ISSUE Nº 06/2020

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REPORT ON NEW SOLUTIONS FOR PHARMACEUTICAL PACKAGING

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A CASE STUDY BY
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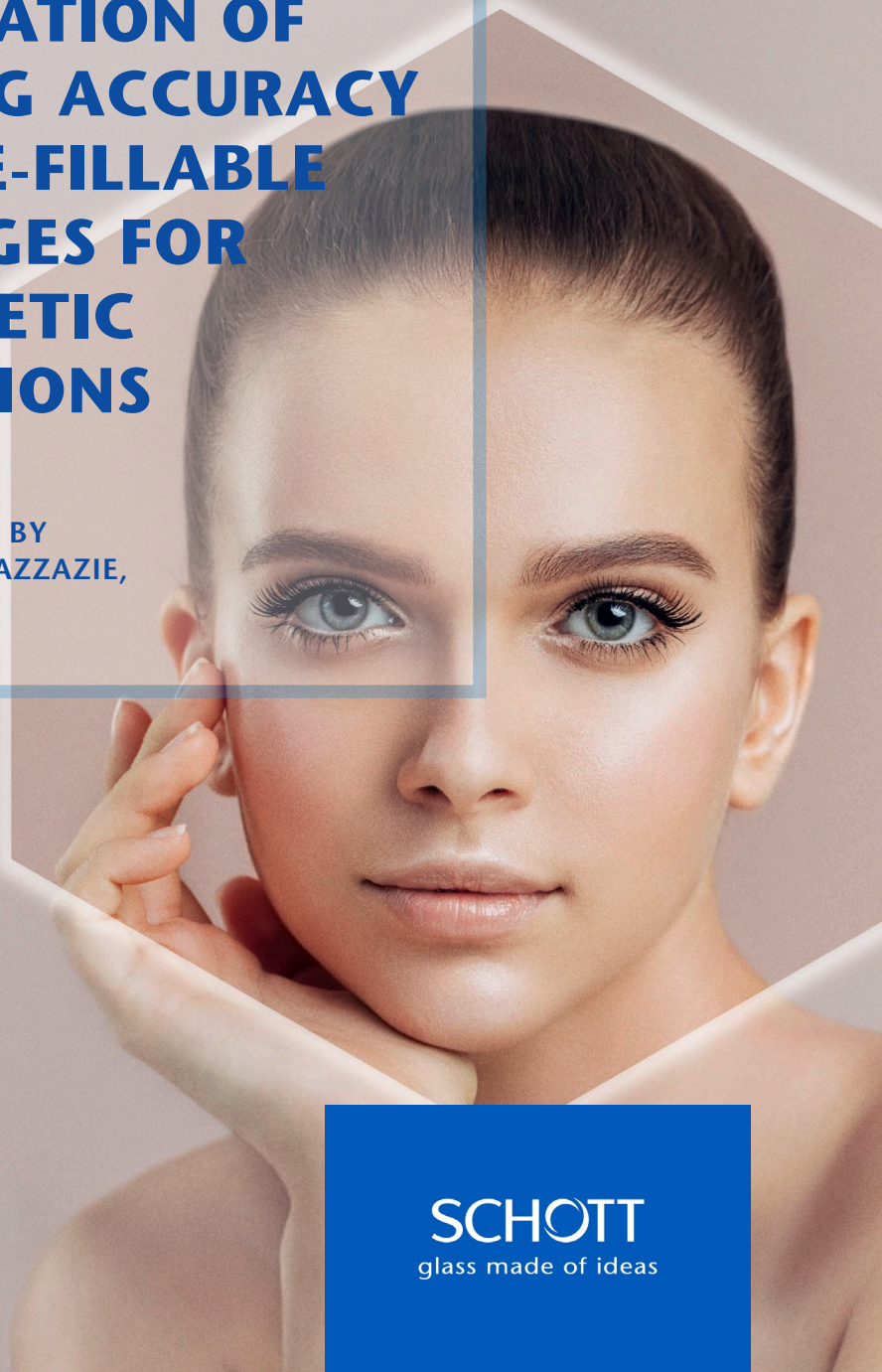

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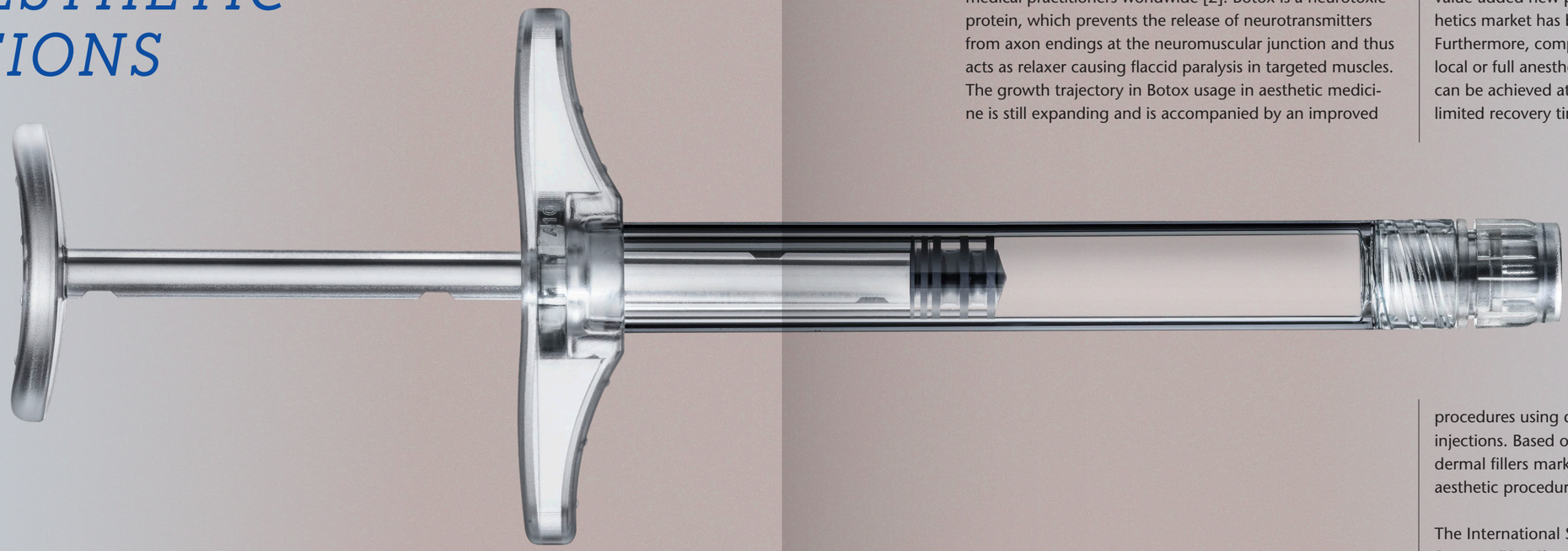
EVALUATION OF DOSING ACCURACY OF PRE-FILLABLE SYRINGES *FOR AESTHETIC INJECTIONS*



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Dermal fillers are rapidly increasing in popularity as they rejuvenate the skin and give aesthetic improvements that were previously only attainable by surgical cosmetic procedures. Dermal fillers such as hyaluronic acid (HA), collagen or body fat fillers, replace lost skin volume in static wrinkles by the injection of a substance under the wrinkle. The injected filler remains there for a limited time or as permanent as possible depending on the type of substance [1].

Additionally, the botulinum neurotoxin type A (Botox) injection for non-surgical treatment and enhancement procedures of facial wrinkles has been widely performed by medical practitioners worldwide [2]. Botox is a neurotoxic protein, which prevents the release of neurotransmitters from axon endings at the neuromuscular junction and thus acts as relaxer causing flaccid paralysis in targeted muscles. The growth trajectory in Botox usage in aesthetic medicine is still expanding and is accompanied by an improved understanding of the need for tailored treatment procedures according to individual facial anatomies, muscle tone, cultural aspects and specific patient preferences [3-4].

Previously, estimates have suggested that there are over 160 commercial dermal filler products available from more than 50 companies worldwide [1]. As public awareness and acceptance of HA and other dermal fillers as well as Botox is increasing along with overall demand for aesthetic beauty, combined with value-added new product launches, the aesthetics market has been constantly growing. Furthermore, compared with surgery under local or full anesthesia, similar aesthetic effects can be achieved at a lower cost and with very limited recovery time by nonsurgical cosmetic procedures using dermal fillers or Botox-based injections. Based on this, the global Botox and dermal fillers markets for minimally invasive aesthetic procedures will continue to grow [5].

The International Society of Aesthetic Plastic Surgery (ISAPS) registered more than 23 million surgical and non-surgical (> 12 million) cosmetic treatments worldwide in 2018 [6]. According to the ISAPS data, more than 6 million non-surgical Botox treatments were performed while almost 4 million dermal filler injection treatments were conducted [6]. Among numerous cosmetic dermal fillers, HA represents the most popular and most commonly used substance with more than 3.7 million treatments. HA is considered the gold standard in dermal fillers and will presumably further account for the largest market share [5].

AESTHETIC INJECTIONS HAVE CERTAIN SPECIAL REQUIREMENTS

HA occurs as a natural component in the body responsible for attracting and retaining moisture. Due to hydrophilic nature combined with its viscoelasticity properties, HA improves cell-to-cell interaction and promotes collagen synthesis, which can prevent wrinkles and improve the skin's texture. For example, HA-based fillers enable the restoration of tissue volume by filling the folds between nose and mouth or lifting cheekbones as well as midfacial volumization and correction of facial asymmetry, raising the mouth corners and plumping up thinning lips.

HA-based fillers are subcutaneously injected into the concerned skin areas within minimally invasive cosmetic treatments. Typically, for pre-filled syringes the duration of the treatment varies between several minutes and half an hour. Highly precise dosing and exact application of the injections are essential tasks in order to achieve excellent cosmetic results. However, high molecular HA is highly viscous and additionally features non-Newtonian flow properties [7]. Hence, administering HA by conventional pre-filled glass syringes with a Luer Lock assembly poses a key challenge, particularly regarding changes in viscosity due to the high mechanical forces necessary for the injection. The high mechanical forces required impedes physicians' ability to inject an accurate dosage of HA through small sized needles, which in turn can lead to patients feeling discomfort and pain. Additionally, there is a significantly increased risk that the high pressure inside the syringe can even disconnect the needle hub from the syringe, in a worst case leading to breakage of the Luer Lock adapter.

SOLUTIONS TO OVERCOME COMMON PROBLEMS

To overcome these challenges a robust syringe system with optimized injection forces are essential for a gentle administration of highly viscous drugs (HVD). To this end, SCHOTT has developed a solution: SCHOTT TOPPAC® cosmetic. This syringe is made of the high break-resistant and highly purified Cyclic Olefin Copolymer (COC) and is designed specifically for injecting HVDs like dermal fillers and to enable safe and convenient cosmetic procedures with accurate administrations. Compared to existing SCHOTT TOPPAC® solutions, the innovative design comprises a longer syringe combined with a smaller inner syringe diameter. Especially the reduced inner diameter leads to lower overall break loose and extrusion forces providing minimized patient pain and discomfort during cosmetic treatments, and a more convenient and accurate injection procedure of physicians. Another beneficial feature in this context is the optimized siliconization, which ensures that the syringe plunger slides, even with low break loose force, thus allowing the medication to be administered with precision. Further benefits for both physicians and patients are derived from the integrated Luer Lock thread, which ensures stable assembly, and secure needle attachment during injection. The closure system utilizes a threaded rigid tip cap, which is easy to open, prevents potential leakages, and maintains stable container closure integrity. Additional ergonomically designed components made of polycarbonate, i.e. optimized backstop and plunger rod, provide

additional injection comfort as well as improved system break resistance and durability. Moreover, the same standard rubber components and reactive silicone cocktail formulations are employed as standard solutions, which allow for easier registration. In this regard, existing screening studies for the extractable profile for several components of the pre-fillable syringes is applicable and can be used as a starting point for leachables analysis. The components for the secondary packaging such as tub, nest, insert liner, sealing lid, and protective bags are also standard components used for existing solutions. Hence, the compatibility with present fill & finish and packaging operations for commercial manufacturing is given. With particular respect to pharmaceutical product manufacturing and filling, the cosmetic syringe can easily be integrated into existing filling lines through a ready-to-use format in the same standardized tub and nest, leveraging the existing packaging of the standard portfolio.

The syringe system is resistant to steam sterilization up to 150 °C and is provided with full technical data package, including design history file, to support the product manufacturer throughout registration. The package is based on SCHOTTs knowledge and expertise and supported by intensive research efforts along with a series of lab testing and validation studies, which have been iteratively conducted by the internal Research & Development department and in collaboration with external laboratories and partners by means of a product development process governed by design control principles.

CHARACTERIZATION OF NEEDLE IMPACT

Dermal fillers such as HA are usually administered by a 27-31 gauge needle. The highly viscous dermal filler gel in combination with small sized needles can cause high pressure inside the syringe, which can lead to injection malfunction resulting in needle leakage, or even needle pop-off – a common phenomenon seen with some existing syringe systems available in the market. Needle leakage describes the needle hub losing its sealing function, which leads to dermal filler leaking out of the syringe between the needle hub and the cone of the syringe. Needle pop-off means that the needle hub is disconnected from the syringe. In order to eliminate these issues, SCHOTT and TSK Laboratory, a well-established supplier of best-in-class CE certified cannulas, combined forces to bring a safer and more ergonomic system to the market.

A joint study is carried out by testing a dermal filler needle from TSK as well as market alternative needles with polymer pre-fillable syringes from SCHOTT with respect to needle pop-off and leakage. The system testing includes two different variations of TSK needles, TSK dermal filler needle with PRC needle hub and HPC needle hub. To compare the SCHOTT-TSK system with present solutions available on the market the test is additionally performed with alternative needles. The applied test method simulates the standard dermal filler injection process: while the needle hub is blocked off preventing the filler to expel out of the syringe, an increasing force is applied on the plunger rod stressing the needle hub until a malfunction occurs, i.e. either needle leakage or pop-off. The maximum force is determined at the point of failure.

IMPROVED PERFORMANCE AND REDUCED RISK OF NEEDLE POP-OFF AND LEAKAGE

The results of the leakage testing are presented in figure 1. The force required to cause needle leakage at the cosmetic syringe with the TSK dermal filler needle with HPC needle hub is about 200 N, which is more than twice the force of the market alternative needle. In other words, the cosmetic syringe combined with TSK HPC needle resists 2.5-fold more pressure than that of its peers before leakage occurs.

Figure 2 shows the results of the pop-off testing. Similarly, there is a major improvement of the TSK dermal filler needle with HPC needle hub compared to standard options. In this case, 140 N of force is required to produce a needle pop-off occurrence, which is almost twice the force of the market alternative needle. In this respect again, the overall risk for needle pop-off is considerably reduced, since TSK and SCHOTT combination resists more than 1.5-times more pressure before pop-off occurs.

The results demonstrate that SCHOTT TOPPAC® cosmetic in combination with TSK Laboratory's STERiJECT® with HPC needle hub features superior performance compared to alternative needles proving that both, the syringe and the needle, matter to realize an optimized robust syringe delivery solution. Moreover, the system by far resists the average maximum force of 95 N, which a male user can apply to the syringe [8], while others show either needle leakage or pop-off.

The results demonstrate that SCHOTT TOPPAC® cosmetic in combination with TSK Laboratory's STERiJECT® with HPC needle hub features superior performance compared to alternative needles proving that both, the syringe and the needle, matter to realize an optimized robust syringe delivery solution.

Needle leakage
Average force causing leakage [N]

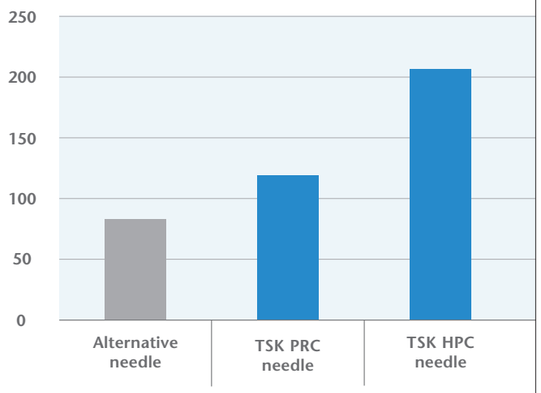

FIGURE 1:
Illustration of the impact of the needle with regard to needle leakage.

Needle pop-off
Average force causing NPO [N]

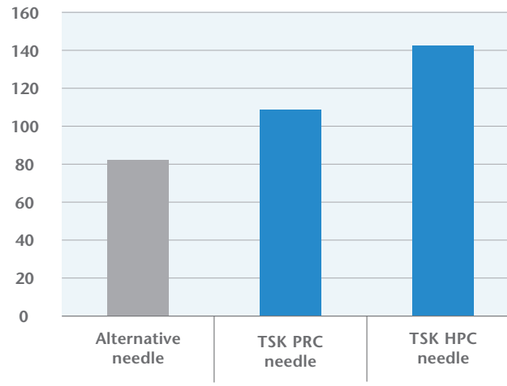

FIGURE 2:
Illustration of the impact of the needle with regard to needle pop-off

INFLUENCE OF PRIMARY PACKAGING MATERIAL AND NEEDLE HUB ASSEMBLY

Apart from the needle hub, when it comes to leakage and pop-off issues, the material of the primary packaging for the syringe is another influencing factor to be taken into account, i.e. the impact of glass compared to polymer are evaluated. The respective tests with glass and polymer syringe, are conducted with syringes of same size with identical needles. The measurements demonstrate less leakage between needle hub and syringe as well as less risk for needle pop-off for the polymer-based syringe compared to the glass-based syringe as shown in figure 3.

A further point of focus within the internal test series performed by SCHOTT is the impact of needle hub assembly. The test outcomes show that assembling the needle with more rotational torque force results in less risk for leakage and needle pop-off as can be seen in figure 4. The integrated Luer Lock allows the user to apply more torque force on the needle without spinning the Luer Lock.

Influence of primary packaging material
Maximum force until leakage or NPO [N]

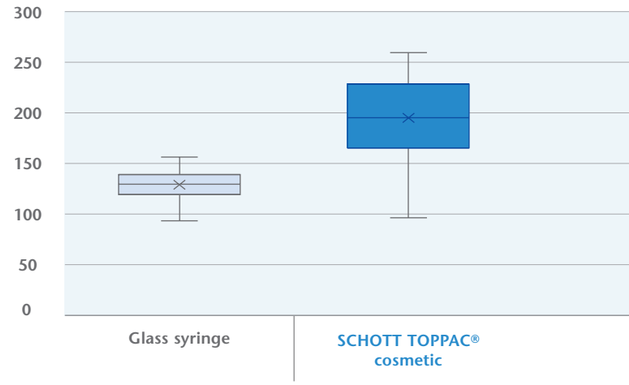

FIGURE 3:
Illustration of the influence of the primary packaging material regarding leakage and pop-off.

Needle hub assembly
Maximum force until leakage or NPO [N]

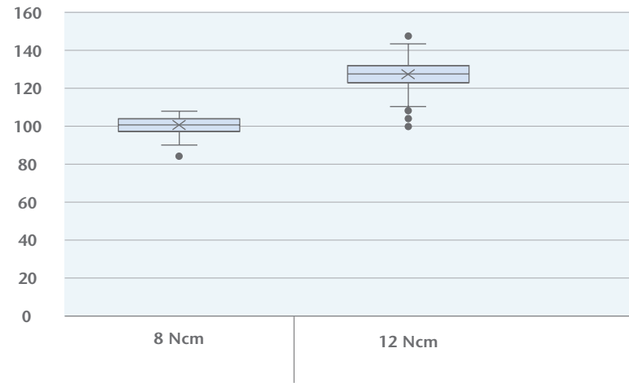

FIGURE 4:
Illustration of the assembly impact regarding leakage and pop-off.

IMPROVED CLOSURE SYSTEM FOR SAFER AND EASIER HANDLING

The new Luer Lock closure system combines superior container closure integrity with an easy, intuitive, and safe opening mechanism. It is easier to open than standard Luer Lock Adapter options and requires a simple unscrewing motion for disengagement. Furthermore, long-term accelerated tests over a period of 105 days at 40 °C show that the new Luer Lock closure system maintains constant opening forces over aging (Figure 5). Further long-term accelerated tests simulating a period up to 210 days are conducted to evaluate the container integrity. The results displayed in figure 6 indicate that with the new Luer Lock thread leakage did not occur with simulated pressures up to 5 bar, which is at least 3-4-times higher compared to the standard tip cap (TC).

The new Luer Lock closure system combines superior container closure integrity with an easy, intuitive, and safe opening mechanism.

Closure system opening characteristics
Closure opening torque [Ncm]

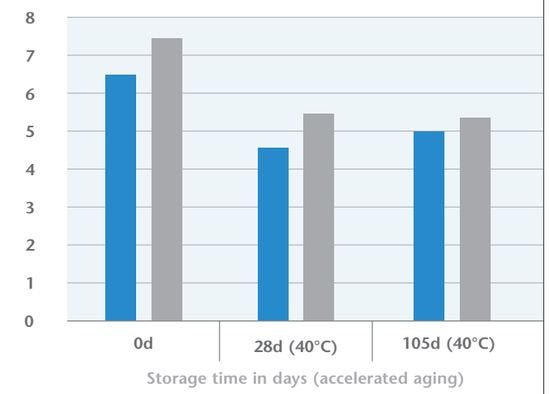

FIGURE 5:
Impact of accelerated ageing on opening torque of the closure system.

Container integrity
Minimal pressure when leakage occurs [bar]

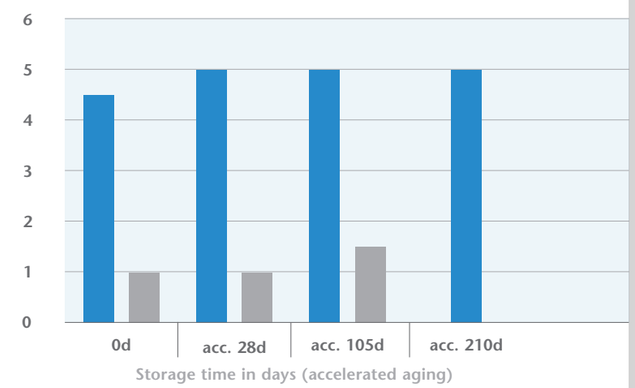

FIGURE 6:
Impact of accelerated ageing on container integrity.

Break loose and extrusion force measurements are performed in order to provide key functional comparisons between the cosmetic syringe and a polymer standard syringe. As part of the design verification, the respective forces are measured within predefined zones according to standardized methods [9]. The syringes are tested under several settings: empty, filled, with and without steam sterilization. Accelerated ageing tests are conducted after 7, 28 and 105

days. The cosmetic syringe passes all acceptance criteria, showing similar and partly improved performance compared to the standard polymer syringe.

Other essential aspects for pre-filled syringes are ageing and steam sterilization. Once a syringe is prefilled, it has to keep functional performance over shelf life with minimized influence of present filler compound, temperature and humidity. Therefore, extrusion force measurements with filled syringes are conducted, in order to examine the impact of ageing and steam sterilization on the cosmetic syringe. The median extrusion force is calculated over a distance of 4 mm after start point and 10 mm

Impact of steam sterilization
Average extrusion force [N]

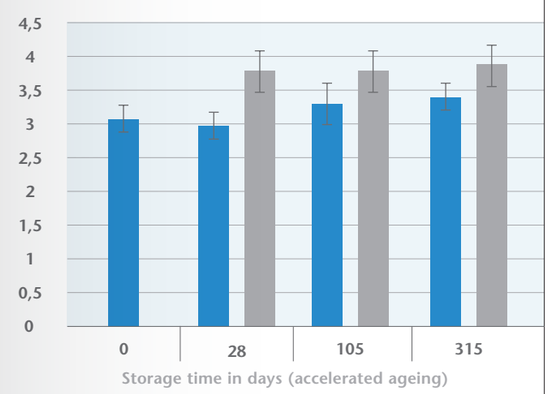

FIGURE 7:
Simulation of the impact of steam sterilization on SCHOTT TOPPAC® cosmetic over shelf life.

before end of measurement. The measurement data presented in figure 7 is collected from 30 syringes tested over the course of 315 days without steam sterilization, as well as from 30 other steam-sterilized syringes tested over the same period. It should also be emphasized that the aforementioned measurements are performed at 100 mm/min, 40 °C and 75 % relative humidity. The results of the accelerated ageing tests outlined in figure 7 demonstrate that the impacts of both long-term storage and steam sterilization on the cosmetic syringe are minimized.

REDUCED EXTRUSION FORCES IMPROVE THE EXPERIENCE FOR BOTH PHYSICIAN AND PATIENT

The functional performance of the syringes is further assessed within a case study specifically simulating a real life application. Within this study, the respective applied forces on the plunger rod required to eject a high viscous filler through a thin needle (31 G) are evaluated for both the cosmetic syringe and the standard polymer syringe. The syringes

Extrusion forces
Average extrusion force [N]

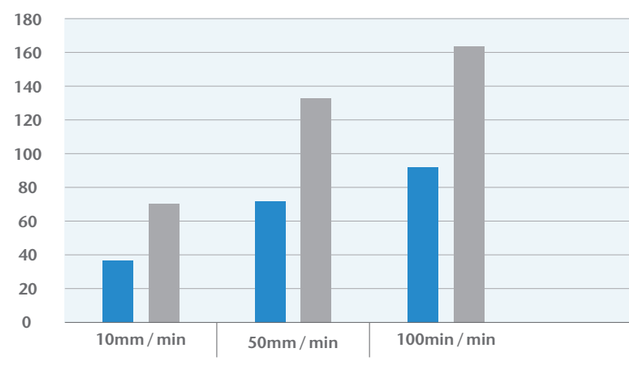

FIGURE 8:
Simulation of a real-life situation and the impact of the applied speed on extrusion forces.

are filled with highly viscous commercial HA-based filler provided by a customer while the needle is assembled with a torque force of 12 Ncm. The forces measured correspond to the forces applied by users in a real-life situation. The measurements are conducted at various speeds according to the assumption that the speed has a high influence on the needed force. The respective speeds are 100 mm/min, 50 mm/min and 10 mm/min (Figure 8).

The applied speed has a significant influence on the required forces. For the standard 1mL long syringe the average extrusion force is 181 N at 100 mm/min, 146 N at 50 mm/min and 75 N at 10 mm/min. In contrast, for the cosmetic syringe, the required forces are 98 N (100 mm/min), 73 N (50 mm/min) and 36 N (10 mm/min). The results demonstrate that 50 % lower extrusion forces are needed for injection by the cosmetic syringe. In this context, it is important to note that the inner diameter of the cosmetic syringe's barrel has been decreased (5 mm vs. 6.5 mm of standard polymer syringe) in order to decrease the extrusion force. Since the actual fill volume needs to be maintained, the syringe length has been adjusted accordingly.

One possible conclusion of these results is that the patient might have more pleasant experience during the injection while the physician might have easier administration of the drug product. The results also indicate that dose accuracy and delivered volume are improved as a result of the reduced inner diameter of SCHOTT TOPPAC® cosmetic as well as considerably lower extrusion forces. Assuming a dose volume for a cosmetic injection of 0.1 mL, it takes roughly 3 mm of plunger movement at the standard polymer syringe. In contrast, it takes about 5 mm of plunger movement at the cosmetic syringe and consequently, the syringe enables the physician to deliver a microliter sized dose in more steps within an extended movement and therefore with improved accuracy.

The results also indicate that dose accuracy and delivered volume are improved as a result of the reduced inner diameter of SCHOTT TOPPAC® cosmetic as well as considerably lower extrusion forces.

ROLE OF NEEDLE GAUGE AND ERGONOMIC COMPONENTS

Another factor to consider for patient comfort level is the needle gauge. A broad-gauge range is beneficial in order to enable maximum flexibility and customization based on product or indication. However, previous studies of Merz Aesthetics and Allergan yielded in improved injection profile and reduced tissue penetration force through thinner needles, allowing smoother delivery of regular amounts of HA over time and consequently decreased pain proven by clinical studies [9-10]. The present investigation compares the use of 31 G and 27 G needles with the cosmetic syringe. At 10 mm/min, the syringe with 31 G needle shows an average extrusion force of 36 N, while the assembly with 27 G needle results in an average extrusion force of 29 N, resulting in a 20 % decrease in force. These findings are in accordance with aforementioned studies [10-11].

In addition to the needle and rigid cap, ergonomic components are designed to round off clinician's and patient experience. The ergonomic finger flange extender helps to avoid accidental slide of flange due to high pressure and supports delivery of highly viscous drugs. The plunger rod thumb pad aims to increase injection comfort by providing additional surface area to apply pressure during injection. Softer materials are used on injection components to add comfort for physicians.

CONCLUSIONS AND OUTLOOK

With advances in non-surgical aesthetic treatments, dermal fillers such as hyaluronic acid or Botox have become the major biopharmaceutical products for cosmetic applications. Pre-filled syringes are primarily used in the administration for these cosmetic drugs. These highly concentrated formulations are delivered subcutaneously and have particular administration challenges due to their high viscosity. The high injection forces required to deliver these drugs pose challenges for conventional glass syringes, including the possibility of needle hub leakage and disconnection.

A joint study conducted by SCHOTT and TSK Laboratory shows that among all tested combinations the new cosmetic syringe with the TSK STERiJECT® needle with HPC hub performs the best with respect to needle leakage and pop-off. The combined syringe system provides an improved injection performance as well as improved needle attachment with minimized risk of injection malfunction.

The new syringe also includes an enhanced Luer Lock closure system, which offers an improved closure system for safer and easier handling as well as easy and intuitive opening. This robust threaded closure provides confidence to dermatologists through an easy-to-use removal mechanism with minimal opening torque forces.

Thanks to a reduced inner diameter of the barrel, the syringe system enables optimized extrusion forces with smoother extrusion force profiles, thus allowing smooth delivery of the dermal filler with improved dose accuracy.

SCHOTT TOPPAC® cosmetic is especially well suited for the injection of highly viscous dermal fillers and makes aesthetic injections easier for the physician and safer for the patient. Through several interconnected features, reduced extrusion forces, syringe design, dimensions and specifications are balanced in order to enable patient well-being along with improved dose accuracy and optimal ergonomics for physicians.

Apart from cosmetic treatments, hyaluronic acid is used in cataract surgery for anterior chamber expansion, in order to simplify the insertion of artificial intraocular lenses. In case of osteoarthritis, hyaluronic acid is injected into the knee joint as a treatment. SCHOTT TOPPAC® cosmetic syringe is hence also suitable for ophthalmic and viscosupplementation applications.

For more information, please visit:
schott.com/innovation/en/schott-toppac-cosmetic

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