# newsflash

## PHARMACEUTICAL PACKAGING

SCHOTT
glass made of ideas

ISSUE 22 | October 2014


NEWS

# Perfectly tuned – Why packaging and filling lines must go hand in hand

New trends in medicine, such as the rise of highly sensitive biopharmaceuticals, are causing a need for the pharmaceutical industry to re-think packaging solutions and related processes. Moreover, manufacturers are urged to reduce overall operational costs – one reason why they turn their eyes towards new filling concepts such as high-speed filling or nested packaging.

In order to ensure efficient processes, however, manufacturers of packaging, filling lines and devices must work closely with pharmaceutical companies. With this in mind, SCHOTT is constantly seeking new ways to develop advanced packaging concepts in joint projects with its partners. "The overall goal is to enable pharmaceutical companies to use their filling lines either in a faster or a more flexible way," says Jörg Döscher, Director Strategic Marketing. Two recent examples show how SCHOTT's close cooperation with leading machine manufacturers such as Bausch+Stroebel, Bosch Packaging Technology, GEA, OPTIMA and VANRX culminates in new packaging solutions: a cartridge specially designed for high-speed filling lines, and adaptiQ™, the first ready-to-use system that allows for vials to be freeze-dried inside the nest.

### 10 % faster: nested freeze-drying

It has been common practice for sterile syringes to be packaged in nests and tubs and supplied with pre-treatment steps such as washing and sterilizing already performed. For pharmaceutical vials, however, this is rarely the case. As a reaction to the demand of pharmaceutical companies

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**Product** – Double chamber cartridges enable shorter time to market for biotech products. Learn more on page 3.

EDITORIAL

Dear Reader,

SCHOTT has always emphasized the importance of collaboration, in all areas. In order to keep up with the trends in our industry – here I am referring to compliance but also the growing number of biotech products – pharma companies, packaging suppliers and filling line manufacturers must develop solutions together. You'll read more about the success that this can lead to in this issue: cartridges developed especially for high-speed filling lines, syriQ™ InJentle glass syringes for less drug/container interaction, and the ready-to-use adaptiQ™ system that enables freeze-drying of nested vials.

Close cooperation with major, globally active customers on optimizing the supply chain is also important to us. In addition, technology transfer between SCHOTT sites is crucial to ensuring quality. Thanks to these efforts, we are able to support our customers' growth plans in established as well as pharmerging markets.

I hope you enjoy reading the latest issue of newsflash.

Andreas Reisse
Executive Vice President
Pharmaceutical Packaging

SERVICE

# Sterilization of primary packaging influences results of E&L studies

Pushed by regulatory requirements pharma companies need to conduct extensive studies on "Extractables and Leachables" (E&L) to exclude possible harmful interactions between the packaging materials and the medication.

Extractables are determined by subjecting the packaging material to aggressive conditions such as different solvents at elevated temperature for extended periods, resulting in substances that elute from these packaging systems. By contrast, Leachables are substances that migrate into a phamaceutical formulation under normal preparation and storage conditions. The primary sources of "organic" E&L are elastomeric and polymeric materials like rubber and plastics. Here, it is important to know the exact composition of the packaging material in order to be able to perform studies efficiently. Since this type of information often cannot be obtained from the material suppliers, most testing laboratories have built up comprehensive databases on materials and additives.

The procedure of E&L studies is specified in a number of guidelines or regulations for the United States and Canada as well as for Europe. These, however, do not include any specific instructions on how to perform E&L studies.

One of the challenges with E&L studies is that the study design has to be adapted to the drug composition and processing as well as the packaging properties. For example, the experts from SCHOTT Pharmaceutical Systems have observed that the extraction profile varies depending on the sterilization method used.

"For some packaging components such as stoppers, sterilization is mandatory before they can be used for medical purposes. However, Gamma irradiation can lead to polymer and additive degradation, whereas steam sterilization can also alter the mechanical and chemical properties. Both have an impact on the extraction profile," says Dr. Thorsten Sögding, laboratory manager at SCHOTT pharma services.

To demonstrate this impact, his team has conducted a study with commercially available stoppers made of bromobutyl rubber for use in syringes. It included five different stoppers from three different manufacturers and three variants of sterilization: steam sterilization, gamma sterilization, and a combination of gamma-irradiation and steam-sterilization.

## Results of the study

The total content of organic components deviates significantly between various bromobutyl stoppers from different manufacturers. In most cases, acetone and bromomethane can be found prior to any sterilization. The concentration of volatile organic compounds (VOC) out of all samples significantly increases upon gamma-sterilization. Additionally, the total amount of extractable palmitic and stearic acid increases. Significant amounts of isobutene and other unsaturated hydrocarbons can be observed only after gamma-sterilization.

Conversely, the concentration of extractable stopper additives, like antioxidants, out of all samples significantly decreases following gamma-sterilization. This might influence the stability of the base polymer material and lead to formation of pyrolysis or radical degradation products of the basic polymer, e.g. formation of isobutene or bromomethane.

Generally, the sum of VOC decreases upon steam-sterilization. That effect is also observed for single substances like isobutene, bromomethane, and acetone. In most cases a more or less pronounced decrease of extractable fatty acids can be observed. But steam-sterilization has no significant influence on antioxidant concentration.

## Need for customized studies based on best practice guidelines

The results of the study clearly demonstrate that sterilization of polymer components influences the respective extraction profile significantly. Thus, it can expected that the amount and the type of leachables from a primary packaging product that comes into contact with a pharmaceutical formulation also depends on the sterilization processing.

Also, while this type of study is useful for giving trends, it is too general to fulfill the specific needs of an individual drug / container system. Therefore, customized E&L investigations should be executed on the basis of best practices extractables guidelines.

Laboratory service providers like SCHOTT pharma services can design and execute customized E&L studies based on best practice guidelines, and they also possess comprehensive know-how on the entire life cycle of commercially available primary packaging. This knowledge is crucial to determining the origin of the substances found. The report and further information on SCHOTT pharma services is available at

pharma_services@schott.com


Typical stoppers used as primary packaging material; volatile, semi-volatile, and non-volatile compounds are analyzed to ensure the safety of the drug.

NEWS

# Perfectly tuned – Why packaging and filling lines must go hand in hand

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SCHOTT – in close cooperation with filling line manufacturers – has developed a system solution for vials which is scheduled for launch at the end of 2014. To prove the advantages of the new adaptiQ™ system, SCHOTT has conducted a case study on freeze-drying of nested ready-to-use-vials together with GEA Lyophil GmbH, a company that specializes in freeze dryers for R&D purposes and small production batches, industrial size freeze dryers, and complete freeze dryer systems. Tests with a 3 % Mannitol solution have shown that the process of freeze-drying can be accelerated by applying the adaptiQ™ nest and tub concept. The main study result: The lower packaging density and the product design allow for a 10 % faster drying cycle. This fact combined with further product features such as simplified and stable loading or unloading, higher loading or unloading speed, and pre-treatment steps that eliminate washing and sterilizing processes, means that adaptiQ™ facilitates lyophilization like no other product on the market and meets the demands of pharmaceutical companies.

## Special cartridge design for high-speed filling lines

Another market demand and good example of close cooperation with machine manufacturers is the topic high-speed filling. High speed filling lines and automated camera inspection systems call for an extremely accurate geometry of the packaging. Therefore laser light and sensors are used to control fill levels. This ensures accurate bubble-free dosing and less product loss through overfilling. SCHOTT has worked with Bosch Packaging Technology to translate their process requirements into developing a cartridge, initially for insulin products, with a new neck specification. The result is a new cartridge that is designed especially for high speed filling lines. It facilitates quicker processing while reducing overfill losses.

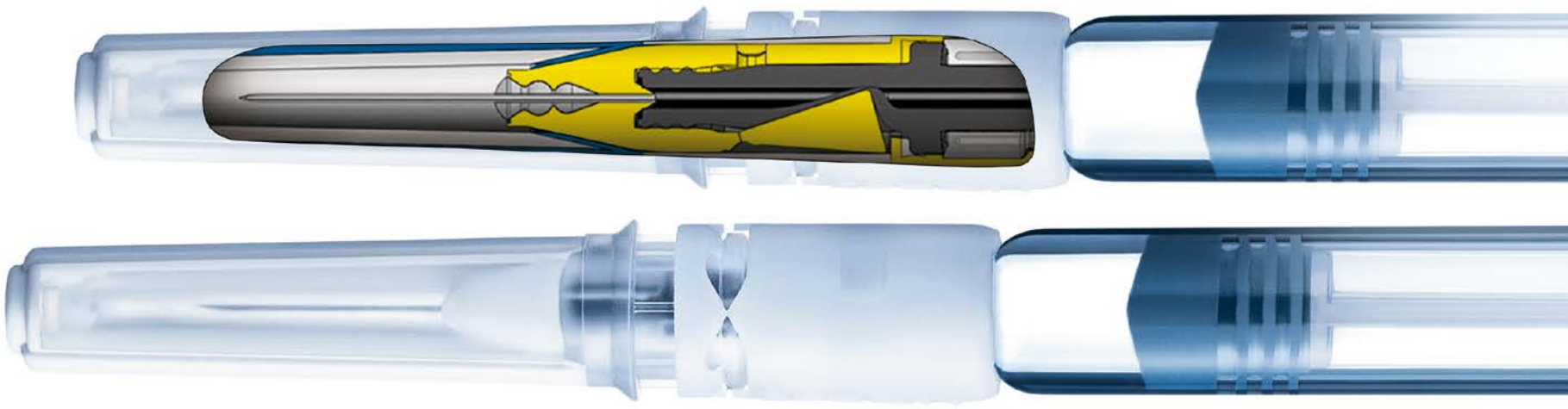
A feasibility study with Bosch Packaging Technology is currently underway, the results of which are expected to be published this fall.

"We discuss product ideas with the machine manufacturers in an early development stage," Jörg Döscher explains. This ensures that the customers benefit from an integrated, highly efficient filling process in which the primary packaging and filling lines are perfectly geared to each other.

The working relationships with leading partners such as Bausch+ Stroebel, Bosch Packaging Technology, GEA, OPTIMA, and VANRX are prime examples of this approach.

PRODUCT

# syriQ™ InJentle: A superior delivery system for sensitive drugs



Interaction between drugs and packaging has become an increasingly important topic. Especially biotech drug substances tend to interact with packaging more easily due to their complex and sensitive makeup. Particular attention should be given to drugs that are filled in prefilled syringes.

"In prefillable syringes, the drug is in contact with more materials than in other types of pharmaceutical primary packaging," says Anil-Kumar Busimi. Busimi is Head of Global Product Management Syringe Business at SCHOTT, and finding new packaging solutions for sensitive drugs is a topic his company has been working on intensively.

In response to these challenges, SCHOTT introduced a new prefillable syringe design to decrease the risk by reducing the number of materials and components the drug comes into contact with during storage. This pre-filled syriQ™ InJentle glass syringe meets the growing demand for systems that offer improved stability of sensitive drugs and also safer and more comfortable injections.

syriQ™ InJentle consists of a glass body and a newly designed syringe cone with a fluid path made of rubber, including a staked-in needle. A "pinch seal" keeps the fluid path closed during storage. And it is exactly this newly designed closure that prevents the drug from coming into contact with the metal needle or the adhesive. As a result, the drug cannot interact with these substances.

This special design of the glass barrel also eliminates the use of a tungsten pin during the glass forming process. Heat-resistant tungsten pins are commonly used to form the fluid path or luer channel in syringe barrels. Numerous studies have shown that tungsten residues could interact with sensitive biological drugs leading to protein aggregation. This not only destabilizes the pharmaceutical formulation, but also possibly could cause an undesirable immune response from the patient following the injection. The special design of the syriQ™ InJentle glass barrel avoids this problem as no tungsten pin is needed to form it. The syringe is thus entirely tungsten-free.

Yet another issue is the silicone oil used to lubricate the inside of the syringe barrel to ensure smooth injection. This lubricant is required for the functionality of the syringe, but it has also been attributed to unexpected reactions with some biological drugs, leading to protein aggregation or an increase in subvisible particles. The syriQ™ InJentle barrel, in contrast, has baked-on silicone, which significantly reduces the interaction between the drug and the silicone while maintaining the functionality.

In an additional effort to ensure packaging and drug integrity, the syringe needle shield has a tamper-evident closure. This enables physicians or patients to determine easily if the syringe is still unused. Yet this closure can be easily opened even after longer storage periods.

### Thin and sharp needles for a more comfortable administration

Additionally, the syringe's design ensures that the needle does not come in contact with the needle shield, preserving the needle's sharpness and minimizing the risk from the occurrence of 'hooks.' This combined with high-tech needle siliconization, leads to needles with a low penetration force. In fact, syriQ™ InJentle syringes are available with thin needles up to 32 gauge, making injections less painful for the patient.

SCHOTT's approach has many novel features – but is delivered in standard nests and tubs so that it can be filled on standard filling lines. This fact makes it easy for pharma companies to use syriQ™ InJentle.

"All in all, one can say that with our syriQ™ InJentle syringe, the drug has the same contact materials as a vial – glass and rubber," Busimi concludes. "This is also important if pharma companies want to switch the packaging from vials to syringes, which normally implies a lot of additional testing for all additional materials. With our solution these efforts can be significantly reduced."

PRODUCT

# Double chamber cartridges: Two become one

If you are looking for a solution that combines safe storage of sensitive formulations and convenient administration, double chamber cartridges have proven to be the container of choice. As the name suggests, this type of cartridge contains two chambers: one for the active substance and the other for the diluent, both separated by a plunger. A bypass in the glass barrel then allows the drug to be reconstituted just before it is injected. The main advantage this approach offers is how easy it is to use.

Instead of deploying two containers to store the lyophilisate in one and the diluent in another, and then drawing two syringes to first mix and then inject the medication, double chamber cartridges carry out mixing and application in one go. They are used together with a pen system, which allows for higher dosing accuracy and a lower risk of contamination. This translates into much higher safety for patients, as literally a push of a button is all that is needed. Patients can reconstitute the drugs themselves and inject them either at the hospital or at home.

The respective pens for use with double chamber cartridges are already available on the market; therefore pharmaceutical manufacturers do not need to develop these devices on their own.

### High quality during the manufacturing process

Not all double chamber cartridges are the same, however. SCHOTT has continuously optimized the production process at its Competence Center in St. Gallen, Switzerland, based on its many years of experience in cartridge manufacturing.

Today, the bypass of the cartridge is created using compressed air during the hot forming process. This avoids any traces of tools and particles. Moreover, double chamber cartridges are produced without any glass to glass contact just like insulin pen cartridges. The

aim here is to reduce cosmetic defects to a minimum.

SCHOTT manufactures double chamber cartridges in standard dimensions, but also customized to meet individual customer requirements. The curled edge as well as the length and position of the bypass can be adjusted to meet the customer's need.

In a nutshell, double chamber cartridges enable manufacturers to market their active substances for injection in non-liquid form. This reduces time to market for new drugs, which is extremely important for both – the pharmaceutical company and the patient.

PROFILE

# Off the beaten track

When you come to visit SCHOTT's German headquarters on an early summer morning, you are likely to see Peter Krüll arriving on his motorbike. "I've always been fascinated by speed and precision, be it on the streets, on and off the ski slopes – or in my job," he explains. And it's exactly these two characteristics that he likes most about his position as Director of Global Key Account Management for Pharmaceutical Packaging at SCHOTT.

Peter and his 5-member team serve as the interface for customers such as Pfizer, Merck, Roche, Novo Nordisk and the Novartis Group. "A key account for us is a company that is leading in its field, either in terms of market penetration or cutting-edge technology – or both. We act as sparring partners for these companies on pursuing joint developments." This includes new or customized packaging concepts, quality management and activities aimed at optimizing logistics and supply chain management. As part of this approach, key account customers have dedicated contacts in all of these areas.

For Peter, the trend toward higher product quality represents the greatest challenge for the primary pharmaceutical packaging market. This is being fueled by the ever higher demands of state regulatory authorities on the one hand and the steady growth of expensive biotech drugs on the other. While some family-run competitors are reaching their limitations due to this development, he feels that SCHOTT is in an advantageous position.

"My goal is for us to help our customers solve their problems by offering new packaging concepts. Our latest innovations are the result of close cooperation and thus support the growth plans of our customers in an effective manner. In fact, many of the products we have launched such as SCHOTT Vials Delamination Controlled and adaptiQ™ would never have been possible without input from our key customers and partners." And SCHOTT has more innovations up its sleeve, he notes. "With syriQ™ InJentle, we have taken a new route to reducing drug/container interaction and presented a new solution for sensitive biotech drugs. In the future, we will speed up even more to ensure our customers' success."

EXHIBITIONS & EVENTS

# Visit SCHOTT at

PDA Universe of Prefilled Syringes, Huntington Beach (US)
October 6–7, 2014

CPhI, Paris (FR),
October 7–9, 2014

ETIF, Buenos Aires (ARG),
October 14–17, 2014

Pharma Expo, Chicago (US),
November 2–5, 2014

Pharmapack, Paris (FR),
February 13–14, 2015

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MASTHEAD

NEWSFLASH
Issue 22 | September 2014

Layout: Knecht Digital- und Printmedien
Photos: SCHOTT AG


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MARKET PORTRAIT

# China finds itself at the crossroads

You don't need to look into the crystal ball to see that China continues to be important for the global economy. The country's GDP has been recording double digit growth rates for more than two decades, and despite a recent downswing it continues to be one of the world's most attractive markets for the pharmaceutical industry. Growth seems to be guaranteed in China – but which direction will the market move in?

The Chinese healthcare sector now makes up around five percent of the GDP. According to a current study published by the IMS Institute for Healthcare Informatics, spending on pharmaceuticals totaled nearly 82 billion US dollars in 2012. The People's Republic is thus already the world's third largest pharmaceutical market. The experts from IMS estimate that these expenditures will increase by 14 to 17 percent every year over the next five years.

China's pharmaceutical success story rests on two pillars. First, the economic and demographic development inside the country is resulting in an increase in certain diseases such as diabetes while awareness of sustainable healthcare and the income it requires continues to grow. Second, the healthcare sector is now a top priority for the Chinese government. For instance, it has been pursuing a comprehensive healthcare reform since 2009 that includes a major expansion of health insurance.

"The pharmaceutical market in China will continue to grow at a rapid pace," the Boston Consulting Group (BCG) confirms in its latest market report from early 2014. BCG's analyses point to two central facts: The healthcare reform will not only expand coverage for the Chinese population but also create stronger budgetary controls and price pressure.

They also expect local players to emerge as "more formidable competitors." As a matter of fact, domestic manufacturers are focusing their attention on the quality of the packaging in order to be able to offer better drugs.

Moreover, they are starting to look for more flexible production setups that enable them to use their existing lines to fill various containers. This generates a rising demand for both, experienced packaging suppliers as well as innovative and flexible packaging products.

SCHOTT covers both with its Joint Venture SCHOTT Xinkang which manufactures in Jinyun, Zhejiang Province and SCHOTT also owns a production site in Suzhou, Jiangsu Province. Moreover, the company's new solutions like the adaptiQ™ ready-to-use system with sterile vials help to address the future needs of the Chinese pharmaceutical industry.

TUBING

# Global quality standards for better glass tubes and well managed risks

As part of its global quality initiative for the manufacture of pharmaceutical tubing, SCHOTT will invest approximately 5 million euros in the modernization of its Rio de Janeiro plant. The site is home to FIOLAX® glass tubing production – a base product, which for more than 100 years has grown to become the gold standard for glass packaging in the pharmaceutical industry.

The modernization of the Brazilian plant, which will include the latest measurement technology for process and quality control, highlights SCHOTT's commitment to high and unified production standards across all of its facilities.

This emphasis on quality ensures that FIOLAX® glass tubing can be used worldwide for the manufacture of high-quality vials, syringes, ampoules, and cartridges for optimal drug storage – supporting the pharmaceutical industry in its efforts to minimize risks and ensure patients' safety. "The premium quality of the tubes is crucial for the production of premium packaging later on," said Reinhard Männl, Vice President Technology.

In addition to South America, SCHOTT also manufactures FIOLAX® glass tubing in Europe and Asia, with a global production capacity of far more than 100,000 tons. These plants not only use the same machines, quality manuals, production and management processes, they also employ the same procedures for the inspection of raw ingredients. The technology transfer between SCHOTT's tubing sites follows a strict process: machines and processes as well as corresponding measurement technology are developed at the main plant in Germany and then implemented globally at all sites in accordance with clearly defined timeframes. Furthermore, all plants adhere to the same quality manuals which are stored in a central database. Any changes are shared with every site within 24 hours and implemented immediately.