

Time to Set Standards

Learn how standardization in primary packaging can reduce complexity and time to market.

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Raise Your IQ

We believe a standardized approach to primary packaging will give companies more filling-line flexibility.



By Gregor Deutschle, Director Business Development Sterile Solutions at SCHOTT Pharmaceutical Systems

The current trend towards high-value medicines for smaller patient populations will likely accelerate with the advent of personalized medicine and diagnostic tests that can better assess which medicines will work in which patients. In some cases, a company may only be filling a few hundred vials at a time. Many pharma facilities were built around a traditional "blockbusters" model – filling millions of identical containers in a single run – so small batches can be a production nightmare. On Monday a company may be filling a 6R vial, and on Wednesday need to swap to cartridges. Most filling lines are not efficient when it comes to short production runs and the frequent changeovers can lead to a lot of downtime. Containers will need to be changed, equipment will need to be cleaned/decontaminated, and ramped up, which can take several shifts.

A New Age of Collaboration

"In the light of particle reduction and smooth handling of the drug product during production, reliable processes have gained importance. This calls for a new type of cooperation mindset between formulation developers and suppliers, as well as amongst the suppliers themselves. The iQ™ approach is a good example of how to step up the dialogue between packaging suppliers and fill and finish specialists." Thorsten Häfner, Director Business Development at Groninger.

"iQ™ works on whatever machine you want. As of today, it is already compatible with over 30 machine platforms of all the leading and also upcoming vendors." Fabian Stöcker, Head of Global Strategy & Innovation, SCHOTT Pharmaceutical Systems.



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There is a key need in the industry for new manufacturing systems that allow for more flexible production, and some filling machines have already been developed that can cope with different types of containers. But how can makers of primary packaging contribute?

At Schott, we believe that the answer is standardization.

Time to agree on a new standard
iQ™ is one of the newest products launched by Schott. The concept is simple: iQ is a flexible filling platform that standardizes nested ready-to-use (RTU) syringes, vials and cartridges in a single tub format (a 3-inch tub as per ISO 11040-7), allowing them to be processed on a single machine. Using the same tub means fewer format parts to swap during changeovers.

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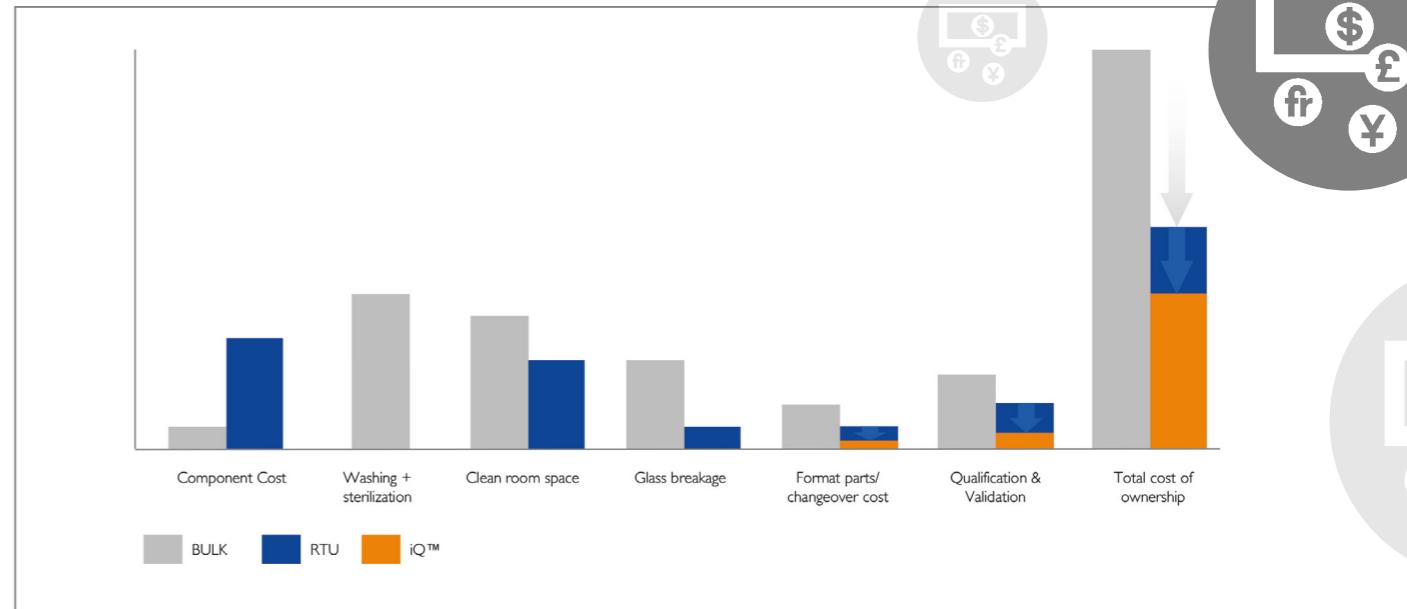
Convincing Inner Strengths

Before we started developing iQ, I attended a conference where one speaker gave a presentation explaining why the size of a tub needed to be specifically optimized for each packaging format. The benefit? Matching the right sized tub to the container is useful for logistics and saving space in warehouses, but in terms of processing it leads to a great deal of tub variety and the need to optimize machines for each tub size during changeovers. Changeovers times can vary depending on machines and formats, but it wouldn't be uncommon for a changeover to take several shifts.

Our view at Schott is that a more standardized approach would be of great benefit. With iQ, there is minimum effort required when changing from one format to another. Using one standard size of tub means less machine adjustment and significantly faster line changeovers. At CPhI 2017 in Frankfurt, we performed live demonstrations of changeovers on our booth, showing that they could be performed on a Bausch+Ströbel filling machine in 10-15 minutes, with just a small handful of components.

The benefits can be summarized as follows:

- Reduced complexity. Validated, RTU containers and components have already had a positive impact on customer processes and product time to market. Now, we're also reducing the complexity of running filling equipment, by ensuring that the process of introducing the containers is fully harmonized.
- Maximized flexibility. Choosing the right container for the right drug is important, but we offer a full range of different container options to our customers in a standardized platform – meaning that customers get their perfect container, in a more flexible format that works on most standard filling lines. iQ™ is compatible with Schott's syriQ® prefilled syringes and adaptiQ® ready-to-use vials, as well as the new cartriQ™ ready-to-use cartridges, which will be available soon.
- Improved patient safety. iQ relies on the proven nest-and-tub format, which prevents glass-to-glass contact and breakage. At Schott, we also have ways of identifying and preventing cosmetic defects that may affect the strength of the glass. We also have particle reduction programs at Schott.



Counting the Cost

Traditional aseptic manufacturing consists of three separate lines – a bulk cartridge line, a bulk vial line, and a pre-filled syringe line – in separate clean rooms. Switching to RTU containers saves space by eliminating washing machines and heat tunnels, but the ultimate cost-saving solution is to invest in one processing line with nested filling that can accommodate different types of containers. Companies save money because they are only purchasing and running one line, and they will also only need one clean room.

- Bulk filling – Total cost of ownership includes components, washing and water for injection usage, sterilization and power usage, clean room space, glass breakage, format parts and

- changeover, and qualification and validation.
- RTU – Initial cost for the components may be higher, but savings can be found in the elimination of washing and sterilization steps, reduction in clean room space, less parts and changeovers, and reduced qualification and validation.
- iQ – The new concept boosts the advantages of RTU filling. Thanks to less cost for format parts and changeover, and qualification and validation, pharma companies can gain even more benefits.

A case study* has found that iQ can:

- reduce investments by up to 40%
- reduce clean room space by 60%
- reduce running costs by up to 40%
- reduce time to market

*The above cost savings are based on the results of an individual case study. The actual savings may largely vary depending on the specific customer's situation. SCHOTT cannot accept any responsibility for the achievement of the above savings.



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The idea for iQ developed over time. Its origins can be traced back to the emergence of RTU syringes. The fact that RTU syringes can immediately enter a sterile environment was a huge boon for manufacturers – getting rid of their washing or sterilization steps, reducing equipment and running costs, and making their processes leaner. RTU has set the standard for syringes and is now offered by a number of vendors, including Schott. In time, the industry began to ask for RTU vials as well, which raised a number of questions.

What should the packaging for RTU vials look like? What is the best tub size? The best nest? Do we optimize the packaging for logistics? Or do we optimize the packaging to make it easier to use from a process perspective? While Schott was considering these questions, the need for more flexible manufacturing processes in the industry began to become more urgent. Rather than tailoring processes and packaging for individual applications, we opted to develop a standardized platform.

Combined wisdom

iQ launched in October 2017, and the feedback has been incredibly positive. For vendors, it is not enough to develop a new vial or machine that is incrementally better than what is already available – vendors must listen to their customers, identify the challenges they face, and then collaborate to come up with holistic solutions that are easy to implement. iQ involved collaboration with a large number of companies, to ensure the platform was truly fit for purpose. We worked with machine vendors (Bausch+Ströbel, Bosch, GEA, Optima, Groninger and Vanrx, among others) to standardize packaging dimensions and to ensure that our platform would run on most filling machines. We also liaised closely with established elastomer component suppliers (including West, Aptar, ARaymond, Daikyo, Datwyler, and Gore) to offer pre-validated and flexible container systems. Ultimately, we are not offering an individual product, but a full, validated solution.

Customers were also involved in the iQ development process – and were pleased to see us adjusting our product portfolio in response to the industry's need for increased flexibility. I believe that standardization is the way forward, without a doubt. Biopharma manufacturing needs to change by becoming easier and more efficient – standardization can enable this. You find standardized solutions almost everywhere, from WiFi and USB to shipping containers and palettes, to the size of credit cards. All these standards have some great features in common: they enable flexibility, simplify and speed up processes, and also save costs. We want to do the same for RTU packaging and filling lines – ensuring that customer processes run smoothly and have the flexibility to adapt to changing industry needs. In essence, we want customers to worry less about packaging components and processes, and instead focus on the real business of making medicine that helps people to live healthier lives.



Finding a Perfect Fit

Manufacturing containers is one thing – but providing holistic container-closure-systems is another. Hence, SCHOTT's concept includes a set of pre-validated elastomer components. The aim is to help pharma companies to significantly lower their test efforts.

ARaymond MORE THAN FASTENING **Aptar** pharma **DAIKYO**

GORE Critical Technologies Worldwide **West** **DATWYLER**



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In today's pharma industry, glass breakage is mainly related to older filling lines, but the increasing number of highly toxic and/or sensitive drugs is driving innovation in glass technology. The key is to work with a supplier to meet your specific needs – and keep down the regulatory hassle.



By Professor Volker Rupertus, Senior Principal Expert for SCHOTT, and Dr. Folker Steden, Director Product Management and Scientific Services, SCHOTT Tubing.

Some may find this surprising, but if you stand on top of a beer bottle and load two or three of your friends onto your shoulders, the only thing you'll risk breaking is your neck. Glass possesses remarkably high strength, and in the pharma industry, breakage out in the "field" – either during logistics or even in pharmacies and hospitals – rarely happens. In fact, a competitor recently told us that they had once spent hours repeatedly dropping glass syringes from an office table in the hope of filming a breakage – with no luck. Hospitals usually have synthetic flooring that helps prevent vial breakage, but the main reason is simply that glass is very resilient.

Glass will only break if the mechanical load applied to the item, multiplied by the "criticality" – pre-damages, such as scratches – is greater than the strength of the glass. This means that a perfectly shaped piece of glass can survive tremendous mechanical loads, but with pre-damage, the risk of breakage is much greater. Glass breakage in the pharma industry tends to occur during processing, and is often related to the age of the filling equipment. Companies with state-of-the-art technology tend to experience very few breaks, whereas companies that run their products on old filling equipment and filling lines will experience more.



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Glass has a memory

The key to reducing glass breakage resulting from old filling technology is to reduce the amount of pre-damage. A common phrase in the glass industry is that "glass has a long memory," which means pre-damage, either to the glass tube or the final container, cannot be undone – the damage will be carried through the whole process. By preventing pre-damage, you can easily secure the breakage resistance of a glass container at its highest value by nature.

With Schott's perfeXion™ initiative, the entire surface of every single tube is checked for pre-damages. Later on during the converting step, further improvements can be achieved with advanced forming technologies combined with inspection technology – this also helps to avoid scratches and reduce particle load in the container significantly. In short, packaging with a high cosmetic quality secures the breakage resistance of the container beyond what is required for most of the industry.

There are certain market niches, however, where the chance of breakage must be reduced beyond what would normally be required. The problem of old filling machines will fade over time as the packaging industry continues to work on improved glass handling, advanced transport and logistic concepts and RTU solutions. Yet radioactive contrast media or certain oncology drugs, for example, can be very toxic, and companies must ensure that breakage never occurs. Another example is drugs intended for use in warzones, where the containers must be highly break resistant (for obvious reasons). The question remains if these applications can be addressed with existing solutions, or if pharma companies have to switch to new solutions and go through all the regulatory headache associated with this.

Is there a perfect type of glass?

Type-I borosilicate glass has been the gold standard for pharmaceutical packaging for over a century. As a result, there are thousands of data sets and long-term trends for all kinds of formulations available. This helps to reduce risks in the selection process for new containers. Containers are now coming onto the market that use a different glass composition – aluminosilicate glass – more commonly found in mobile phone covers and halogen lights. Schott is in a good position to comment on both glass types, as they have been part of our portfolio for decades. We

have been supplying aluminosilicate glass to consumer electronics industries worldwide, and this glass is also the basis for glass-ceramic applications such as CERAN® cooktops.

Aluminosilicate is certainly an interesting glass type, but the feedback we get from our customers is that there is reluctance to perform the studies to characterize drug-container interaction, the extractable and leachable profile over the lifetime of a drug product, and so on. There's no scientific track record in terms of interaction between drug components and the glass surface, and, understandably, companies that don't have any problems aren't keen to take on additional validation.

"A high cosmetic quality will already secure the naturally high breakage resistance."

It's also important to differentiate glass properties from container characteristics – achieved during post-processing. What drives the break resistance is not the glass composition, but rather the post-treatment process. Borosilicate glass is a very neutral material, which – without further treatments – shows the lowest reaction between chemical products and glass itself. Aluminosilicate glass, in turn, needs intense treatment (e.g. ion exchange in the glass surface and therefore an undefined gradient in the near-surface glass composition) to reach the same level.

The good news is that literally any desired property, such as reduced risk of delamination or breakage resistance can be achieved with borosilicate glass that has already been approved by regulatory bodies. For example, it can be chemically strengthened through an industry standard ion exchange process to produce tougher metrics: a five to ten-fold higher break resistance. For an industry that wants to reach a cost/benefit optimum this is the better way to go.



Using Drones to Examine Breakage

Sometimes little things can make a huge difference. When a leading pharma company approached Smart Skin Technologies to develop a (break)force analysis tool for their manufacturing line, the Canadian experts signed on immediately. "Our company has been supplying the food and beverage industry with drone-based online monitoring systems for many years," says Joe Norris, who is responsible for the company's New Product Development. "Imagine the drone as a container that has feelings. Up to 200 sensors on its surface measure how it moves through the production line, and where forces occur that could affect its integrity," he says. As a result of the project, the pharma company could practically eliminate breakage on the respective lines by performing simple, low-cost changes. "Adjusting certain edges and ensuring that moving parts were synchronized in a better way made all the difference," says Norris.

This is a straightforward approach to a significant problem, and is receiving more and more interest from pharma manufacturers. Today, Smart Skin's system works on syringe, vial, and cartridge lines.

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Creating a chemically stable inner container surface is an ongoing quest for packaging makers. Different options can help to minimize the risk of delamination, protecting sensitive drugs or improving lyophilization results.



By Dr. Bernhard Hladik, Senior Business Development Manager at SCHOTT Pharmaceutical Systems

Combating Delamination with SCHOTT Vials DC

Glass delamination has been known about for decades, but the problem only permeated pharma's consciousness in recent years, following a number of product recalls. It was found that drugs were corroding the inner surfaces at the bottom-near area of some glass vials and causing thin, flexible fragments called "glass lamellae," or "flakes," to detach. Delamination typically occurs weeks or months after filling, and there are a variety of container, processing, storing and drug formulation factors that contribute to the problem.

In order to tackle this challenge, we looked at all the relevant steps in glass production to identify which step increases the risk of delamination the most – and we found that conventional converting processes might generate inhomogeneities on the inner surface of the vial in the bottom-near wall area. In light of this, we optimized the manufacturing process to create vials with a unique surface homogeneity and chemical stability: SCHOTT Vials Delamination Controlled (DC).

The key point is to use already established manufacturing principles and to more tightly control those process steps, which has an impact on the delamination propensity. The end result is that pharmaceutical companies do not have to reregister a drug when changing the Type I packaging container to SCHOTT Vials DC.

As a matter of fact, only a very small portion of conventionally manufactured vials have an increased delamination propensity. Yet these "outlier vials" are the ones which might cause a delamination

recall. Therefore, the key point of our DC technology is to cut off those seldom outliers by tighter control of the process steps that influence the delamination propensity. But how could this delamination propensity be monitored during packaging production? SCHOTT developed and patented a quick routine test to tackle this challenge – the SCHOTT Delamination Quicktest. This Quicktest is used to validate the process for SCHOTT Vials DC and serves as release criteria based on a quantitative limit value.

The Quicktest works as follows: random vial samples are taken out of production according to ISO 2859 and autoclaved bottom up for four hours to tease out the delamination critical zone. In a second step, the vials are filled with WFI (water for injection) and autoclaved again. The extracted amount of sodium correlates with the likeliness that the vial will experience delamination later on. By monitoring these values and adhering to certain thresholds, the delamination propensity of the vials is minimized to the highest extent possible.

The capabilities of SCHOTT Vials DC were proven in a case study. Within a period of 48 weeks, no delamination was observed with 2 ml SCHOTT Vials DC stored at 40 °C with three different model buffer/solution systems (citrate, phosphate and sodium bicarbonate), whereas the reference vials (standard quality) developed delamination or pronounced pre-indicators for delamination for phosphate and sodium bicarbonate. The study was the Parental Drug Association's most frequently downloaded Technology/Application paper in 2017 (1), which demonstrates the industry's growing interest in delamination.

Finding suitable vials for delamination screenings SCHOTT also uses DC technology to produce typical "outlier vials" with an increased risk for delamination in accordance with regulatory requirements like the European pharmacopoeia and the US Pharmacopeia. Although this may seem surprising at first, there is a good explanation; using conventionally produced vials for a predictive screening study might be misleading. Most likely,



you will not see delamination even for a critical drug/formulation, as the majority of the conventionally produced vials exhibit a low delamination propensity.

Therefore, we produce outlier vials with increased delamination propensity with a defined parameter setting and a high process capability on purpose. These so-called Dela Test Vials should be used for a predictive screening study to elaborate if the drug formulation is sensitive to typical outlier vials. Our Dela Sample Kit combines such Dela Test Vials plus SCHOTT Vials DC in a complete package – and is a good basis for predictive screening studies.





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Another way to improve the chemical stability of a pharmaceutical container is to apply coatings to its inside surface. For drugs in need of even greater protection, or for applications that are subject to lyophilization, such functional coatings offer a proper alternative.

These thin, yet highly effective layers are applied with the help of a PICVD technology, which stands for "Plasma Impulse Chemical Vapor Deposition." The vials are washed, dried and then placed inside a reactor where a plasma reaction takes place. Multiple vials can be coated simultaneously within a single cycle that only lasts about a minute. Afterwards, the thickness of the coating and quality of the vial itself are checked with the help of automated inspection systems.

Over the past decade, we have seen our coating capabilities evolve. Today, they enable us to offer vials whose inner surface show additional properties – an ion barrier or hydrophobic behavior, for example.

SCHOTT TopLyo® coated vials for efficient lyophilization
Lyophilization places high demands on pharmaceutical packaging. It needs to be able to withstand mechanical and thermal stresses, guarantee low chemical and physical interaction of the container walls with the drug and, last, but certainly not least, allow for an intact lyo cake and complete removal of the dosage after reconstitution to reduce overfilling.

SCHOTT TopLyo® vials are endowed with a stable and hydrophobic interior surface and are especially recommended for lyophilization. The hydrophobic properties are similar to the so-called lotus effect: liquid residues are drawn together to form individual drops and consequently leave minimized residual volume. The adhesion of substances to the surface of the containers is thereby reduced.

The coating further ensures an aesthetic lyo cake as fogging and disruption of the lyo cake during the lyophilization process is avoided. Further, residual silicone typically found in siliconized vials is fully avoided for SCHOTT TopLyo® vials using the PICVD process. There is a pronounced trend for high potent biotech drugs to avoid residual silicone as the efficiency of the drug might be affected.

SCHOTT Type I plus® – inert SiO₂ layer
The inside SiO₂ coating of SCHOTT Type I plus® vials provides an



Razor-thin coatings create an ion barrier with a superior E&L profile to protect the drug formulation

Hydrophobic coatings have a double advantage: less fogging during lyophilization and a flawless lyo cake...
...plus easier emptying and less residual volume after reconstitution, reducing the need for overfilling.

ion barrier that significantly reduces the interaction between drug product and container surface. Consequently, the coating ensures that the formulation remains stable over shelf life by reducing ion leaching from the packaging. Sensitive drug formulations thus benefit from increased shelf life stability and minimized adsorption of proteins in liquid formulations. Further, a pH-shift for unbuffered formulations is avoided using SCHOTT Type I plus®.

Demand on the rise
Due to the rise of biotech drugs and the need for superior

packaging solutions, we are significantly increasing our coatings capabilities at our production facility in Müllheim, Germany. Our 20 years of experience in manufacturing coated vials have been incorporated in the conception, focusing on minimizing glass-to-glass contact and reducing particle load.

Reference

- I. U Rothaar et al., "Comparative delamination study to demonstrate the impact of container quality and nature of buffer system", PDA J Pharm Sci Technol, 11/12, 70, 560-567 (2016). PMID: 27325595.

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