

Customer Newsletter
July 2015

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WELCOME



Gerresheimer has a strong commitment to product quality because optimum quality is absolutely essential in the healthcare market. It's all the small improvements that make the difference, providing added value to customers and users. We conducted detailed tests on more than 20,000 syringe systems so that we could optimize them in terms of function. You can read more about the study in our cover story. Bünde's successful recertification audit is further confirmation of the excellent quality of our syringe systems.

Even right at the beginning of the value chain, where the concepts for future mass manufactured products are developed, small improvements can make a big difference. From page 5 onwards you can see how Gerresheimer item, our industrial design specialist, optimized a delivery system for the implantation of artificial aortic valves. The result of the ergonomic improvement project is a handle with one single operating element permitting simple and intuitive operation, even in time-critical and tense surgical situations.

And improvements are also possible at the end of the value chain, as Gerresheimer Morganton (page 8) has proved with its optimized material systems strategy.

Jens Kürten
Group Senior Director
Communication & Marketing
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2011–2015

COVER STORY

Long-term study on syringe function

What factors are significant to break loose and gliding forces?

Prefilled syringes aren't just a primary packaging for pharmaceutical drugs, but also the application systems used to administer the drug. The pharmaceutical manufacturer fills the drug into prefillable syringes such as the RTF® syringes manufactured by Gerresheimer Bünde GmbH, and then seals them.

Pre-filled syringes simplify the administration of injectable pharmaceutical drugs because they eliminate the step of drawing the medication up into the syringe from the vial, they already contain the correct dosage and they can be used straight away. This speeds up processes at hospitals and medical clinics, and pre-filled syringes can also be safely used to administer the drug by people without medical training, or even the patients themselves. As a result, the trend is moving away from vials to prefillable syringes.

Auto-injectors, which contain a pre-filled syringe, are increasingly being used by patients in their homes. For example, they allow arthritis sufferers to inject their medication without another person's assistance.

Extensive tests guarantee syringe quality

Requirements of syringe quality and function have naturally increased as a result of the new applications being introduced, so our Center of Excellence in Bünde has implemented a comprehensive study to ascertain the factors which are decisive to optimum syringe function. Between 2011 and 2015 more than 20,000 syringe systems for different applications in various sizes and configurations were tested.

A syringe system has the components of the glass syringe, the siliconization and the plunger stopper. Needle length and diameter, the viscosity of the syringe's content and the pressure applied to the plunger to push out the content are decisive criteria in the assessment of syringe function.

Scrutinizing 20,000 syringes

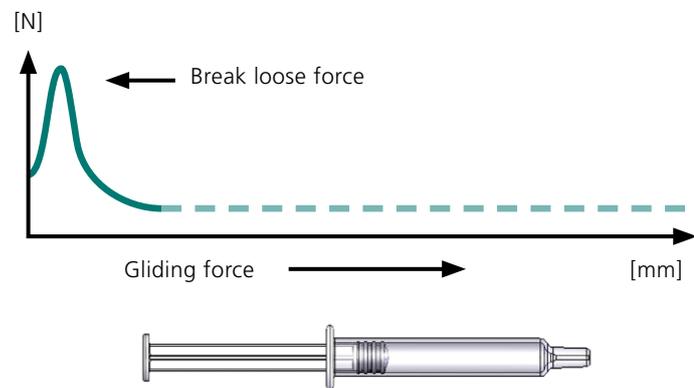
Long-term study 2011–2015

All kinds of factors can affect syringe system performance.

Our study focused on all the parameters that affect break loose and gliding forces.

The study investigated the influence of syringe diameter (1ml short and 1ml long inside diameter 6.35 or 8.65 mm), the siliconization process (RTF® spray-on siliconization with pure silicone oil and RTF® baked-on siliconization with silicone oil emulsion), the content (empty syringes and syringes filled with water for injection), plunger stopper placement (vacuum or vent tube placement), the plunger head itself (established plunger stoppers and plunger stoppers being developed by various manufacturers, in various dimensions/designs, with different rubber formulations, uncoated and surface treated/coated, various siliconization levels). The comparison also extended to different storage periods. Measurements were taken immediately after plunger placement, as well as after 3, 6, 12, 24 and 36 months of storage at room temperature. Further measurements were taken in an accelerated aging environment (40°C, 75% humidity) after 3 and 6 months. In order to verify the statics of the results, 20 parallel samples of all the aforementioned syringe systems were studied to create a data base of more than 20,000 individual data records. The study determined the minimum, maximum and mean values, as well the standard deviation of break loose and gliding forces. However, the graphs showing the gliding force curves provide the most information, particularly when they are displayed underneath one another.

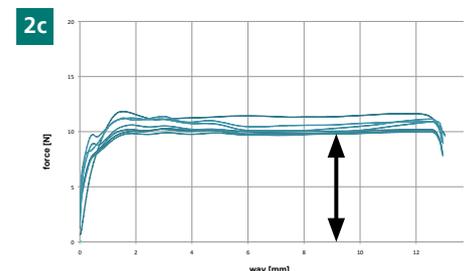
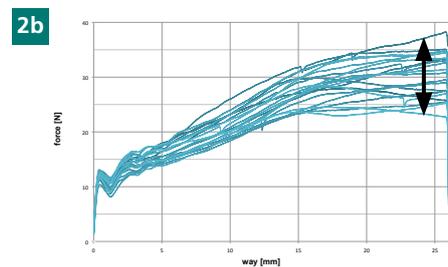
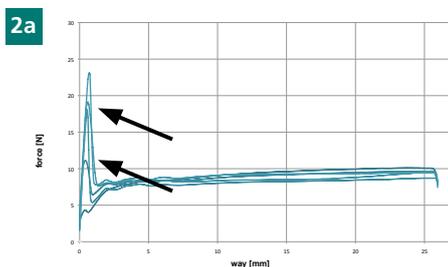
1 Typical gliding force curve for empty syringes



When the content of a syringe is discharged there are two phases with different force profiles. First of all it is necessary to overcome the resistance between the syringe barrel and plunger stopper in order to move the plunger stopper. This is called break loose force. Then, as the plunger stopper moves down the syringe barrel, it encounters friction resistance until the syringe barrel is emptied. That's gliding force. Ideally, the gliding force curve is horizontal. The study identified a range of critical parameters which can cause problems in syringe usage. These are initially too high break loose forces, especially in connection with a sharp decline at the transition from break loose to gliding force. Both

can cause distinct problems for the syringe user. Significant deviations between the same syringe combinations (parallel samples) are also critical because they make their use in auto-injectors problematic. Auto-injectors depend on a "reliable" syringe and constant forces. When syringes are used manually, such deviations mean that the user will experience some syringes with plungers that are easy to depress and some with plungers that are hard to depress. Syringe systems with gliding forces that increase from the start to the end of the injection were also problematic. Changes occurring over storage time, e.g. higher gliding forces after several months of storage, are also critical.

Critical parameters of break loose forces, force variation and increasing gliding forces



Siliconization – the correct quantity makes the difference

Gerresheimer believes that the syringe's siliconization is a decisive factor that can be influenced in the production process.



Baked-on siliconization equipment

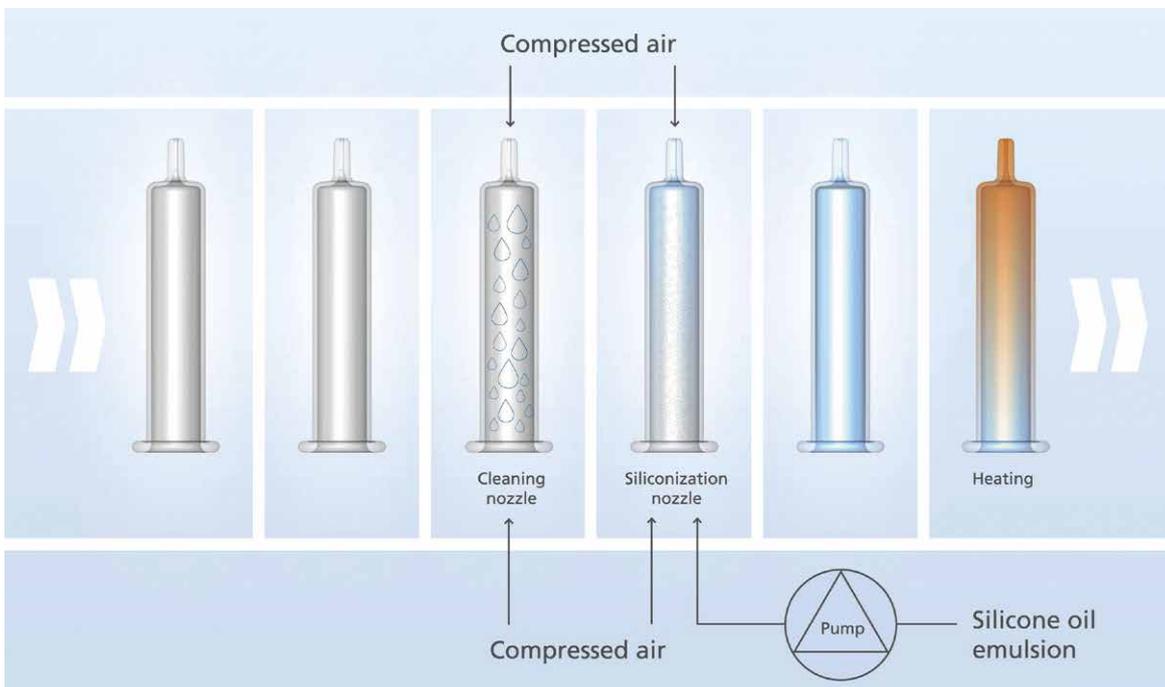
The mechanical function of a syringe depends on the precise dimensioning of all parts and, more importantly, the optimum interaction of the syringe barrel and plunger stopper. Other criteria include simple and safe handling, the complete discharge of all content – if possible – especially when the syringe is incorporated in a spring-driven au-

to-injector that always builds up exact pressure. The syringe's siliconization has decisive influence on all these factors. It reduces the break loose and gliding forces during use, creates a tight connection between the plunger stopper and the glass and provides a hydrophobic surface that facilitates the more effective discharge of syringe content. The adsorption of pharmaceutical drugs by the glass surface can also be reduced with some formulations. Medical silicone oils are long established because they are harmless to health, more or less inert, viscoelastic and hydrophobic. They are also included in the relevant pharmacopeia (Ph. EUR and USP).

When using silicone oil as an anti-friction coating in ready-to-fill syringes it is necessary to take several decisive factors into consideration in order to guarantee syringe function. A silicone coating that is too thin or uneven can impair the syringe's mechanical function. Vice-versa, too much silicone oil can in some circumstances result in free silicone oil droplets forming. Visible droplets

are a cosmetic defect that is categorized as critical, particularly when the syringes contain ophthalmological medications. Droplets in biotech drugs can also cause sub-visual problems because the active ingredient binds with them, thereby reducing the quantity of available active ingredient.

In many cases, therefore, the objective when developing prefillable syringes is to reduce the quantity of silicone oil to the minimum level possible without impairing the syringe's mechanical function. In particularly critical fields of application the silicone oil can be thermally bonded to the glass surface. In this case the silicone oil is applied as an emulsion and then "burnt on" at temperatures of over 300°C. This creates stable covalent bonds between the glass surface molecules and the silicone oil to form a permanent hydrophobic anti-friction coating. The quantity of free droplets is less than 10% of those associated with traditional spray-on siliconization.



Baked-on siliconization process

The results – a comprehensive data base for customized solutions

The results of the study contribute to a clearer picture of the factors of influence which are crucial to syringe function. Several common hypotheses were verified, while others were refuted.

For example, the study design confirmed that accelerated aging is a reliable way of achieving faster and more informative results. This can considerably reduce the time required to perform future studies. The comparison of baked-on and spray-on siliconization revealed higher gliding forces in the case of baked-on siliconization, which is due to the lower quantities of silicone oil used. On the other hand, the number of free silicone particles was significantly lower in the case of baked-on siliconization. The wide-

spread assumption that break loose forces in syringes with spray-on siliconization increase at a faster rate over the storage period than in syringes with baked-on siliconization was not fundamentally confirmed. Generally, the effect of long-term storage tends to be moderate. However, the type of plunger stopper used is of decisive significance. The choice of plunger stopper design, the rubber formula, the coating and the siliconization have considerable influence on syringe function. Whether the plunger stopper is inserted by



vacuum or vent tube placement only affects break loose and gliding forces in some plunger stopper types. The complex interrelationship between the components and the siliconization makes it clear that there is no universal solution for syringe function. Rather, a syringe system has to be individually tailored to the pharmaceutical drug, user and, in some cases, to requirements for integration in auto-injectors. The comprehensive data obtained in our long-term study enables us to provide customers with detailed advice on the choice of the right syringe system and to offer customized solutions that are optimized for all the parameters of their specific application.

Reviewing quality management Recertification at the Bünde plant



Bünde underwent a recertification audit for its quality management system in 2015. Over the 7.5 day audit, the plant's quality management system was reviewed to assess its compliance with the DIN EN ISO 9001, DIN EN ISO 13485 and DIN EN ISO 15378 standards. The audit had a very positive outcome. Only one minor non-compliance was ascertained and immediately

remedied, which meant that all the certificates could be reissued without a problem. This is a very positive result considering that the framework was extremely challenging. Firstly, the audit was implemented with only one team, which shows that our quality management system is very well established and stable. Secondly, the recertification audit was a witness audit, so the auditors them-



selves were also being assessed. It was performed by the DQS auditors, who were assessed by auditors from the German Accreditation Body (DAkKS) in order to retain their accreditation. A witness audit doesn't change the recertification process, but it does mean that the audit is generally very stringent and in strict conformity with the rules.

Simple and reliable Heart valve insertion

Gerresheimer item optimizes a delivery system for minimally invasive implantation



We are one of the world's leading partners to the pharma and healthcare industry with a comprehensive range of primary packaging and drug delivery products. As a full-service provider, we cover all stages of the value chain.

The company in the Gerresheimer Group that is responsible for the earliest phase of the value chain, when a concept is developed into series production readiness, is Gerresheimer item GmbH. This Münster-based service company has over 10 years of experience in the fields of product design and development. In its projects, Gerresheimer item works hand-in-hand with our Technical Competence Centers in Wackersdorf (Germany), Peachtree City (USA) and Dongguan (China). This allows us to contribute our extensive industrialization competence to the

development of the product even in the design phase. Decisive criteria include function, ergonomics and design quality, as well as ensuring that the design can actually be manufactured in plastic, and then subsequently assembled and tested. Our customers profit from shorter development times, lower development costs and lower project risk exposure because the process of plastic-compatible optimization is eliminated. Another advantage is that Gerresheimer item is an independent company. When the product development phase concludes, the cus-

tomers can decide whether to have its product manufactured in series at one of our facilities, or whether to go to another manufacturer. An innovative delivery system for use in heart valve transplantations is one example of a product developed by Gerresheimer item for JenaValve. It is manufactured at another company.

Continued on the following pages

PLASTICS & DEVICES

Artificial heart valves: for hearts that can't pump effectively



Above illustration:

The "CATHLETE plus" delivery system with catheter shaft (left) and operating handle (right)



Illustration left:

Compressed (left) and expanded (right) aortic valve

Each heart ventricle has two valves to prevent the blood from flowing backwards. They make it possible for the heart to pump blood from the veins and into the arteries by way of alternating contraction and relaxation. Sometimes people are born with deformed heart valves, or their function is impaired by a disease.

If the heart valves are constricted or don't close properly the heart cannot pump blood effectively. In this case, it makes sense to replace the defective heart valve with an artificial one. There are mechanical heart valves and heart valves made of biological tissue. Traditionally, heart valves are replaced by way of open heart surgery. The chest and heart are opened up, and the patient's blood circulation and breathing are performed by a heart-lung machine during most of the operation. Older patients, in particular, are often unable to cope with this kind of major surgery. They generally take advantage of the new minimally invasive method of posi-

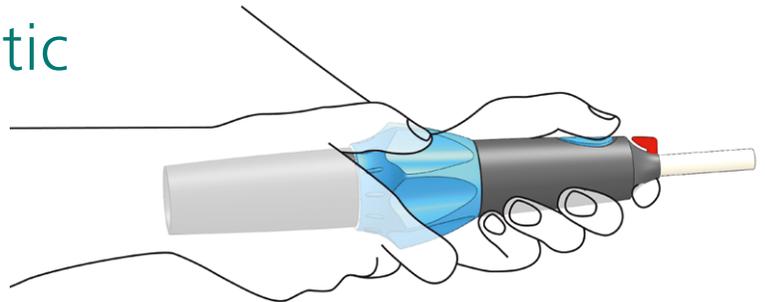
tioning an artificial valve in the heart through a catheter. The valve can either be inserted via a femoral artery or via the apex of the heart. One leading, highly specialized manufacturer of transcatheter aortic valve implantation (TAVI) is JenaValve GmbH.

An artificial heart valve that can be compressed small enough to fit into the catheter is necessary for minimally invasive aortic valve implantation. JenaValve uses a self-expanding Nitinol stent with a tissue prosthesis for this purpose. This material, a nickel-titanium alloy, has an excellent shape memory. It is very elastic at low temperatures and

does not revert to its original shape until it warms up. During surgery the stent is placed by a nurse into the catheter shaft on the end of the delivery system. The surgeon then inserts the artificial valve into the beating heart via the defective aortic valve. When it warms to body temperature it expands and immediately starts to perform its function.

PLASTICS & DEVICES

An innovative second-generation aortic valve delivery system



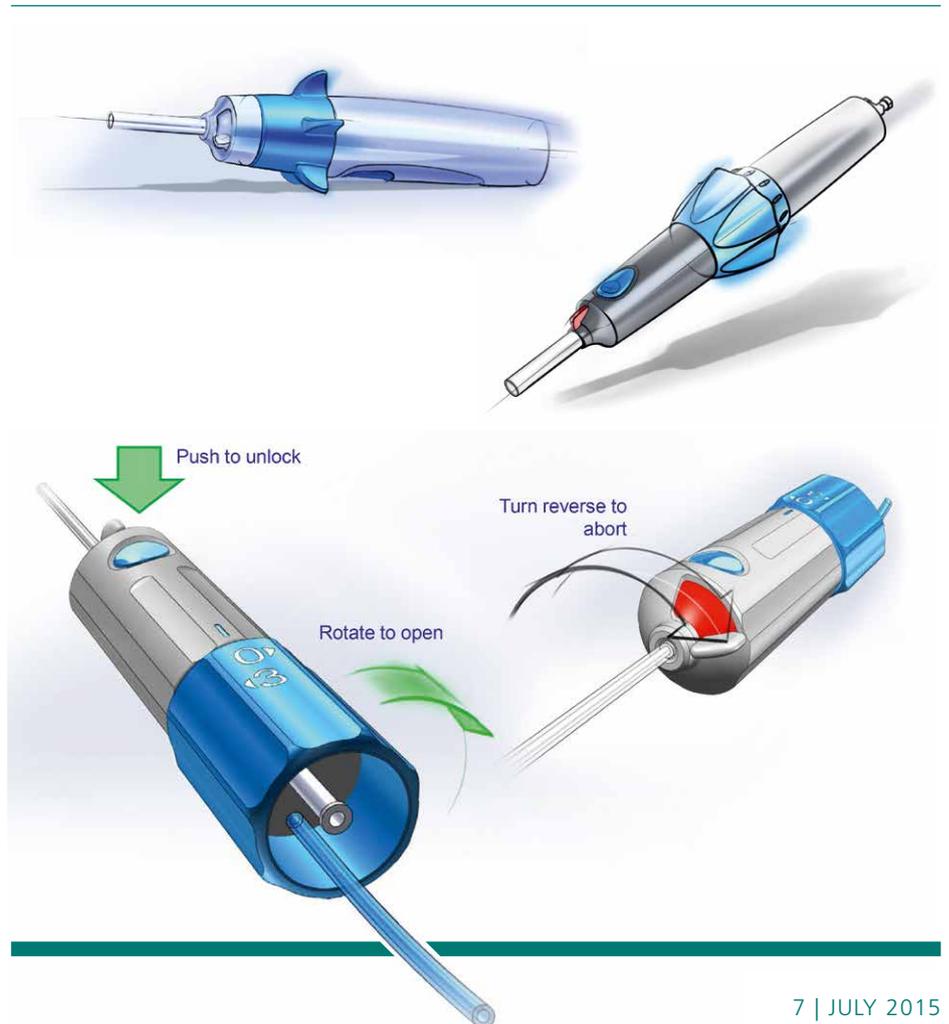
JenaValve supplies both the artificial valve for implantation and the delivery system as a disposable product. When it introduced a second, optimized generation of aortic valves, it needed an optimized delivery system that considerably simplified the surgical procedure. Gerresheimer item was requested to optimize the design of the operating handle in terms of its ergonomics.

The customer naturally had high requirements of product design for several reasons. Firstly, it wanted a system that underlined its status as innovation leader in its market. The basic mechanical concept had been defined by JenaValve at the outset of the development phase. It was optimized by an external company while the product was being designed, so it was necessary to adapt the design to the changed parameters during the development process. Above all, however, the product had to have a simple and intuitive operating concept in challenging heart surgery situations. Although the delivery system's basic function is error tolerant – i.e. the artificial heart valve's position can be corrected without a problem until it is actually released from the device – there is always time pressure in this kind of complex surgery. This applies both to the work of the surgical nurses, who place the valve in the catheter shaft, and to the work of the surgeon. So the most elementary product requirement is easy handling without the assistance of a second person at all times. Ergonomic use is another requirement. It has to be possible to operate the controls reliably even if their surface is slippery and the user is wearing surgical gloves. The number of operating elements also has to be reduced to the minimum to ensure that processes are as simple and plausible as possible, thereby preventing mistakes in time-critical situations.

Design studies in the development phase

The ergonomic optimization comprised a handle with just one single control element plus a lock button. During the process of positioning the artificial heart valve, the lock button is released by rotating it one position to the right so that the operating ring can be used. This rules out any uncertainty about operating sequences or incorrect use. When the handle is turned to position 1 the catheter

shaft opens so that the stent's sensors are released. These sensors allow the valve to be placed in the correct anatomical position inside the heart. Then handle is turned to position 2 to clip the valve securely onto the patient's native aortic valve. In position 3 the valve is completely released. The catheter can then be removed and the artificial valve can start its work.



PRIMARY PACKAGING GLASS

Gerresheimer Morganton:
optimized
material systems
strategy



Historically, the Logistics Team at Gerresheimer Morganton received sales orders in less than optimal quantities, resulting in sales orders entered in Less Than Full (LTL) truck loads. Shipments of two trucks instead of one not only increase freight costs, but also require brokers to schedule multiple trucks. If they lack drivers or equipment a risk of late shipments arises. It was evident that there was a great need to systematically optimize lot sizes to aid in consolidating orders and combining trucks for shipments. The goals were defined as follows:

- Enable the split of large quantity orders into smaller releases to reduce the liability in case of a rejection
- Optimize order quantity and offset the price quote to cover machine setup cost.
- Align the ship dates with other shipments to make a full truck load

Gerresheimer Morganton developed a team from Logistic Managers, Warehouse Personnel and Customer Service who identified an approach to automate the calculation of pallet count within SAP and to incorporate the number of pallets per order. The project included, splitting large orders into smaller releases and shipping on the same day, as requested by the customer. Orders were optimized and setup costs were applied as needed. In addition, shipment dates were evaluated to determine opportunities to combine orders with future shipments to maximize the truck load.

The process improvements were shared with customer service and other facilities to use during scheduling. These enhancements led

to improved customer production requirements and continued open communication between the plant, Customer Service, and customers. Special guidelines regarding lot size and risk mitigation as well as production efficiency were also created for entering new orders into SAP.

After evaluating the project for 12 to 18 months the outcomes showed significant improvements. The On Time in Full (OTIF) KPI improved by 1.2 percentage points and freight costs decreased by 30 percent. The project also resulted in minimized risk of damage during transit and decreased financial exposure at customer incoming inspection of optimized lots if a rejection were to be incurred. Gerresheimer Morganton received the GMS (Gerresheimer Management System) Award in 2015 for Material Systems because of these outstanding improvements.



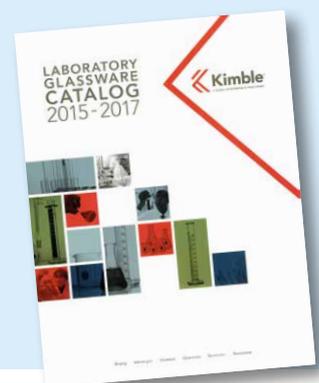
For the first time an award for Material Systems was awarded to a team entirely led by ladies. Standing Left to Right – Frances Benfield, Kathy Beach, Pam Lunsford and Shavonn Tate; Seated Debra Rose.



New Kimble
laboratory glass
catalog
2015 – 2017

Kimble has published a new laboratory glass catalog with more than 450 pages covering the entire portfolio of KIMAX®, Kimble® and Kontes® products. The largest manufacturer of laboratory glass products in the world designs, manufactures and markets a comprehensive range of reusable, disposable and specialty laboratory glassware for pharmaceutical, environmental, petrochemical, life sciences, education and chromatography applications. On the basis of tubular glass conversion and paste mold technology, the Kimble portfolio includes everything the laboratory needs to simplify its work processes.

Kimble Chase Life Science and Research Products LLC was formed in July 2007 through a joint venture between Thermo Fisher Scientific and Gerresheimer Glass, Inc., a US subsidiary of Gerresheimer AG. Kimble has global operations and almost 1000 employees working at six strategic locations.



PEOPLE

Plastics & Devices

Ariel Antoniletti is Senior Director Spain & Argentina Plastic Packaging



Ariel Antoniletti was appointed as Senior Director Spain & Argentina Plastic Packaging on June 1, 2015. He has also taken over the function of Managing Director in Zaragoza, Spain, and is still Managing Director of Buenos Aires, Argentina. Ariel is also responsible for all polyethylene terephthalate (PET) business in Europe and Argentina.

Previously Ariel Antoniletti was Managing Director of EdP Argentina S.A., the company that was taken over by Gerresheimer in January 2008. He has degrees in engineering and economics.

Primary Packaging Glass

Chandan S. Bhosale is General Manager Tubular Glass Converting India in Kosamba, Gujarat



Chandan S. Bhosale was appointed as General Manager Tubular Glass Converting India in Kosamba on May 18, 2015 after an induction and training program. He is responsible for the plant that is currently being constructed in Kosamba to manufacture vials and ampoules.

Chandan S. Bhosale has 15 years of experience in the production of ampoules and vials from tubular glass. He is a qualified electrical engineer. Prior to joining Gerresheimer he worked at Forbes & Company Ltd.

RECOMMENDED READING

Perfection in plastic

Niels Düring, Global Senior Vice President of Gerresheimer Plastic Packaging, has been in the plastic packaging business for 15 years now and he was a significant contributor to the successful integration of the former Superfos A/S in the Gerresheimer Group. In this interview he explains the details of his business and the synergies between Gerresheimer's glass and plastic divisions.

[Drug Development & Delivery May 2015](#)
Vol. 15 no. 4, p. 65–67

Gerresheimer Querétaro (Mexico) invests in its employees

The tubular glass converting plant in Mexico has been part of the Gerresheimer Group since 2002. In this interview, the General Manager Hector Garcia talks about how the company that was founded in 1978 started out and its continuous investments in machines and inspection systems, as well as its 400 employees.

[Glass International April 2015, p. 18–19](#)

WEB & EVENT

CPhI 2015 in China

Focusing on vials for aggressive active ingredients



Gerresheimer has over 1800 employees at seven production plants in China and India. They manufacture products to meet the ever-growing demand for specialty glass and plastic pharmaceutical packaging in Asia. The Gerresheimer experts demonstrated the products to existing and potential customers, and offered them advice at CPhI in Shanghai in the New International Expo Center (SNIEC) between June 24 and 26. There was considerable interest in the new Gx Armor vials. On June 24 at 1.30 p.m. the Gerresheimer experts hosted a workshop on the subject of "Pharmaceutical Glass and Drug Safety".

"At CPhI we will be focusing on Gerresheimer's competence in glass and inviting our customers and anyone who is interested

to our workshop on June 25," said Jianfeng Chao, Director Operations China Tubular Glass Converting.



Carol Rea Flynn, Director of Technical Services at Gerresheimer in Vineland (USA) and tubular glass expert, talked about the regulation of pharmaceutical packaging and other pharmaceutical materials, as well as trends and new developments. She also explained the composition and physical prop-

erties of pharmaceutical glass. Other topics that Carol covered include the phenomenon of delamination and how Gerresheimer solves this problem with its new generation of Gx ARMOR vials. Gx ARMOR stands for Gerresheimer Advanced Risk Management and Operational Response, a new product line called Gx Armor vials which are specifically designed for parenteral solutions with aggressive active ingredients and specially equipped to prevent delamination.

Gerresheimer also showcased its well-known and proven portfolio tubular and molded glass products at CPhI. It includes ampoules, cartridges and vials in diverse filling sizes and formats and is rounded off by the RTF® syringes that are manufactured by Gerresheimer Bünde in Germany.



GMS & Sales Conferences 2015 – award winners and guided tours

The standardization of processes, workflows and technology improves quality and efficiency. Standardization should be the focus of Gerresheimer Management System (GMS) applications at all the Gerresheimer plants around the world. That's one of the key messages communicated by our CEO Uwe Röhrhoff to participants of this year's GMS Conference, which was held in Lohr/Germany in May. The Sales Conference that was held concurrently focused

on knowledge and experience sharing, improving the collaboration of the sales team and a unified corporate identity as One Gerresheimer.

Around 110 participants from all plants and the global sales team attended both conferences. After a full conference morning on Tuesday (May 5, 2015) participants were given guided tours of the molded glass plant in Lohr and the ampoule plant in Wertheim.

Everyone was very impressed by the exemplary production processes at both plants, and by the interesting GMS projects that are being implemented there. The day ended with the GMS Award Dinner, where five proud teams were presented with their awards.

On the second conference day there were workshops and best practice presentations at both conferences.

WEB & EVENT

The Brazilian Sindusfarma Quality Award

goes to Gerresheimer again in 2015

Gerresheimer received the Brazilian Sindusfarma Quality Award again this year in the category of National Plastic Bottle and Cap Manufacturers. This award is a tribute from the Brazilian pharmaceutical industry to the suppliers and service providers who have contributed to continuous quality enhancements and to increasing conformity with safety requirements in all phases of pharmaceutical drug production.

The award was presented to Gerresheimer at a ceremony on May 15, 2015, which was also one of the concluding highlights for exhibitors at FCE Pharma in São Paulo. It was attended by around 2000 representatives of the pharmaceutical industry.

With four production facilities in Brazil plus one in Argentina, Gerresheimer is the pharmaceutical plastic packaging market leader in South America. The product portfolio includes dropper bottles for eye drops, spray bottles for nasal sprays, PET bottles for cough medicine, PE containers for tablets, plus a wide range of caps, closures and all kinds of accessories such as dosing caps, droppers, measuring cups, dosing syringes and applicators.



Gerresheimer São Paulo (Brazil) builds a new clean room

In order to improve the quality of its products and processes, and also employee working conditions, Gerresheimer Sao Paulo started planning the construction of a clean room for plastic injection molded products at its plant in Butanta in 2014.

The project was initiated on the basis of the results of a customer and employee survey, which were used to develop the project objective of significantly reducing contamination through dust, particles and insects and thus customer complaints. Many employees

had complained about the high temperatures at the work place, so another project objective was to control and stabilize room temperatures with an air-conditioning system.

The 1,100 m² new clean room was finished in January 2015 and has resulted in significant improvements. There has been a 90% reduction in customer complaints about contamination. In fact, it was so successful that the plant is considering extending the concept to other production lines.

GERRESHEIMER EVENT CALENDAR 2015 / 2016



SEPTEMBER 22. – 24.

MedTec China
Shanghai, China | Stand P301

OCTOBER 13. – 15.

CPhI Worldwide
Madrid, Spain
IFEMA, Feria de Madrid | Stand 4F30

NOVEMBER 03. – 04.

PDA Universe of Prefilled Syringes
Vienna, Austria | Stand 64/65

NOVEMBER 16. – 19.

Compamed/Medica
Düsseldorf

DECEMBER 01. – 03.

CPhI India
Mumbai, India

DECEMBER 09. – 11.

Drug Delivery to the Lungs
Edinburgh, Scotland

FEBRUARY 03. – 04., 2016

PCD Congress
Porte de Champerret,
Espace Champerret | Stand AD49
Paris, France

FEBRUARY 10. – 11., 2016

Pharmapack Europe
Porte de Versailles | Stand 802
Paris, France



High Quality Gx RTF[®] Syringe Systems for Parenteral Drugs

- | High performance design
- | High barrier properties
- | Superior resistance

