
Filling: phosphate buffer pH 7. Storage: 24 weeks at 40 °C

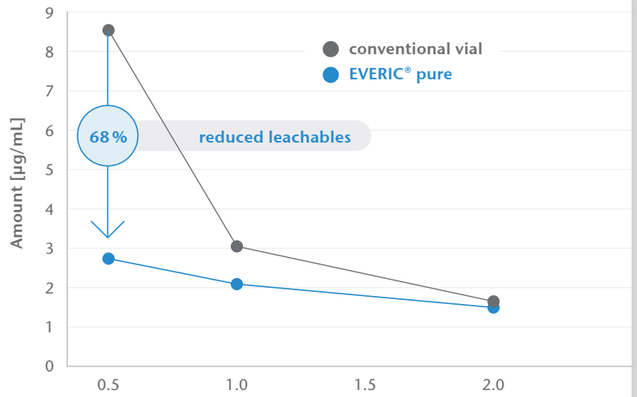


LOWER LEACHABLE LEVEL

It has been identified that a lower leachable level is especially relevant for low filling volumes. Since the changed heel zone is the leading cause of the higher leachable level of conventional vials, the impact of an improved, homogenous inner surface is much more pronounced for low-fill volumes.

While the 2 mL (nominal) filling volume shows no significant difference between **EVERIC® pure** and a conventional vial for leached sodium per ml, a considerable difference can be identified for a filling volume of 0.5 mL. So, for drugs typically filled below the nominal volume, greater attention should be paid to leachables analysis.

FIGURE 3:
Leachables level for different filling volumes



Filling volume [mL]
2R vial. Filling: purified water. Storage: 24 weeks at 40 °C

EVERIC® PURE – THE RIGHT VIAL FROM THE START

Choosing **EVERIC® pure** as your default container solution during drug development offers the most significant reduction of risk, which is vital for patient safety, cost, and time to market. **EVERIC® pure** delivers reduced leachable levels because of the improved chemical durability of the heel zone Therefore, there's an increased likelihood that a formulation remains stable – less risk for the stability of the protein or for the pH shift of a diluent.

Many factors influence stability during drug development, including buffer systems, pH range, post-treatments such as terminal sterilization, or storage conditions, the interplay of which cannot be foreseen at the beginning of the vial selection process. **EVERIC® pure** offers a safe platform that provides a broader range of formulation options, potentially avoids additional re-formulation cycles if one formulation fails, resulting in a faster time-to-market.

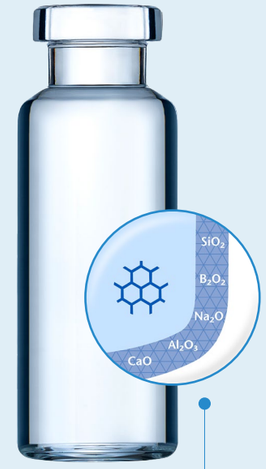
THREE REASONS TO CHOOSE EVERIC® PURE

1. Improved patient safety and shorter time-to-market
- Proven drug stability
- Increased formulation options
- No additional screening studies
- Less delays due to reformulation

2. A tried and tested solution
- More than ten years in the market
- More than 100 commercial products
- More than 40 customers
- Only solution with an in-production release test

3. Simple switching
- Available in formats between 2R-50R and in adaptiQ®, a pre-sterilized nest configuration
- No re-registration due to unchanged glass composition

For more information, please visit:
www.schott-pharma.com



Homogeneous inner surface

EVERIC® pure

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

DIANA LÖBER

Diana Löber (Global Product Manager Vials at SCHOTT Pharma) 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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