TERUMO'S PLAJEX™ AND NEMERA'S SAFE'N'SOUND®: A COLLABORATION THAT SAYS YOU'RE IN SAFE HANDS

Nemera and Terumo have established compatibility between Terumo's PLAJEX™ COP prefillable syringes and Nemera's Safe'n'Sound® passive safety add-on platform. Here, William Dierick, Director Technology Development, Terumo; and Pascal Dugand, Technology Product Manager Device Development and Adrien Tisserand, Global Category Manager, Parenteral, both of Nemera, describe the collaboration focusing specifically on two of the main functions, resistance to drops, and residual volume after delivery of the intended dose and activation of the sharps protection device.

We are in an exciting new era of drug development. The relentless R&D efforts made by the pharmaceutical industry and the advances in both science and technology could facilitate many innovations making treatments widely available and accessible to patients. Such efforts have already contributed to considerable improvements in patient well-being alongside life expectancy, which has also increased dramatically compared with the past century.[1]

Parenteral drug delivery is one of the largest segments of the drug delivery market and accounts for approximately 30% of the market share. This is a result of various factors, including the increase of new biotherapeutics in the market place. Thanks to advancements in biotechnology, monoclonal antibody drug development makes a major contribution in this market, providing improved therapies for various disorders, such as autoimmune and cardiovascular indications, infectious diseases, cancer and inflammation. The emergence of these new biological products and the introduction of new biosimilars demands more attention for the development of advanced drug delivery technologies for these sensitive biological products.[2-3]

According to market analysts, the global market for prefilled syringes (PFS) will grow at a steady pace. PFS consumption has more than tripled over the past decade due to the increasing number of drugs in this format. To date, more than 3.5 billion PFS are being produced each year and that number is expected to grow by approximately 10% on an annual basis.[4]

Therapeutic proteins are typically administered by injection using PFS. However, these proteins may be sensitive to heat and oxidation and they have the tendency to aggregate. Protein aggregation and the elicitation of anti-drug antibodies (ADAs)

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may have a detrimental effect on drug efficacy, pharmacokinetics and safety for the patient.[5]

In order to meet the growing regulatory demands and to produce a PFS as an appropriate primary drug container for use with these biotherapeutics, Terumo developed a polymer-based PFS. By using the advancements in polymer science Terumo has expanded its technological development and innovation in this area.

> "PLAJEX™ 1 mL Long with staked needle offers an opportunity to mitigate potential interactions with the biological drug product."

More than 16 years ago, Terumo launched a polymer PFS for its own branded products and has continued to develop this application for many different drug products, including applications for biotherapeutics.[6]

Terumo has set up an integrated manufacturing process for all steps of manufacturing, including:

- Integrated moulding operations and robotised transfer
- Automation and subsequent assembly steps
- Fill & closure
  - Aseptic filling (biotherapeutics)
  - Terminal sterilisation (small molecules)
- Secondary packaging operations.

Assembly and integration of add-on safety devices (sharps injury protection devices) and auto-injectors is also an option that is on offer from Terumo's CMO services.[7]

Based on this vast experience, in 2012, Terumo launched a sterile ready-to-fill prefillable syringe called PLAJEX™. A combination of Zeonex® cyclo olefin polymer (COP) for the syringe barrel with a chlorobutyl rubber (CIIR) plunger stopper and its proprietary coating (i-coating™) is used for the creation of a PFS system without the use of silicone oil lubrication inside the syringe.[8-9]

The PLAJEX™ 1 mL Long with staked needle (27G TW x ½" or 29G TW x ½") offers an opportunity to mitigate potential interactions with the biological drug product for numerous reasons:[9-10]

- No internal syringe lubrication with silicone oil minimises the occurrence of protein aggregation
- Low sub-visible particles (SbVPs)
- Insert-moulding for bonding the stainless steel needle without the use of glue; no tungsten issues
- Tub/nest Syringe component sterilised by steam sterilisation, avoiding protein oxidation by the occurrence of free radicals (from irradiation sterilisation)
- Selected materials for minimising extractables and leachables.

By combining the i-coating™ plunger stopper, several functional properties provide further advantages for syringe applications:[8-9]

- Securing container closure integrity
- The absence of a break-loose peak force to initiate plunger movement; break-loose and gliding forces (BLGF) are consistent and predictable and do not deteriorate over time.

Polymer prefillable syringes produced from COP also offer physical properties that serve the application and integration for advanced parenteral drug delivery technologies, such as auto-injectors for self-injection and for use with add-on devices for protecting the user and healthcare provider from the risk of needlestick injuries. These features include:

- High transparency
- Resistance to breakage
- Narrow dimensional tolerance of the moulded parts.

To serve the needs of our clients to the very highest degree, Terumo and Nemera have collaborated to create a compatibility between Terumo's PLAJEX™ prefillable syringes with Nemera's Safe'n'Sound® platform of add-on passive sharps injury protection devices for PFS. Under this collaboration, Nemera together with Terumo have defined a development plan to confirm compatibility of Safe'n'Sound® with PLAJEX™ prefillable syringes as illustrated in Figure 1.

This development plan was defined around three main activities: (1) adaption of the sharps injury protection device to PLAJEX™ characteristics; (2) verification of the performances through a design verification plan; and (3) validation of the performances through a simulated clinical user study.

Figure 1: Nemera's Safe'n'Sound® combined with Terumo's PLAJEX™ COP prefillable syringe.

Safe'n'Sound® is a customisable platform of add-on passive sharps injury protection devices for PFS, which not only aims to prevent needlestick injuries but also to ease usage, facilitating the injection process. As a passive sharps injury protection device, no extra gesture is required by the user with Safe'n'Sound® compared with a naked syringe. The sharps injury protection feature activates automatically after completion of the entire dose, simplifying use. User interface has been integrated since the beginning in the design and development of the device, integrating many ergonomic features: a large thumb pad surface to smooth the injection; large built-in finger flange to facilitate handling; a round shape for easy and comfortable handling; a spring located at the syringe flange position to provide good visibility

Figure 2: Safe'n'Sound® before syringe assembly, drop test without syringe.

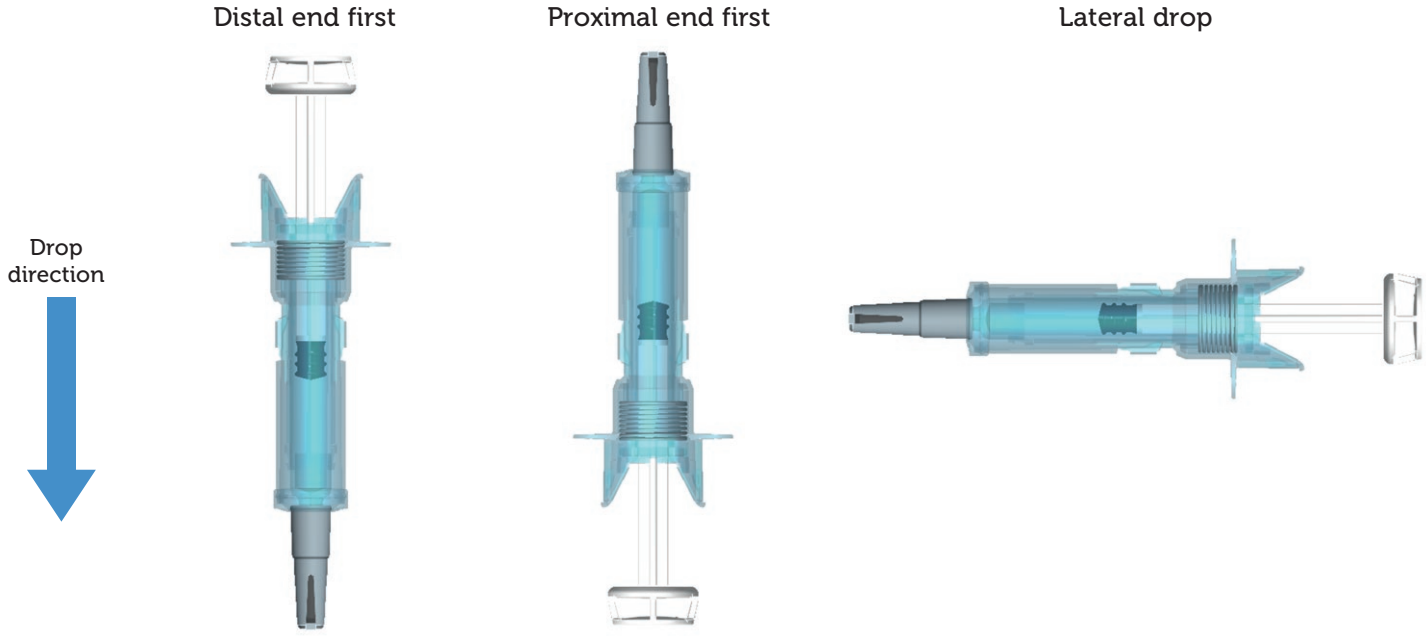

Figure 3: Safe'n'Sound® with WFI filled PFS, drop test before use.

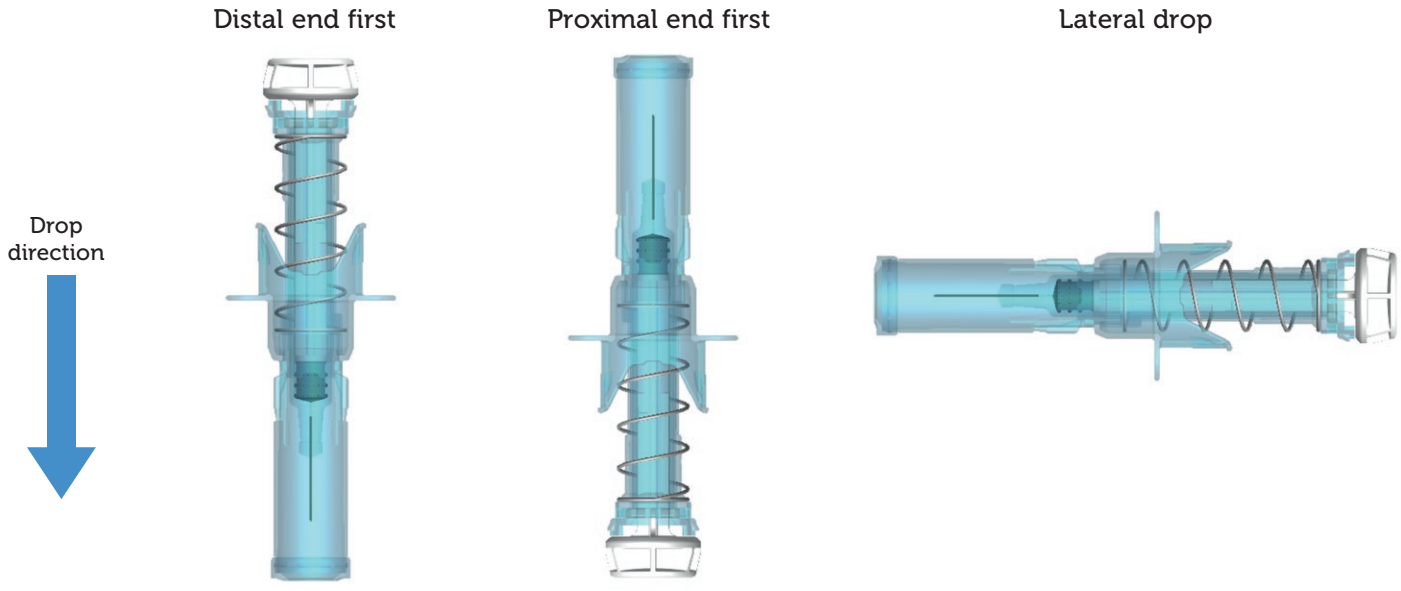

Figure 4: Safe'n'Sound® with PFS, drop test after dose delivery and activation.

"Of the 1000 simulated injections performed with Safe'n'Sound® / PLAJEX™ without EFF and the 1000 simulated injections performed with Safe'n'Sound® / PLAJEX™ with EFF, zero failures were observed."

of the tip and front side of the syringe for easy inspection of the drug even with low filling volume drugs. Optional add-on ergonomic extended finger flanges have also been developed to improve handling, gripping and comfort for the user.

Safe'n'Sound®, based on high molecular weight polycarbonate, is a fully transparent device, very resistant to breakage. PLAJEX™ COP prefillable syringes are in accordance with ISO 11040-6 and present distinct design features. For example, the flange geometry is more pronounced with the edges accurately defined and having narrow tolerances, based on injection moulding process capabilities. These features of PLAJEX™ COP provide strong performance and interaction with the Safe'n'Sound® add-on device, such as interlocking and avoidance of inadvertent dislocation. Therefore, Safe'n'Sound® device matching was conducted to create device compatibility with PLAJEX™ 1 mL Long-staked-needle PFS.

Nemera developed a specific sleeve (the inner part of the sharps injury protection device in which the syringe is snapped-in) and a specific plunger rod was prepared to be compatible with PLAJEX™ syringes and the i-coating™ plunger stopper. All performances associated to the syringe specific design and those new components were checked during the design verification plan.[11]

DEVICE PERFORMANCE BEFORE AND AFTER DROP

Resistance to accidental shocks is key not only from a patient perspective but also a cost point of view. A high resitance to shocks and vibrations may improve patient safety by avoiding dangerous dislocation of the add-on device. Moreover, it allows bulk packing of the safety device (lowering the transportation costs) and a more efficient process on the assembly line for higher productivity. In addition, once assembled together with the syringe, it eliminates the potential loss of expensive drugs through accidental activation.

In developing the design verification plan, and to determine performance testing criteria, reference was made to ISO 11608-1:2014, "Needle-based injection systems for medical use. Requirements and test methods, Part 1: Needle-based injection systems". Where a PFS by itself is not regarded as needle-based injection systems (NIS), it was considered to be a sound rational to refer to preconditioning and free fall testing requirements of this standard as it represented a potentially very effective means of really challenging and confirming the robustness of the design of the needle injury protection feature, assessing the operation and functionality of the accessory as mounted onto the PFS.

Safe'n'Sound® was developed with the aim of achieving a high drop resistance.

DESIGN VERIFICATION: DROP RESISTANCE

To assess the drop resistance of the Safe'n'Sound® device with PLAJEX™ syringes, free-falling drop tests were performed following three different drop directions (as shown in Figures 2-4). Tests were conducted following Nemera internal protocols on: 30 units of Safe'n'Sound® without syringe (Figure 2); 30 units of Safe'n'Sound® with PFS filled with water for injection (WFI) before use (Figure 3); and 30 units of Safe'n'Sound® after dose delivery and activation (Figure 4).

Drop tests were performed on the devices at room temperature before and after accelerated ageing conditions, and also after cycling conditions described hereafter.

Ageing conditions:

- 77 days at 65°C before syringe assembly
- 77 days at 65°C before syringe assembly + 60 days at 65°C after syringe assembly.

Cycling conditions:

- Four days at -40°C and four days at +70°C
- The devices were left to cool down to room temperature (20°C) before being tested.

The acceptance criteria were defined as per ISO 11608-1. Failure is considered as syringe unloading/dislocation, breakage and/or device activation. An overview of the results of the testings with the different conditions are shown in Figure 5 and Figure 6.

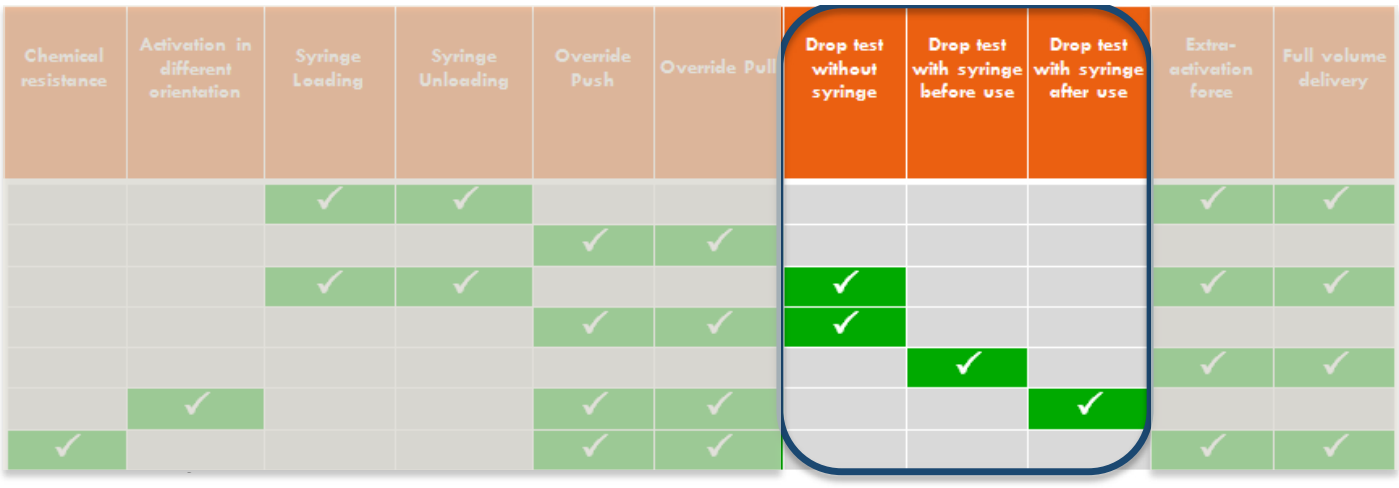

Figure 5: Test result overview, without preconditioning.

Group	Test conditions	Activation in different orientations	Syringe Loading	Syringe Unloading	Override Push	Override Pull	Transport	Drop test without syringe	Drop test with syringe before use	Drop test with syringe after use	Extra-activation force	Full volume delivery
8a	Transport (single carton)		✓		✓	✓	✓			✓	✓	
8b	Transport (pallet)		✓		✓	✓	✓			✓	✓	
9	77 days 65°C										✓	✓
10	77 +60 days 65°C		✓	✓							✓	✓
11	77 +60 days 65°C				✓	✓						
12	77 days 65°C		✓					✓			✓	
13	77 +60 days 65°C								✓		✓	
14	77 +60 days 65°C	✓			✓	✓				✓		
15	Cycling				✓	✓		✓	✓		✓	
16	Cycling	✓	✓	✓								✓
17	Operating 40°C										✓	
18	Operating 5°C										✓	

Figure 6: Test result overview, after preconditioning (drop, ageing, transport, cycling).

Chemical resistance	Activation in different orientation	Syringe Loading	Syringe Unloading	Override Push	Override Pull	Drop test without syringe	Drop test with syringe before use	Drop test with syringe after use	Extra-activation force	Residual volum
		✓	✓						✓	✓
				✓	✓					
		✓	✓			✓			✓	✓
				✓	✓	✓				
							✓		✓	✓
	✓			✓	✓			✓		
✓				✓	✓				✓	✓

Figure 7: Test result overview for residual volume, without preconditioning.

Group	Test conditions	Activation in different orientations	Syringe Loading	Syringe Unloading	Override Push	Override Pull	Transport	Drop test without syringe	Drop test with syringe before use	Drop test with syringe after use	Extra-activation force	Residual volum
8a	Transport (single carton)		✓		✓	✓	✓			✓	✓	
8b	Transport (pallet)		✓		✓	✓	✓			✓	✓	
9	77 days 65°C										✓	✓
10	77 +60 days 65°C		✓	✓							✓	✓
11	77 +60 days 65°C				✓	✓						
12	77 days 65°C		✓					✓			✓	
13	77 +60 days 65°C								✓		✓	
14	77 +60 days 65°C	✓			✓	✓				✓		
15	Cycling				✓	✓		✓	✓		✓	
16	Cycling	✓	✓	✓								✓
17	Operating 40°C										✓	
18	Operating 5°C										✓	

Figure 8: Test result overview for residual volume, after preconditioning (ageing, cycling).

"Safe'n'Sound® / PLAJEX™ with EFF was considered to be an effective needlestick protection device, without use problems, which allows an injection to be performed using a one hand technique, and which does not need extensive training for correct manipulation."

Out of the 72 devices tested in every configuration, all devices passed the test successfully. No inadvertent device activation nor syringe unloading has been observed in any of the conditions described above. No breakage was noted on the PLAJEX™ PFS nor the Safe'n'Sound® device. These results confirm the robustness and compatibility of the Safe'n'Sound® device in combination with PLAJEX™ PFS.

DESIGN VERIFICATION: RESIDUAL VOLUME

Residual volume is considered as the volume of drug left in the syringe after completion of the injection of the intended dose. In order to confirm the compatibity of Safe'n'Sound® with PLAJEX™ syringes, tests were performed according to Nemera's internal protocols on devices at room temperature before and after accelerated ageing conditions, as well as after cycling conditions.

Ageing conditions:

- 77 days at 65°C before syringe assembly
- 77 days at 65°C before syringe assembly +60 days at 65°C after syringe assembly.

Cycling conditions:

- Four days at -40°C and four days at +70°C
- The devices were left to cool down to room temperature (20°C) before being tested.

The acceptance criteria were defined as residual volume should be ≤70 µL according to ISO 7886-1:1993, "Sterile hypodermic syringes for single use, Part 1: Syringes for manual use", as well as being equivalent to the syringe without Safe'n'Sound® device. An overview of the results is shown in Figures 7 and 8.

72 devices were tested by each condition. All devices passed the test successfully. It is important to note that the results presented a very low residual dose, an important aspect for use with valuable biopharmaceuticals. Indeed, average values registered went from 1-4 µL. It has been demonstrated that the residual volume remains the same whatever the device pre-conditioning.

In order to confirm the compatibility of Safe'n'Sound® with PLAJEX™ syringes, once the design adjustment and design verification plan have been successfully executed, a simulated clinical user study was performed to validate the functionality of the device.

SIMULATED CLINICAL USER STUDY VALIDATION

A simulated clinical user study[12] was designed to evaluate the safety of use of Safe'n'Sound® PLAJEX™ version with and without an extended finger flange (EFF) in the prevention of needle stick injuries. The primary objective was to evaluate the number of injuries or non-activation of the safety feature reported by the evaluators for each device. Success was defined as a complete activation of the safety feature following injection without a needlestick injury, whereas failure was defined as a non-complete activation of the safety feature following injection.

The study was designed in accordance with ISO 23908:2011, "Sharps injury protection: Requirements and test methods. Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling", and US FDA Guidance for Industry and FDA Staff, "Medical Devices with Sharps Injury Prevention Features, Section 10, Simulated Clinical Use Testing".

In accordance with the FDA recommendations, 1000 safety devices (n=1000) of each configuration (with and without EFF) were tested. Acceptance criteria were defined in accordance with ISO 23908 and the FDA Guidance.

The study was performed in the US by a total of 60 evaluators. The evaluators were composed of 30 non-healthcare professionals (NHCP) and 30 healthcare profesionals (HCP). Of the 2000 injections performed with Safe'n'Sound® PLAJEX™ version with / without EFF, 1320 were performed by a HCP and 680 by a NHCP. The order of testing was determined randomly among evaluators so as not to favour one version over another.

To mimic real clinical conditions of device use, HCPs performed injections with gloves and NHCPs without gloves. Injections were performed using an appropriate patient's substitute and with Safe'n'Sound® / PLAJEX™ PFS filled with WFI.

The analysis of the injury onset and success of manipulations showed the following results:

- zero injuries and zero failures of the Safe'n'Sound® / PLAJEX™ without EFF performed by a HCP
- zero injuries and zero failures of the Safe'n'Sound® / PLAJEX™ without EFF performed by a NHCP
- zero injuries and zero failures of the Safe'n'Sound® / PLAJEX™ with EFF performed by a HCP
- zero injuries and zero failures of the Safe'n'Sound® / PLAJEX™ with EFF performed by a NHCP.

Of the 1000 simulated injections performed with Safe'n'Sound® / PLAJEX™ without EFF and the 1000 simulated injections performed with Safe'n'Sound® / PLAJEX™ with EFF, zero failures were observed. According to the tables given in the FDA guidance, these observations have determined that the primary objective of the simulated clinical user study was achieved for Safe'n'Sound® / PLAJEX™, both with and without EFF.

This study not only confirmed the performance of the two versions of the sharps injury protection device but also gave the opportunity to capture feedback from the evaluators on several aspects of the safety device. Figure 9 shows a summary (results expressed in percentage) of the ratings from all the evaluators on the Safe'n'Sound® / PLAJEX™ version with EFF.

From this survey, evaluators confirmed the performance of the device and its ease of use. Safe'n'Sound® / PLAJEX™ with EFF was considered to be an effective needlestick protection device, without use problems, which allows an injection to be performed using a one-hand technique, and which does not need extensive training for correct manipulation.

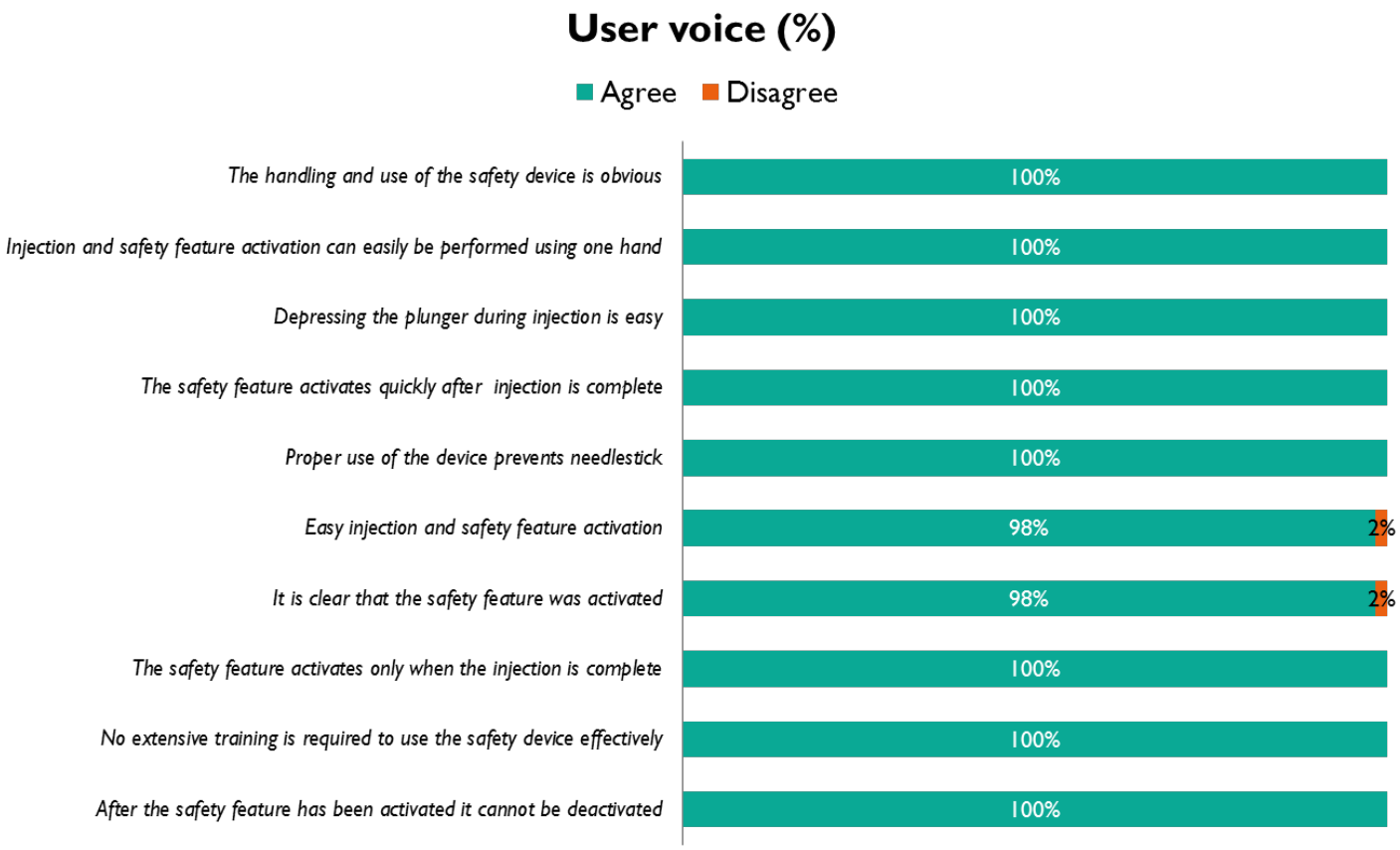

Figure 9: summary of evaluators rating one of the tested Safe'n'Sound®/PLAJEX™ device.

CONCLUSION

In this article, the compatibility of the PLAJEX™ prefillable syringes with Safe'n'Sound® passive sharps injury protection device has been highlighted. Nemera and Terumo have leveraged their polymer science know-how and competences to serve the needs of their clients and provide a unique offering for the delivery of biopharmaceuticals products.

Safe'n'Sound® combined with PLAJEX™ is a fully compatible offer which has been verified technically and validated by users. Among the key advantages, this compatibility offers the biopharmaceutical industry a passive sharps injury protection device with robustness and resistance to shocks and vibrations, minimising the risk of potential needlestick injuries and loss of expensive and lifesaving drugs. Furthermore, a very low residual volume is obtained thanks to Safe'n'Sound® functioning and specific PLAJEX™ design and performance characteristics. The ergonomics and functionality were confirmed and appreciated by users during the simulated clinical user study.

In conclusion, Safe'n'Sound® compatibility has been established and validated with PLAJEX™ COP prefillable syringes and Safe'n'Sound® / PLAJEX™ is prepared and ready for commercial supply.

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ABOUT TERUMO

Tokyo-based Terumo Corporation is one of the world's leading medical device manufacturers

with over US$5 billion in sales and operations in more than 160 nations. Founded in 1921, the company develops, manufactures and distributes world-class medical devices including products for use in cardiothoracic surgery, interventional procedures and transfusion medicine; the company also manufactures a broad array of syringe and hypodermic needle products for hospital and physician office use. Terumo contributes to society by providing valued products and services to the health care market and by responding to the needs of health care providers and the people they serve. Terumo Corporation's shares are listed on the first section of the Tokyo Stock Exchange (No. 4543, Reuters symbol <4543.T>, or Bloomberg 4543: JP) and is a component of the Nikkei 225, Japan's leading stock index.

ABOUT THE AUTHORS

William Dierick is Director, Technology Development – Pharmaceutical Solutions at Terumo, a global R&D company, offering a wide range of innovative products related to drug delivery devices and injection technology, cardiology and cardiovascular systems, transfusion, patient monitoring and clinical systems. With extensive experience in the medical and pharma sectors for more than 40 years, Mr Dierick has held various positions in Terumo, covering quality assurance, manufacturing, product development and engineering, project management, marketing, corporate planning and business development. Mr Dierick serves as an expert in ISO/TC76 and ISO/TC84. He is an active member of Eucomed (MedTech Europe) and volunteer for PDA.

Adrien Tisserand, Global Category Manager at Nemera, is in charge of the parenteral range of proprietary products including Safe'n'Sound®. Mr Tisserand joined the company in 2013. In his previous career he worked for Janssen in the strategic marketing division. He holds: a Bachelor in International Business from HUBS, UK, a Masters in Marketing from URJC, Madrid, Spain, and a Masters from Kedge Business School, France.

Pascal Dugand, Technology Product Manager, Nemera, graduated as a polymer engineer from EAHP in Strasbourg, France. He holds a Masters in polymer mechanics and joined Plastic Omnium in 1990 where he started to work in development and innovation. In 2004, the medical division of Plastic Omnium was acquired by Rexam and more recently the four drug delivery devices plants, including the Innovation Centre, became Nemera. Today, Mr Dugand is an experienced medical device developer engineer specialised in the development of parenteral delivery devices. He developed for Nemera own IP products including Safe'n'Sound and Safelia auoinjector as well as working on several customer injectable product development projects.

ABOUT NEMERA

More than five million diabetics rely everyday on parenteral devices manufactured by Nemera.

With over 1,300 people and four plants across two continents, Nemera is a world leader in the design, development and manufacturing of drug delivery solutions for pharmaceutical, biotechnology & generics industries. Nemera's expertise covers several modes of delivery: Parenteral, Nasal, Buccal, Auricular, Ophthalmic, Pulmonary, Dermal and Transdermal.

Nemera leverages decades of manufacturing and development experience in the parenteral devicesegment (passive safety devices auto-injectors, pens, and implanters), from full development to pure contract manufacturing, through customised solutions. Nemera applies the same quality-oriented process to the development of proprietary devices and to customised solutions under contract with laboratories.

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