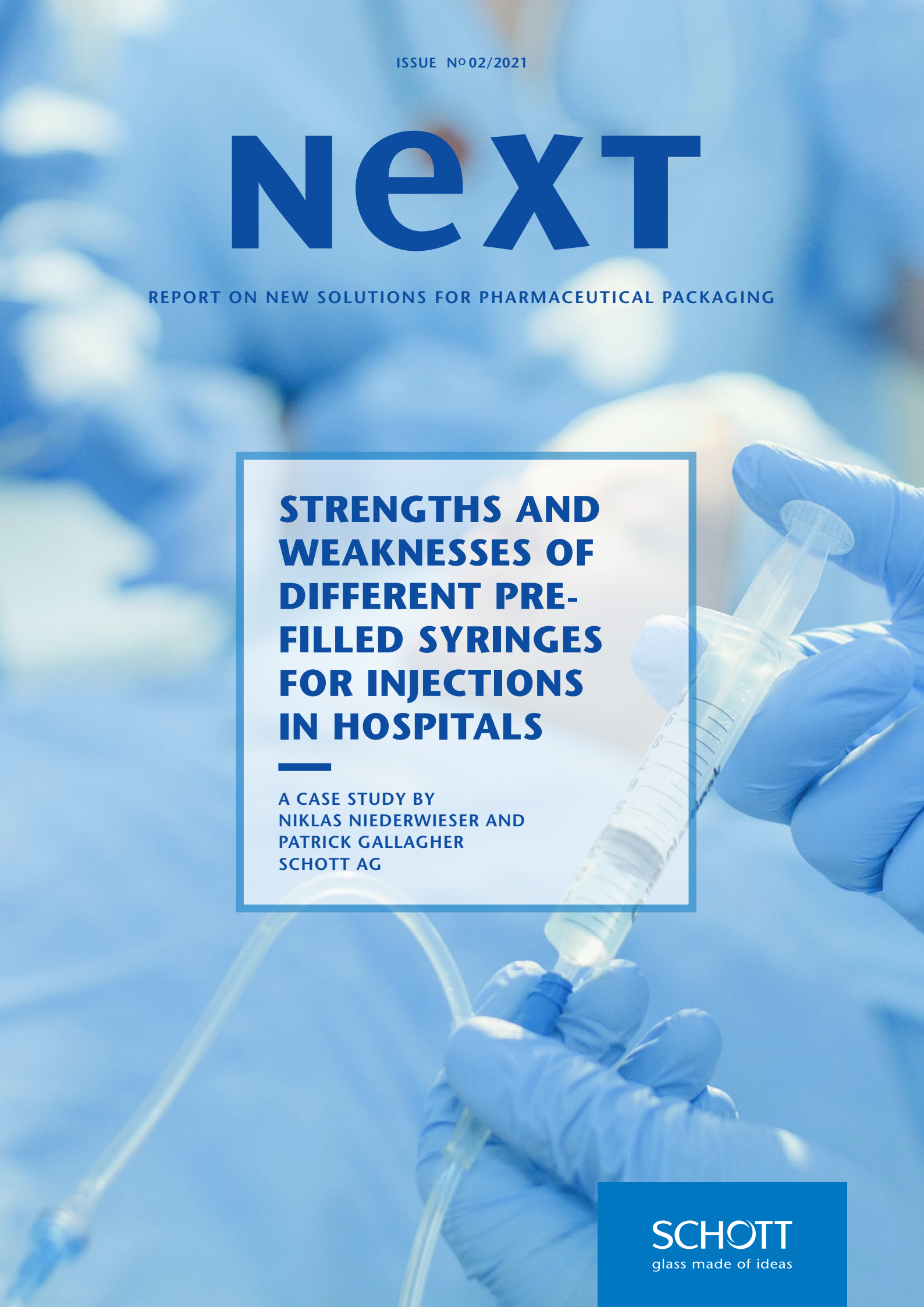
ISSUE Nº 02/2021

next

REPORT ON NEW SOLUTIONS FOR PHARMACEUTICAL PACKAGING



STRENGTHS AND WEAKNESSES OF DIFFERENT PRE-FILLED SYRINGES FOR INJECTIONS IN HOSPITALS

A CASE STUDY BY
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SCHOTT
glass made of ideas

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PARENTERAL INJECTIONS IN HOSPITALS HAVE DEMANDING REQUIREMENTS

next
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CASE STUDY

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Hospitals are key health care institutions that provide continuous availability of services for acute and complex conditions [1]. Most injectable drugs administered at hospitals are infused intravenously (IV) directly into a patient's bloodstream. Studies assume that more than 80 % of hospitalized patients in the US receive some form of IV therapy [2]. IV drugs are used in all hospital wards and are especially important in critical areas like emergency rooms, operating theaters, and intensive care units [3]. The IV route of administration allows a fast onset of drug action, a high accuracy, and a nearly 100 percent bioavailability of the medication [4]. However, IV drugs also have some disadvantages. The preparation and administration process of these drugs is a complex and time-consuming process that needs to be carried out by trained personnel and is associated with a high risk of causing harm to patients [5]. Medication errors related to IV drugs, such as the wrong drug, dose, or intravenous rate, can lead to adverse drug events that can end up in serious and sometimes even life-threatening situations.

Unfortunately, medication errors are common in hospital settings, especially during the preparation and administration of IV medications [6]. A recent study estimates that 101 intravenous medication errors happen per 1,000 injections in the UK [7]. According to an evaluation of the WHO, medication errors cause at least one death every day and injure approximately 1.3 million people annually in the United States of America alone [8]. Apart from harming the patients, medication errors also drive up the costs for the health care system. Adverse drug events in US community hospitals cost more than 3,000 USD on average and lead to a medium increase of hospital length of stay of 3.1 days [9]. The WHO estimates that the total global cost of medication errors is 42 Billion USD per year [8].

Another critical issue that may occur with IV drugs is microbial contamination. This contamination can cause severe bloodstream infections in patients, resulting in a high mortality rate of 15-30 % and produce substantial costs for the health care system [10]. Studies emphasize that critical infections also happen in countries with high nursing standards and found that 6 % of disposable syringes were contaminated in the operating room and 16 % in the general ward [11].

Global trends shape the future of IV drugs: Reduction of medication errors, environmental sustainability, mitigation of drug shortages and ready-to-use containers

The global health issue of medication errors is gaining more attention, and agencies such as the FDA and the WHO are taking initiatives to prevent them. In 2017, the WHO launched a global effort to halve medication-related errors every 5 years [12]. One possibility to address the issue of medication errors is by technological advancement and innovation, for example, the use of technology-assisted drug identification and delivery systems, such as barcode readers that confirm the identity of the drug in a container [13]. Furthermore, newly developed infusion devices such as syringe pumps are getting smarter and often equipped with software that contains a drug library, dosing units and limits, or an automatic detection system of syringes. This automatic detection of the syringes could be achieved through different systems, for example, a barcode, RFID chip, or even the geometrical parameters of the syringe. This will also improve the inventory management in hospitals and allow traceability of drugs along the whole supply chain.

Efficient inventory management in hospitals can help to mitigate the negative effects of drug shortages. Unfortunately, on a global scale, IV drug shortages are becoming more frequent and have been reported from high-, middle- and low-income countries [14]. Several reasons could account for this shortage. A leading cause in hospitals is that most IV medications are generic drugs. Hence, manufacturers, especially big pharmaceutical companies, lack incentives for producing these drugs as they can be less profitable than other groups of medications such as biotech drugs. Drug shortages may adversely affect patient care by substituting safe and effective therapies with alternative treatments or compromising or delaying medical procedures [15]. There are several possible solutions to tackle drug shortages, for example, reducing drug waste, producing drugs with longer shelf life, or using alternative producers, such as 503(b) compounding centers in the US or hospital pharmacies [16].

Another trend that will become increasingly important in hospitals is environmental sustainability; the health care sector is responsible for more than 5 million tons of waste each year and emits 4.4 % of the world's greenhouse gas emissions [17]. If the global health care industry were a country, it would be the world's fifth-largest emitter of greenhouse gases [18]. Innovative solutions will help to further improve the sustainability of the health care sector and reduce its carbon footprint.

One way to respond to many of these global trends is ready-to-use containers and pre-fillable syringes (PFSs) in particular. PFSs are easy to use, reduce the complexity of IV preparation and administration and increase patient safety by minimizing medication errors.

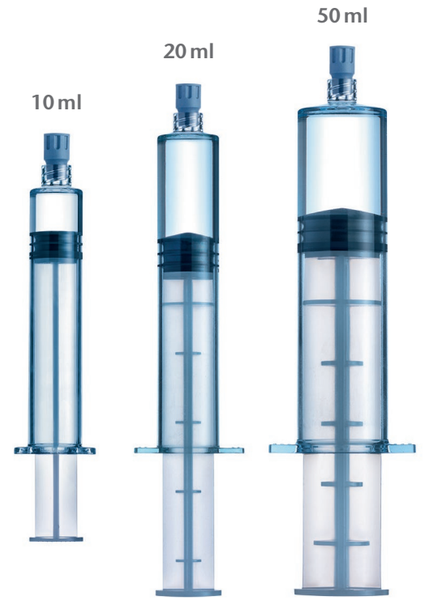


FIGURE 1:
Excerpt of the SCHOTT TOPPAC® pre-fillable syringes portfolio

PFS, an ideal solution to overcome the challenges of IV injections in hospitals and to improve patient safety

Pre-filled syringes (PFSs) are suitable packaging solutions for IV drugs and the challenging hospital environment [19]. Compared to the conventional preparation method (CPM) of using a container (e.g. ampoule, bottle, vial) that stores the drug and a disposable syringe for the injection, using a PFS, the storage container and the injection device in one, has a wide range of advantages. PFSs allow a faster preparation and administration of drugs, which minimizes adverse effects to the patient through fewer medication errors and microbial contamination. PFSs also decrease drug waste and may save money for hospitals and the health care system. Numerous studies have shown these benefits of PFSs in hospital settings.

TIME

PFSs reduce the number of steps and, thus, the time necessary to prepare IV drugs significantly compared to the conventional preparation method. According to the Textbook of Basic Nursing, the preparation and administration of a drug through the conventional method requires 20 steps, while PFSs need only 12, thus saving 40 % of the steps [20]. Fewer steps indicate faster administration, which is crucial in emergencies, or clinical scenarios where drugs are required for rapid use. Lawson et al. (2020) investigated the time needed to perform endotracheal intubations in simulated pediatric emergencies. The study revealed that the time to intubation using PFSs of 159.5 s was over three times faster than with standard care (497.5 s), allowing intubations to occur on average 5 min and 38 s earlier [21].

In another study, health care workers were able to administer adrenaline 12 s faster with PFSs in cardiac arrest situations, increasing the chances of survival of the patients. The study also revealed that 88 % of the users preferred PFSs [22].

MEDICATION ERRORS AT SIMULATED PEDIATRIC EMERGENCIES

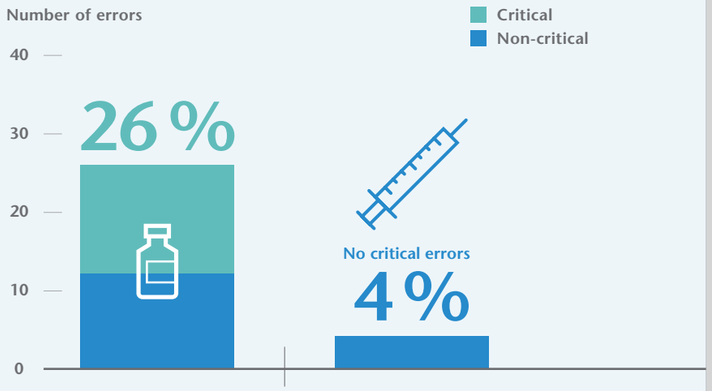


FIGURE 2:
Assessment of medication errors with the conventional method and with pre-filled syringes in simulated pediatric emergencies (adapted from Moreira et al., 2015)

MEDICATION ERRORS

PFSs reduce medication errors significantly, for example, by eliminating the risk while transferring or diluting a drug from a storage container to a disposable syringe because this step no longer exists. Adapa et. al (2012) examined the number of errors that nurses made in septic shocks and revealed that medication errors were 17 times less likely when pre-filled syringes were used [23]. A study from Moreira et al. (2015) investigated medication errors that happened in simulated pediatric emergencies. With the conventional method, 118 doses were administered, and 31 dosage errors occurred (26 %) – 20 out of these were critical; with PFSs, 123 doses were administered, and 5 dosage errors occurred (4 %) – none were critical [24].

MICROBIAL CONTAMINATION

PFSs are normally filled under aseptic conditions, mostly by automatic or semiautomatic production lines. Moreover, PFSs do not need to be manipulated by health care workers at the injection site. These manual preparation steps performed by health care professionals entail a high risk for microbial contamination. This risk is especially high if the drug is not injected immediately, as it is often the case in operating rooms for anesthesia-induction agents, neuromuscular blockers, or resuscitative drugs [11]. A systematic review and meta-analysis of microbial contamination in hospital wards showed a contamination rate of 7.47 % for all injections with CPM but only 0.08 % for those made with PFSs [25]. Another study mimicked the preparation and infusion of 960 dobutamine injections and revealed that contamination occurred in 43.1 % of conventional infusions and only in 0.2 % of those carried out with PFSs [26].

WASTE

PFSs reduce the wastage of drugs in hospitals created by unutilized disposable syringes. Especially in anesthesia, drug wastage is a big concern and studies found high wastage rates of 95.24 % (adrenaline), 92.63 % (succinylcholine), or 92.51 % (lignocaine) in operating rooms [27]. A prospective observational study of twelve Italian hospitals revealed, that 38 % of all prepared disposable syringes in ICUs and operating rooms were discarded without being used. This wastage results in a substantial financial loss for the hospitals that could be minimized with PFSs. The study summarized that decreasing drug wastage holds the potential to save millions of euros for the Italian health care system every year and would also significantly improve the environmental sustainably of hospitals [28]. The reduction potential of drug wastage is particularly high with PFSs made of materials that enable a long drug shelf life, for example, Cyclic Olefin Copolymers.

COSTS

A shortcoming of PFSs is that they are more expensive than conventional methods of drug preparation (CMP) like vials or ampoules. Despite higher purchasing costs, PFSs can considerably reduce the total costs by saving nursing time, minimizing medical errors, and reducing drug waste.

A study from an acute care setting discovered that PFSs result in a 49 % reduction in labor costs due to a reduced complexity in preparing IV drugs [29]. Benhamou et al. (2017) showed that even though atropine PFSs are more expensive than atropine CMP, their use leads to significant cost savings [30].

To assess the impact of PFSs on the total costs of a hospital that produces its own PFSs in the hospital pharmacy, Larmene-Beld et al. (2020) performed a cost analysis of the Isala hospital in the Netherlands. The study found out that the implementation of PFSs will lead to lower total costs for the hospital compared
to the conventional method and that the hospital could save up to 1.15 million Euro per 100,000 injections with PFSs [31]. Under the, according to the authors, realistic scenario of replacing 50 % of its injections with PFSs, the hospital could save 4.9 Million Euros per year.

KEY FEATURES OF PFSS FOR HOSPITALS

When evaluating the key features of an optimal PFS for IV drugs, several factors should be considered, including the barrel material, the functionality of the syringe, and the compatibility with key hospital devices such as needleless connectors.

SYRINGE BARREL MATERIALS

The barrel material is a crucial component of a PFS as it has a significant and direct influence on the stability and shelf life of the filled drug.

There are three common material options for PFSs barrels:

— Glass
  · Borosilicate glass
— Standard Polymers
  · Polypropylene (PP)
— High-performance Polymers
  · Cyclic Olefin Copolymer (COC)
  · Cyclic Olefin Polymer (COP)

YEARLY COSTS OF THE ISALA HOSPITAL FOR IV DRUGS

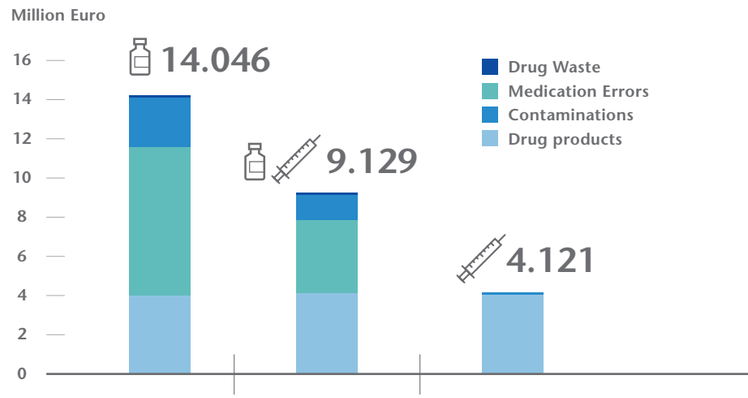


FIGURE 3:
Yearly costs of the Isala Hospital in Zwolle, Netherlands for IV drugs with 100 % CMP, 50 % CMP and 50 % PFSs, and 100 % PFSs (adapted from Larmene-Beld et al., 2020)

SYRINGE FLANGE BREAKAGE

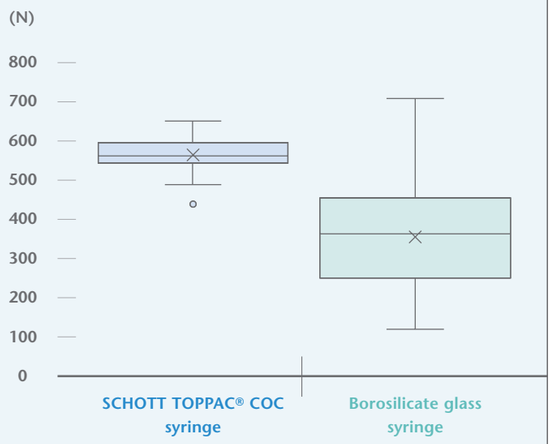


FIGURE 4:
Break resistance of the syringe flange of the SCHOTT TOPPAC® (COC) polymer syringe and a borosilicate glass PFS (SCHOTT, 2021) [34] 100 syringe samples were tested for each material. The average break resistance for SCHOTT TOPPAC® syringes is 561 N. The average break resistance of the tested borosilicate glass syringes is 355 N.

BOROSILICATE GLASS

Borosilicate glass is a specialty glass developed by the glass chemist Otto Schott in 1911. Since then, borosilicate glass has been used as the benchmark material in primary pharmaceutical packaging for ampoules, cartridges, vials and PFSs [32]. Borosilicate glass shows a high chemical durability, has excellent barrier properties, is inert, and has a low extractables and leachables profile. These properties make it an ideal material option for many primary packaging solutions for parenteral drugs, for example for vaccines and biological drugs. For IV drugs, however, additional container specific properties need to be fulfilled, such as the possibility to produce large syringe formats and the compatibility with needleless connectors.

The production of borosilicate glass tubing as well as the subsequent converting into a syringe are complex production processes that involve high temperatures and require a lot of manufacturing expertise. With increasing size, tight tolerances and precise container syringe geometries, as they are required for syringes, are getting close to the limit of technical and economic feasibility. Furthermore, glass has a higher propensity to breakage, which may lead to a malfunction of the IV syringe and ultimately to events that delay the drug administration, especially in combination with needleless connectors. Reported adverse events of IV glass syringes include syringe tips breaking, needles detaching during injection, and syringes breaking or jamming the IV lines or other patient use lines [33]. Because of these reasons, alternative materials, such as polymers would be the better material solution.

Health care professionals seem to prefer polymer syringes as well. A survey of 660 health care workers in the USA and six European countries revealed that 77 % prefer a polymer syringe to a glass syringe. The percentage is especially high in anesthesiology where 90 % of operating room nurses said that they prefer polymer syringes [35].

POLYPROPYLENE

Polypropylene (PP) is the standard material for disposable syringes in hospitals. PP is a cost-effective polymer material that allows easy production of a wide range of syringe formats, from small volumes of 1 ml up to larger formats of 50 ml or even more. Medical grade PP has a high purity and is a suitable material for disposable syringes. Furthermore, PP is used in hospitals as a PFS to store saline for flush syringes, for example, to clear intravenous lines. When used as a container material for drugs, PP should, however, be treated cautiously. PP has low oxygen and moisture barrier properties and PP syringes often have a high amount of extractables and leachables. These properties can directly affect the stability and shelf life of the filled drug.

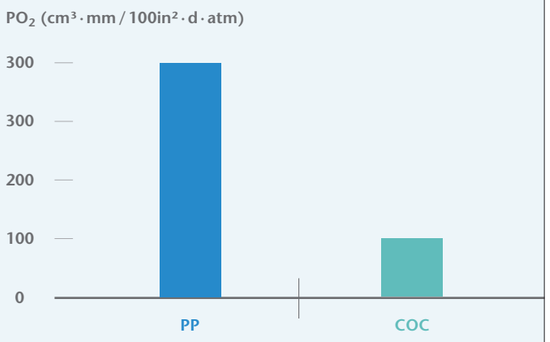
The stability of drugs in PP syringes depends on the exact type of the filled medication. Some drugs, for example, Lorazepam have a stability of 48 h [36]; Sufentanil has shown to be stable for 28 days [37]; and others, such as Fentanyl, can stay stable up to 100 days under optimum storage conditions [38].

For these reasons, the FDA is cautious and has not cleared PP syringes for use as a closed container storage system for drug products. The FDA has cleared PP syringes as medical devices for general purpose fluid aspiration and injection only [39].

Another weakness of PP is the lower transparency of the material compared to glass and Cyclic Olefin Copolymers. This can make an automatic inspection after filling difficult and hamper the final assessment of the drug by the health care professional prior to injection.

FIGURE 5:
PP Disposable Syringe

OXYGEN PERMEABILITY



WATER VAPOR PERMEABILITY

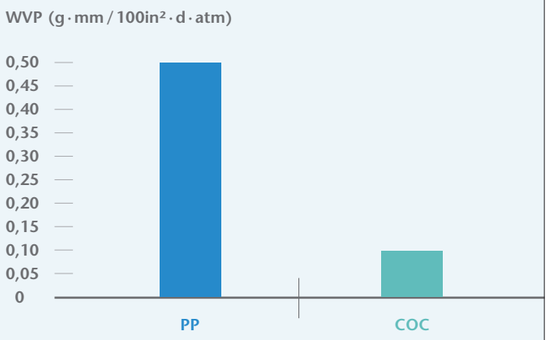


FIGURE 6:
Comparison of the oxygen and water vapor barrier properties of a typical PP medical grade and the COC grade TOPAS® (TOPAS, 2019) [42]. The samples were analyzed on a MOCON Multi-Tran 400 instrument utilizing a TCD sensor.

CYCLIC OLEFIN COPOLYMER / CYCLIC OLEFIN POLYMER

Cyclic Olefin Copolymers and Cyclic Olefin Polymers are a relatively new class of high-performance thermoplastics that are characterized by a high purity and transparency. This class of materials contains two main types that differ in terms of the production process: Cyclic Olefin Polymer (COP) and Cyclic Olefin Copolymer (COC) [40]. This article focuses on the latter, as all shown measurements were tested with COC syringes.

Cyclic Olefin Copolymers combine the advantages of borosilicate glass and standard polymers as they are chemically inert, have good barrier properties, low extractables and lecheables, and are also commercially available in large formats up to 50 ml. A disadvantage of Cyclic Olefin Copolymers is the currently limited production capacity, as it is a relatively new material for PFSs. Manufactures are currently ramping up global production so that this issue will become less critical in the future [41].

Compared to PP, Cyclic Olefin Copolymers have higher barrier properties, especially for gasses such as oxygen and water vapor. This is an important factor for hospital medications as oxygen is a leading cause for the loss of potency of a drug. A barrel material with a higher oxygen barrier enables the filling of PFSs with a longer drug shelf life.

Another important factor that affects drug stability are extractables and leachables. A prominent extractable is silicone oil, which is typically applied on the inner surface of syringe barrels in order to enable a smooth plunger movement. On the other hand, silicone oil is known for interfering with medications and to reduce drug stability. PP syringes have a significantly higher amount of extractable silicone than COC syringes do. Furthermore, the silicone value is fluctuating considerably depending on the syringe. The silicone level for COC syringes is lower and more constant.

The high barrier properties and low extractables and leachables profile of Cyclic Olefin Copolymer syringes enable a high drug stability and long drug shelf life. These properties make Cyclic Olefin Copolymer (gross) a suitable material for PFSs for IV drugs in hospitals.

CONCLUSION AND OUTLOOK

PFSs are ideal packaging solutions in response to the demanding requirements of IV hospital drugs. PFSs significantly increase patient safety by reducing medication errors and microbial contamination. PFSs may also bring down the total costs for hospitals and the health care system by saving labor time, reducing adverse events and drug waste. By reducing waste, PFSs may also increase the environmental sustainability of hospitals and have a positive impact on drug shortages. Because of these advantages, the use of high-quality PFSs in hospitals will become more widespread in the following years.

This article showed that materials like borosilicate glass or standard polymers such as polypropylene have some weakness when used for hospital PFSs. Borosilicate glass PFSs are not always compatible with needleless connectors and can cause syringe cone breakage. Polypropylene syringes have low barrier properties and a high amount of extractables and leachables, such as silicone oil. These properties can negatively affect the stability and shelf life of the filled drugs. In the meantime, we saw that new high performance polymers like Cyclic Olefin Copolymers have good barrier properties and a high purity, which enables an extended drug stability. These properties make Cyclic Olefin Copolymer a suitable material for PFSs for IV drugs used in hospitals.

The possibility to add additional features to Cyclic Olefin Copolymer PFSs like smart labels, RFID chips, barcodes as well as tamper-evident technologies will further increase patient safety and the use of PFSs in hospitals.

EXTRACTABLE SILICONE-OIL OF PP AND COC SYRINGES

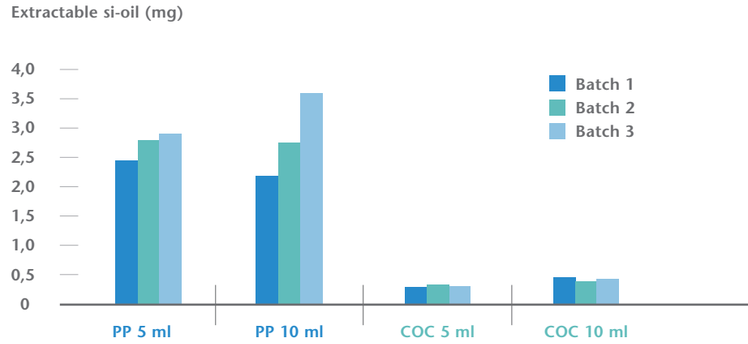


FIGURE 7:
Comparison of the extractable silicone oil levels for PP 5 ml and 10 ml disposable syringes and SCHOTT TOPPAC® (COC) 5 ml and 10 ml syringes (SCHOTT, 2021). The total amount of silicone was extracted with heptane in an ultrasonic bath. The silicone level was subsequently determined with graphite furnace atomic absorption spectrometry (GFAAS).

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Niklas Niederwieser works as Business Development Manager for Polymer Solutions at SCHOTT in St. Gallen, Switzerland. Before joining SCHOTT in 2019 he worked for Heraeus in the field of raw materials for polymers and excipients. He holds a MBA from Durham University as well as a MSc in Materials Sciences and a MSc in Earth Sciences from the University of Innsbruck.

PATRICK GALLAGHER

Patrick Gallagher has over 7 years of experience in the pharmaceutical packaging industry and has worked in both technical and commercial customer-facing roles. In his career Patrick has sought to provide primary container solutions for elastomeric, glass, and high performance polymer containers ranging from vials to syringes and cartridges. Prior to his experience in pharmaceutical packaging, Patrick worked in Quality Assurance and Project Management roles in the environmental chemistry industry. Patrick has a BS in Biochemistry from Grove City College and a MS in Science and Religion from Biola University. In his current role Patrick is responsible for Business Development of SCHOTT's Polymer Solution platform globally.

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