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PREFILLABLE SYRINGE DEVELOPMENTS TO MEET BIOTECH DRUG NEEDS

Claudia Petersen, Global Director Business Development at Gerresheimer MDS, looks at the technological advances being made to ensure prefillable syringes are compatible with protein-based, biotech-derived drugs. She reviews the various options available to tackle the three main syringe components – glue residuals, tungsten residuals and silicon oil particles – as well as outlining advances in safety.

The global biopharmaceuticals market accounted for US$160 billion (£116 billion) in 2014, and it is expected to grow with a $CAGR_{2015–2020}$ of 9.6%, outpacing the overall global pharmaceutical market growth. Many biotech-derived drugs have to be administered by injection using vials, cartridges or prefillable syringes as primary packaging containers. The specific needs of these protein-based drug product formulations pose new challenges to existing primary packaging solutions.

Some of the trends which are affecting the injectable device market are:

- A shift to self-medication to increase patient convenience and save costs, linked to an increasing demand for easy to use delivery devices such as autoinjectors and pump systems.
- Increased regulatory scrutiny and quality requirements for patient safety.
- Increased focus on understanding and anticipating user needs (continuous exploration of the patient experience, patient adherence/compliance).

In addition to this, there are some trends which are affecting biopharmaceutical manufacturing specifically:

- Increased flexibility is being requested from suppliers.
- More biological product applications are being made, but often for small indications which results in smaller batch sizes with high – and specific – quality demands. This is supported by the growing market for biosimilars/biogenerics.
- As a result, more automation, monitoring and process control during production means higher quality packaging materials are needed.

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For syringes, these trends can be grouped into four different areas which each require different innovative primary packaging solutions as well as continuous production process improvements (Figure 1).

Regarding the biocompatibility of a prefillable syringe system, three main topics have kept the industry busy in recent years:

- Glue residuals
- Tungsten residuals/oxides
- Silicone oil particles.

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Biocompatibility	• Glue residuals • Tungsten oxides • Silicone oil partides	▮ Clearject™ Plastic Prefilable Syringes ▮ Metal free cone bore forming ▮ Low tungsten process ▮ Baked on RTF® siliconization
End user safety	• Screw cap closures • Needle stick prevention • Breakage resistance	▮ Gx TELC® ▮ Gx InnoSafe® (safety syringe) ▮ Modern glass forming technology
Device compatibility	• Specific dimensional requirements for device applications like auto injectors	▮ Modern glass forming technology ▮ State of the art proprietary camera system
Total Cost of Ownership	• Low cosmetic defects • Secure supply chain • Low particle load	▮ State of the art proprietary camera system ▮ No glass-to-glass contact during forming and ready to fill processing ▮ Washing machine after glass forming

Figure 1: Global pharma injectable packaging market trends.

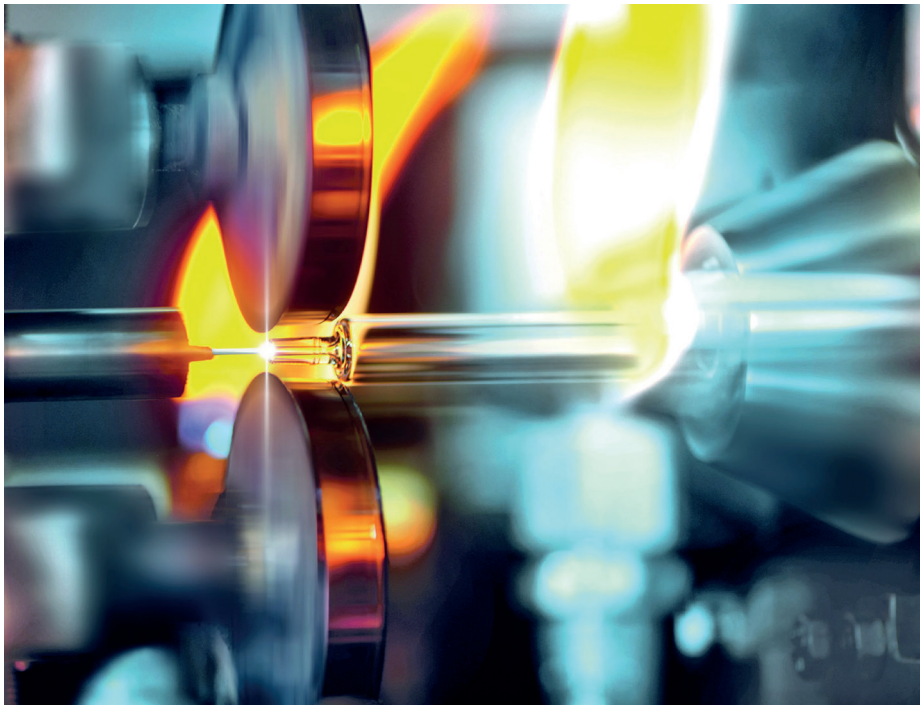

Figure 2: Cone bore forming step.

GLUE RESIDUALS

To fix the metal cannula inside the syringe bore, an organic, UV-activated, methacrylate-based glue is the industry standard. However, glue residuals may l each into the drug product solution and interact with the protein.[1] The level of glue residuals can be controlled by using optimised curing process conditions. After implementation of this process improvement, product specifications with methacrylate in the picogram range per syringe have been realised.

TUNGSTEN

Tungsten pins are used to form the bore in the syringe luer cone (Figure 2). Tungsten is the pin material of choice, offering a range of advantages. It is a heavy metal that melts at 3422°C, with the highest tensile strength at ≥1650°C, and the thermal expansion is very similar to borosilicate glass. These features make tungsten a preferred contact material for the forming of glass syringes. The glass forming temperature of borosilicate glass is around 1200°C.

The downside is that tungsten pins always leave tungsten residuals inside the syringe cone. This can be either tungsten oxides, caused by the high temperatures used for glass forming, or abrasive particles. For many proteins this does not pose a problem, but there have been several reported incidences when tungsten residuals did interact with proteins causing protein aggregation.[2]

As a result, regulatory bodies like the US FDA asked pharmaceutical companies to define tungsten limits for their drug products. In *Guidance for Industry – Immunogenicity Assessment for Therapeutic Protein Products*, the FDA recommends that a dedicated leachables and extractables laboratory assessment for packaging components is performed. Spiking studies are also suggested to assess the risk of tungsten-induced protein agglomeration.

Also the PDA TR No. 73 (Parenteral Drug Association Technical Report) *Prefilled Syringe User Requirements for Biotechnology Applications* recommends performing spiking studies to determine the effect of tungsten.

As the sensivity of different proteins to tungsten residues varies a lot, there is no fixed tungsten limit defined. Also the achievable low tungsten specifications for luer cone and staked-in needle syringes vary drastically due to the size of the pin used to form the bore.

On the syringe manufacturing side, there are several ways to counter this problem:

1. All syringe suppliers offer so-called “low tungsten” syringes. This can be achieved either by improving the glass forming conditions and/or adding an additional

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washing step after glass forming, thus lowering the tungsten load.
2. Tungsten pins can be substituted with other metal pin materials.
3. Metal-free, glass syringe cone-bore forming can be done using ceramic pins instead of tungsten pins.
4. Injection-moulded, plastic polymer syringes made from cyclic olefins can be used.

Metal-Free Glass Syringe Cone-Bore Forming

The best way to avoid any problems with tungsten residues is to replace the tungsten pin with a non-metal one. This can be achieved using ceramic materials, which require some adjustments in the glass-forming process. We have identified a ceramic material with optimal properties that shows nearly no abrasion and does not leave any new residues behind. This allows us to offer tungsten-free (below the detection limit), "ready-to-fill" (RTF) syringes. In the first step, this process was qualified for luer cone syringes and can be combined with other specialities such as baked-on siliconisation.

SILICONE OIL

As a lubricant, silicone oil is required to enable the plunger stopper to glide inside the syringe barrel. However, silicone oil particles, especially in the sub-visible range, are also known to be able to induce protein aggregation.[3] In addition, silicone particles increase the overall particle load inside a syringe and are difficult to differentiate from protein particles. The overall particle load is of specific importance in the field of ophthalmic applications, with the most stringent particle requirements for parenterals defined by USP 789 "Particulate matter in ophthalmic solutions" and especially with regard to protein formulations. Also sub-visible particulates in the 2–10 µm range should be characterised and quantified.

Baked-on Siliconisation

The so-called baked-on process (Figure 3) enables syringe suppliers to lower the amount of free silicone oil particles significantly by fixating a certain amount of the silicone oil emulsion on the inner walls whilst still maintaining functionality. Figures 4 & 5 show particle measurements derived from a recent study comparing oily (0.5 and 0.8 mg/syringe) and baked-on siliconised syringes. WFI and a Tween 80 0.03% solution were chosen as model liquids. The samples were stoppered (fluoropolymer-coated plunger stoppers) and the number of silicone oil particles was determined according to EP 2.9.19 after one day of storage, three months storage and after three months under stress conditions to simulate a transport situation. Results shown are for the "after three month under stress" conditions.

It is obvious that baked-on siliconised syringes (BoS) syringes show much lower particle loads compared to oily siliconised syringes in both cases for all particle classes examined.

For RTF syringes, baked-on siliconisation is an off-line process using a specific oven. The amount of free silicone oil inside a 1 mL long baked-on siliconised syringe is no higher than 0.1 mg. Also in this case, fixed and diving nozzles are used for siliconisation to ensure an even silicone oil distribution in larger syringes which enables Gerresheimer to specify USP 789 compliance if necessary.

When selecting the appropriate syringe it should be remembered that plunger stopper siliconisation contributes heavily to the overall silicone oil particle load. It is therefore recommended to choose silicone oil-free or crosslinked, siliconised, fluoropolymer-coated plunger stoppers, offered by several suppliers.

Gx® RTF Baked-on Needle Syringe

Baked-on siliconisation has only been

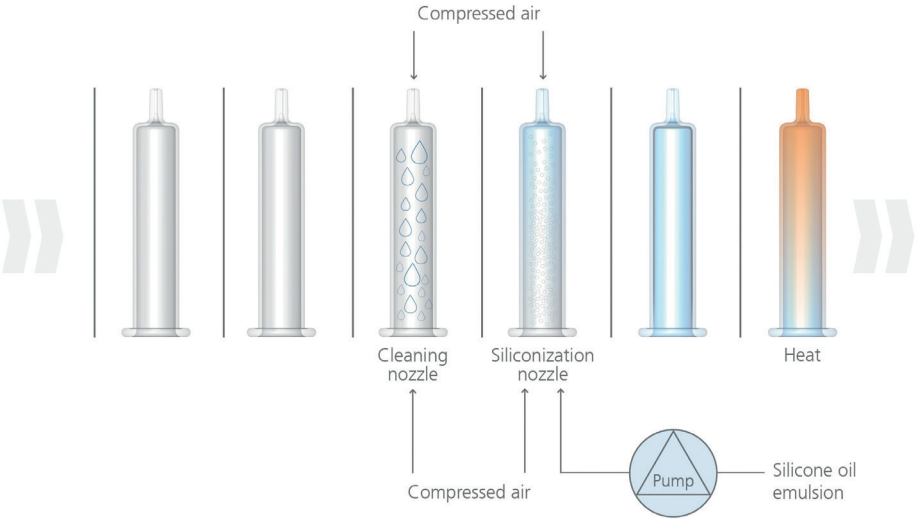
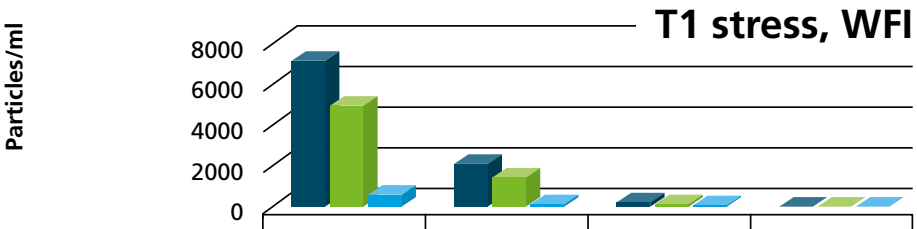
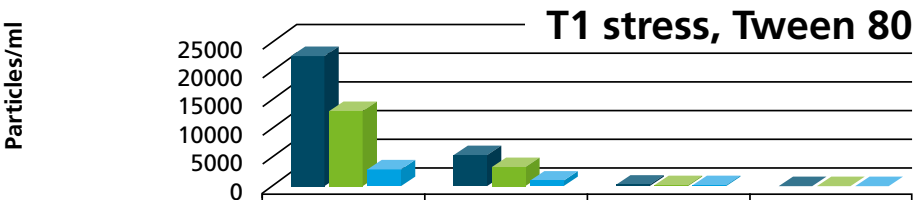


Figure 3: Baked-on siliconisation processing steps.



	≥2 µm	≥5 µm	≥10 µm up to 25 µm	≥25 µm up to >50 µm
WFI 0.8 mg	7153	2040	185,6	2,4
WFI 0.5 mg	4906	1334	123,0	1,4
WFI BOS	585	105	6,5	0,2

Figure 4: Sub visible silicone oil particles ≥ 2 µm WFI solution.



	≥2 µm	≥5 µm	≥10 µm up to 25 µm	≥25 µm up to >50 µm
Tween 0.8 mg	22089	5287	412,5	7,7
Tween 0.5 mg	12839	3327	318,1	4,6
Tween BOS	3023	1061	165,5	1,1

Figure 5: Sub-visible silicone oil particles ≥ 2 µm Tween 80 0, 03% solution.

applicable to luer cone syringes, as the high temperatures during the baking process negatively impact the organic glue used for the fixation of the cannulas inside the syringe cone. Using an additional process step, which involves atmospheric plasma to remove potential silicone oil residuals from the inside of the syringe bore and provides a defined surface for the subsequent cannula gluing process (Figure 6).

Using low temperature plasma flame at atmospheric pressure inside the syringe bore converts any residual silicone into nearly carbon-less layers. This conversion is accompanied by a 50% layer thickness reduction and requires no aggressive or contaminant primers. The already siliconised inside barrel of the syringe is shielded to avoid any impact of the plasma on the surface.

Baked-on, siliconised, staked-in needle syringes are therefore the optimum choice for sensitive protein therapeutics.

END USER SAFETY – GX® INNOSAFE

Next to biocompatibility, end user safety is also a major trend. The use of staked-in needle syringes is very convenient/user friendly but always bears the risk that healthcare workers may stick themselves after injection and thereby infect themselves. To avoid this, a needlestick safety and prevention act was put in place in the US in 2000, which was followed by similar regulations in Europe in 2013. Since 2000 all staked-in needle syringes sold in the US have to be equipped with a needlestick prevention feature. So far most of these safety devices have to be assembled on the filled syringe during secondary packaging operations.

Recently, to tackle this problem, a

Figure 6: Luer cone bore plasma cleaning for baked on staked in needle syringe.

safety syringe called the Gx® InnoSafe was launched. In this second generation safety syringe, the safety feature is an integral part of the RTF syringe and looks similar to a rigid needle shield. Syringes are supplied sterile using standard RTF packaging (nest & tubs). The safety system is very intuitive and fully passive, meaning it does not require any activation step by the end user. For the pharma company, it has the advantage that no additional assembly step after filling is required. The slim design also allows the use of a small blister and thereby more cost-efficient secondary packaging and storage (Figure 7).

PLASTIC PREFILLABLE SYRINGES

Glass as a primary packaging material has many advantages, like gas tightness, transparency and high chemical inertness. For the production of glass prefillable syringes only borosilicate glass Type I is used (either 51 or 33 extension). Nevertheless there are also some drawbacks, especially with regard to breakage. Sensitive areas for breakage are the finger flange and cone area.

Plastic prefillable needle syringes made from cyclic olefins have now been available for a few years (Figure 8, next page). They are break-resistant, have the same transparency as glass and allow for a much higher grade of customisation. Furthermore, no glue is used to fix the cannula inside the syringe bore and no tungsten pin is required for forming, causing tungsten residuals. ClearJect with needle syringes (Figure 9, next page) are siliconised using highly viscous DC MD 12500 silicone oil to reduce specifically the amount of sub-visible particles compared to conventional oily siliconisation. The syringes are supplied with standard rigid needle shields, plunger stoppers, back stops and plunger rods.

Also in this case the appropriate plunger stopper selection is important regarding the final total silicone particle load. Figure 10 shows results from the same particle study as Figures 4 & 5 extended by ClearJect with needle syringes (CJ). The silicone oil amount per syringe was 0.8mg. A significant reduction compared to glass syringes can be observed, especially for particles below 10 µm. This provides another reason to recommend the use of these syringes for silicone oil particle-sensitive protein therapeutics.

CONCLUSION

Considering the complexity of modern biopharmaceutics there is no "one-size-fits-all" solution for all protein formulations. The container closure system has become a decisive factor for sustained market success, with autoinjectors and injection pumps being growing areas of interest. This demands an even earlier involvement of packaging specialists in the drug product development process to avoid development risks.

It is recommended that the packaging supplier should be consulted early on in the

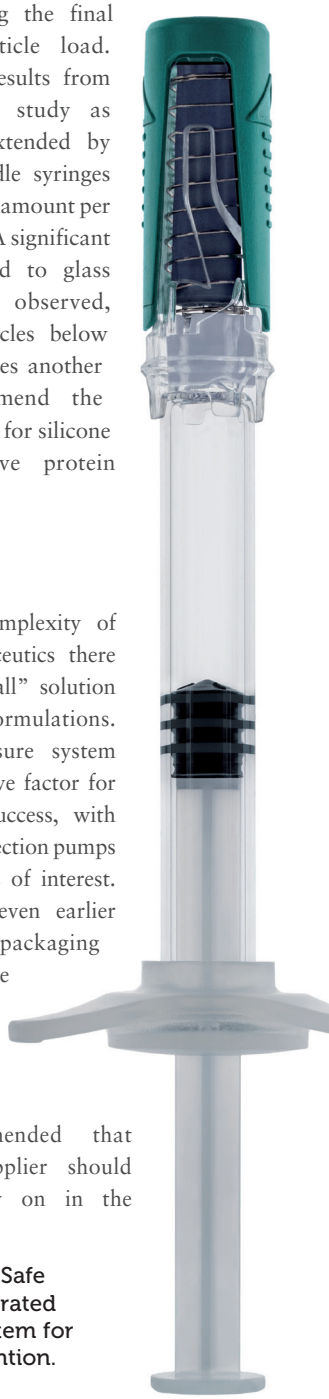


Figure 7: Gx® InnoSafe syringe with integrated passive safety system for needlestick prevention.

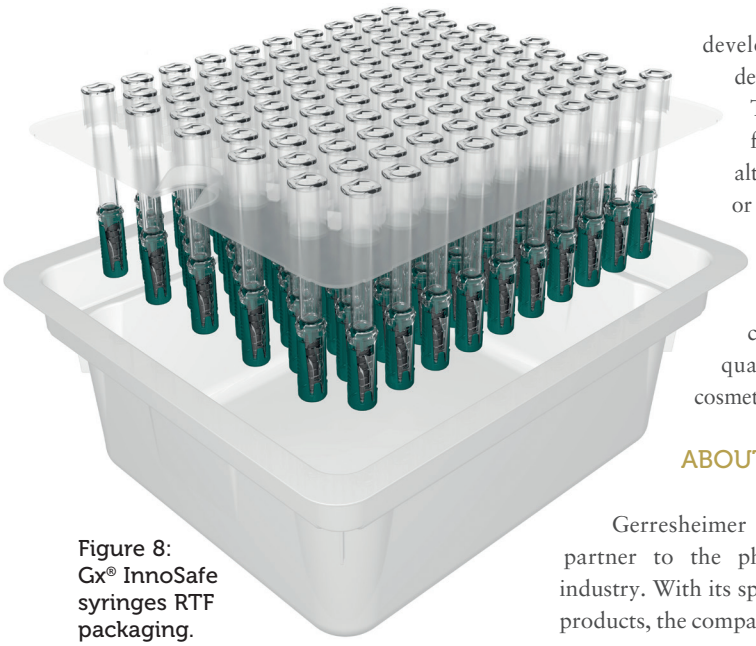


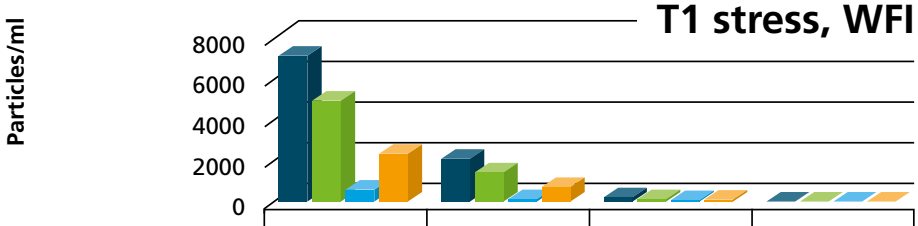
Figure 8: Gx® InnoSafe syringes RTF packaging.

development process to determine what is feasible. The future may see further developments for alternative syringe coatings or silicone oil-free solutions, especially as modern syringe production technologies provide continuously higher qualities in terms of cosmetic defects.

ABOUT THE COMPANY

Gerresheimer is a leading global partner to the pharma and healthcare industry. With its specialty glass and plastic products, the company aims to contribute to health and wellbeing. Gerresheimer operates worldwide and its approximately 10,000 employees manufacture products in local markets, close to its customers. With plants in Europe, North America, South America and Asia, Gerresheimer generates revenues of around €1.4 billion (£1.2 billion). The comprehensive product portfolio includes pharmaceutical packaging and products for the safe, simple administration of medicines: insulin pens, inhalers, prefillable syringes, injection vials, ampoules, bottles and containers for liquid and solid medicines with closure and safety systems, as well as packaging for the cosmetics industry.

Figure 9: Gx RTF ClearJect with needle syringe using common syringe accessories.



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WFI 0.5 mg	4906	1334	123,0	1,4
WFI BOS	585	105	6,5	0,2
WFI CJ	2344	713	85,4	3,2

Figure 10: Sub-visible particle load ClearJect with needle syringes.

REFERENCES

1. *Markovic I, "Considerations for Extractables and Leachables in Single Use Systems: A Risk-Based Perspective". Presented at the PDA Single Use Systems Workshop, Bethesda, US, June 22-23, 2011*
2. *Bee JS, Nelson SA, Freund E, Carpenter JF, Randolph TW, "Precipitation of a Monoclonal Antibody by Soluble Tungsten". J Pharm Sci, 2009, 98(9), pp 3290-3301.*
3. *Mahler H-C, Friess W, Grauschopf U, Kiese S, "Protein Aggregation: Pathways, Induction Factors and Analysis". J Pharm Sci, 2009, 98(9), pp 2909-2934.*

ABOUT THE AUTHOR

Claudia Petersen studied bioprocess engineering at the Technical University of Berlin from from 1990 to 1996. In 1998, after two years' post-graduate work in the field of oncology research she joined Life Sciences Meissner & Wurst, where she became a lead validation engineer mainly on projects for biopharma customers. From 2000 to 2007 Mrs Petersen held different positions at West Pharmaceutical Services' European Technical Support and Marketing department, becoming Senior Manager Biotechnology, before starting as Director Business Development for the Tubular Glass Division at Gerresheimer. Since Dec 2014, she is the Global Director Business Development for the Gerresheimer Medical Systems unit.

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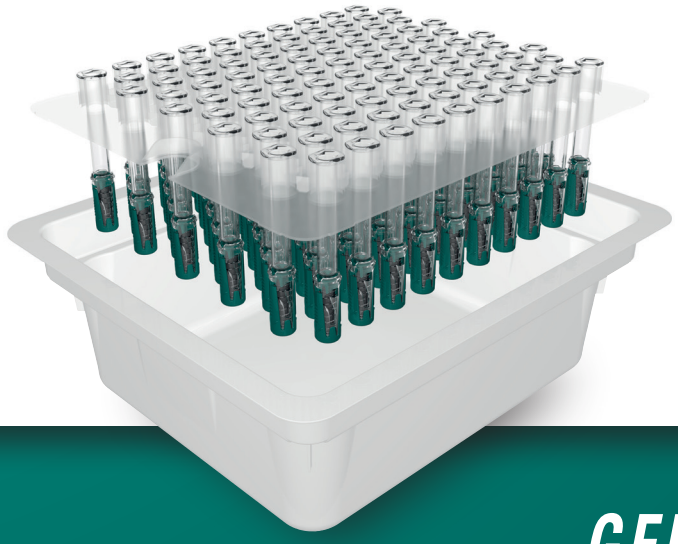
Gx® InnoSafe™

Integrated Safety System

- Protection against needlestick injuries
- Eliminates the possibility of reuse
- Fully passive safety function:
  protection mechanism is activated automatically – no additional actions required
- Fully integrated system:
  delivered pre-assembled in nest and tub



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