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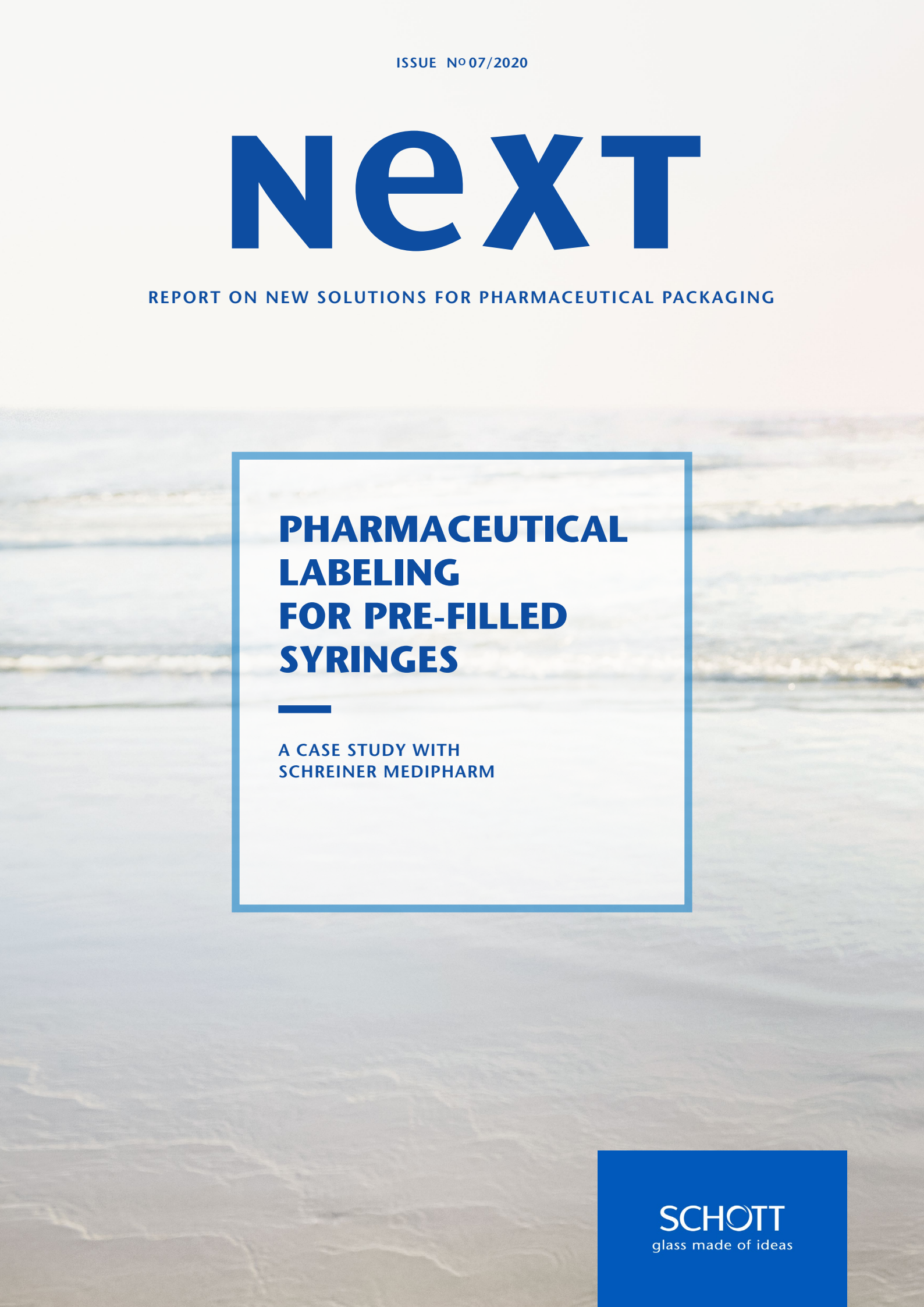
REPORT ON NEW SOLUTIONS FOR PHARMACEUTICAL PACKAGING



PHARMACEUTICAL LABELING FOR PRE-FILLED SYRINGES

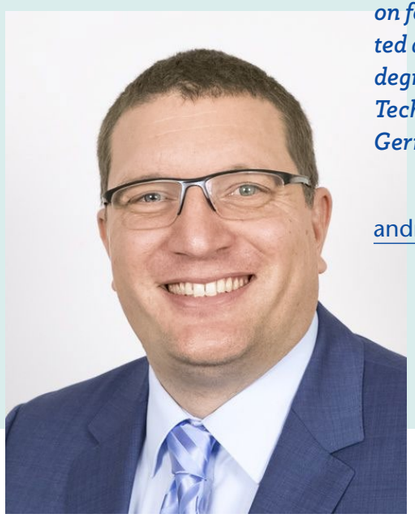
A CASE STUDY WITH
SCHREINER MEDIPHARM

SCHOTT
glass made of ideas

DR. ANDREAS HOFENAUER

Dr. Andreas Hofenauer is Manager Innovation and Strategic Partnerships Healthcare at Schreiner MediPharm, a business unit of Schreiner Group GmbH & Co. KG. Schreiner MediPharm develops and produces innovative, multi-functional specialty labels with value-added benefits for the pharmaceutical industry.

Andreas is in charge of identifying new product solutions that are optimally tailored to specific market and customer requirements and is responsible for strategic partnerships with companies in the pharmaceutical packaging sector. Prior to joining Schreiner MediPharm in 2013, Andreas worked as Department Head in the paper industry in the field of innovation for several years. He graduated and received the doctoral degree in natural sciences at the Technical University of Munich, Germany.



andreas.hofenauer@schreiner-medipharm.com

STEFAN KRAUSS

Stefan Krauss is Team Leader Innovative Products within Product & Process Development at Schreiner MediPharm. Stefan is in charge of identifying market needs and new corresponding product solutions that are optimally tailored to specific market and customer requirements.
Prior to joining Schreiner MediPharm in 2008, Stefan worked in the global Lean Six Sigma Team of Infineon / Qimonda. He graduated from university as a Master of Business and Engineering.

stefan.krauss@schreiner-medipharm.com

TOM VAN GINNEKEN

Tom Van Ginneken studied Chemical Engineering in Antwerp and added an MBA from the University of Sankt Gallen to his resume. After working in the chemical and pharmaceutical sector in Belgium for 3 years, he joined SCHOTT in 2008. After different positions in the pharmaceutical product development department, he became part of the product management team with focus on the SCHOTT TOPPAC® portfolio. In this role he works on the strategic orientation and innovation pipeline of the product group.

tom.van-ginneken@schott.com

PHARMACEUTICAL LABELING FOR PRE-FILLED SYRINGES

PROVIDING MORE THAN JUST INFORMATION

A case study with Schreiner MediPharm

Pre-filled syringes (PFS) are continuously gaining market share as a convenient form of administering drugs. Especially PFS made of high-quality polymer such as Cyclic Olefin Copolymer (COC) have become a well-established alternative because they offer greater design flexibility while reducing the breakage rate throughout the value chain. Due to its properties and manufacturing process, COC is heavy metal and tungsten free and also exhibits low or no siliconization. This makes it an attractive choice for a wide range of applications. However, the polymer also has a different E&L profile and a lower oxygen and gas barrier threshold than borosilicate glass, which increases the potential for drug interaction.

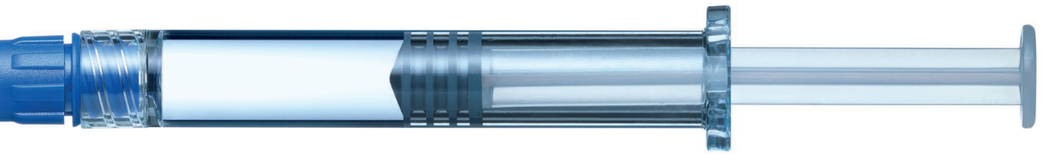
These barrier properties are of concern when it comes to labeling. Labels are an approved and well-established form of providing the required information about the pharmaceutical product directly on the primary packaging. However, as adhesive labels are affixed directly to the container, there is a potential risk of adhesive migration into the polymer. This can be overcome by using functional labels, which even have the potential to enhance the primary packaging by adding specific functionalities – from overt or covert as well as analog and digital security features to effective first-opening indication – or specific protection through UV-blocking or enhanced gas barrier properties.

MATCHING SYRINGES WITH LABELS OFFERS HIGH POTENTIAL FOR SYNERGIES

In order to exploit the full potential of functional labeling and to provide pharmaceutical customers with a comprehensive rather than a partial solution, it is necessary to match the label with the primary container. A key aspect to be considered in this context is that the label has to fit the container and can be processed in the packaging line without any problems. As part of a joint approach pursued by global pharma packaging specialist SCHOTT and specialty labels and self-adhesive marking solutions specialist Schreiner MediPharm, COC syringes and label solutions were examined with a particular focus on evaluating:

— The combination of a low-migration label with COC syringes
— The addition of an oxygen barrier to COC syringes
— The addition of UV protection to COC syringes
— The addition of first-opening indication to COC syringes

The barrier properties of the COC syringe combined with specific label concepts involving a low migration profile guarantee that there is no migration of chemical components from the label or the glue.



COMBINING A LOW-MIGRATION LABEL WITH A COC SYRINGE

Although labels are not considered to be part of the primary packaging (i.e. there is no direct contact with the drug product), they are a potential source of drug impurities via migration through the primary packaging into the drug product. Knowledge of label and adhesive technologies – combined with in-depth understanding of the physical properties of polymers that may affect the extent of label-adhesive migration – is the key to understanding the risks associated with this phenomenon. Schreiner MediPharm and SCHOTT initiated a study of leachables to investigate the migration properties of two different label concepts with SCHOTT TOPPAC® pre-filled syringes made of COC.

Leading global provider of laboratory testing, Nelson Labs, compared the profiles of labeled syringes with the profiles of the respective non-labeled (reference) syringes in terms of leachable chemical compounds. Sample syringes were filled with Water for Injection (WFI), sealed, labeled, and then stored for a total of 36 months under well-controlled room temperature conditions. By choosing a challenging environment with a temperature scenario of 25 °C, all storage conditions at lower temperatures (i.e. 2 – 8 °C) are covered from the perspective of migration. After the 36 months, the syringes were emptied and the contents submitted to multiple analytical methods in screening mode to detect all possible compounds. The analytical methods allowed screening for volatile organic compounds, semi-volatile organic compounds as well as non-volatile organic compounds.

The results of the two label-syringe-systems show that, after 36 months of aging, no additional compounds were found compared to the reference sample. This means that the barrier properties of the COC syringe combined with specific label concepts involving a low migration profile guarantee that there is no migration of chemical components from the label or the glue.

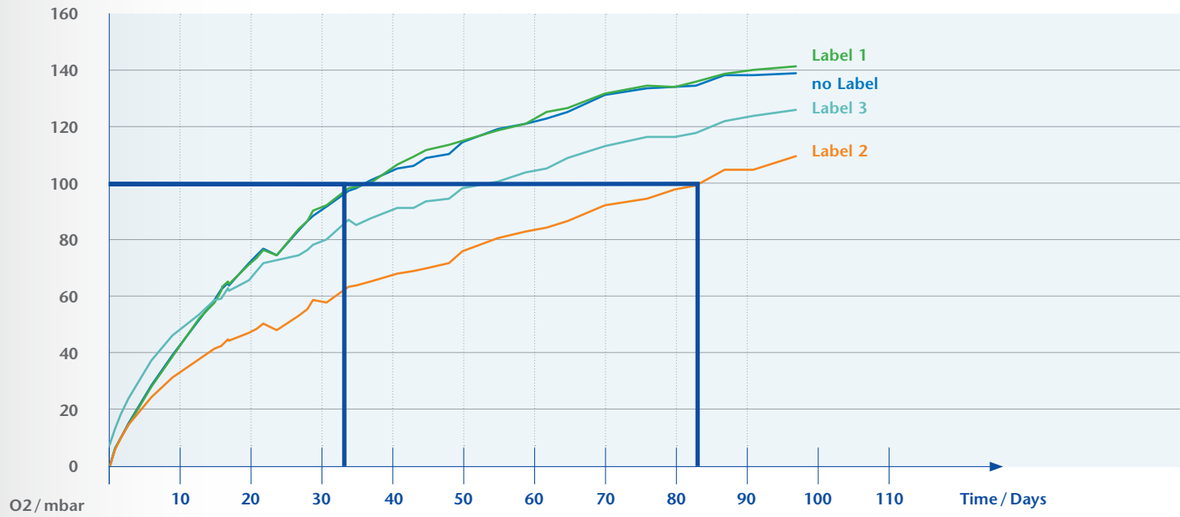
ADDITION OF AN OXYGEN BARRIER TO COC SYRINGES USING FUNCTIONAL LABELS

Oxidation can significantly affect the shelf life of pharmaceutical products, particularly of those based on large and complex molecules such as biologics and biosimilars. Therefore, pharmaceutical packaging has to provide sufficient protection against oxidizing factors. Accordingly, an oxygen barrier is a crucial functional feature of primary containers in this context. As discussed above, primary containers made of polymer show a significantly lower gas and oxygen barrier compared to glass, which could be a reason to exclude their use for oxygen-sensitive drugs. There are solutions on the market to overcome this issue such as the addition of an inorganic layer based on silicon oxide, for instance, onto the polymer layer by chemical vapor deposition. Triple layer constructions, in which a polyamide barrier layer is sandwiched between two COP layers, are another solution for primary COP-based containers. These approaches provide an excellent oxygen barrier, but are complex, cost intensive and require major changes to existing processes.

Therefore, SCHOTT together with Schreiner MediPharm tested a different approach. Functional labels made of gas barrier films were used to provide an additional oxygen barrier for COC pre-filled syringes. The label design covers as much of the syringe surface as possible for maximum protection. Various barrier films were tested for suitability as label material, printability, combinability with pressure-sensitive adhesives and effectiveness as an additional oxygen barrier. For the test, a COC pre-filled syringe (type: 1 ml long with Luer Lock closure) was used without the plunger. The syringe samples with various barrier labels were flushed with nitrogen and, using duroplastic adhesives, sealed on the back with a glass plate inside a glove box. Afterwards, the samples were exposed to the standard atmosphere at 23 °C and 50 % relative humidity. The oxygen content within the syringes was measured by a conventional oxygen sensor.

Figure 1 shows the oxygen content within the syringes as a function of time and the significant effect of barrier labels on oxygen permeation. The green curve (“Label 1“, syringe with standard label) is almost identical to the blue curve (“no label”, syringe without label). The curves of the variants with a barrier label (“label 2” and “label 3”) show a considerably smaller slope, with “barrier label 2” (orange curve) showing clearly a higher effect compared to the other tested barrier label (“label 3”, light blue curve). In this test, a partial pressure of 100 mbar in the syringe labeled with barrier label 2 would only be reached after more than

FIGURE 1:
Oxygen permeation test performed on COC syringes functionalized with barrier labels



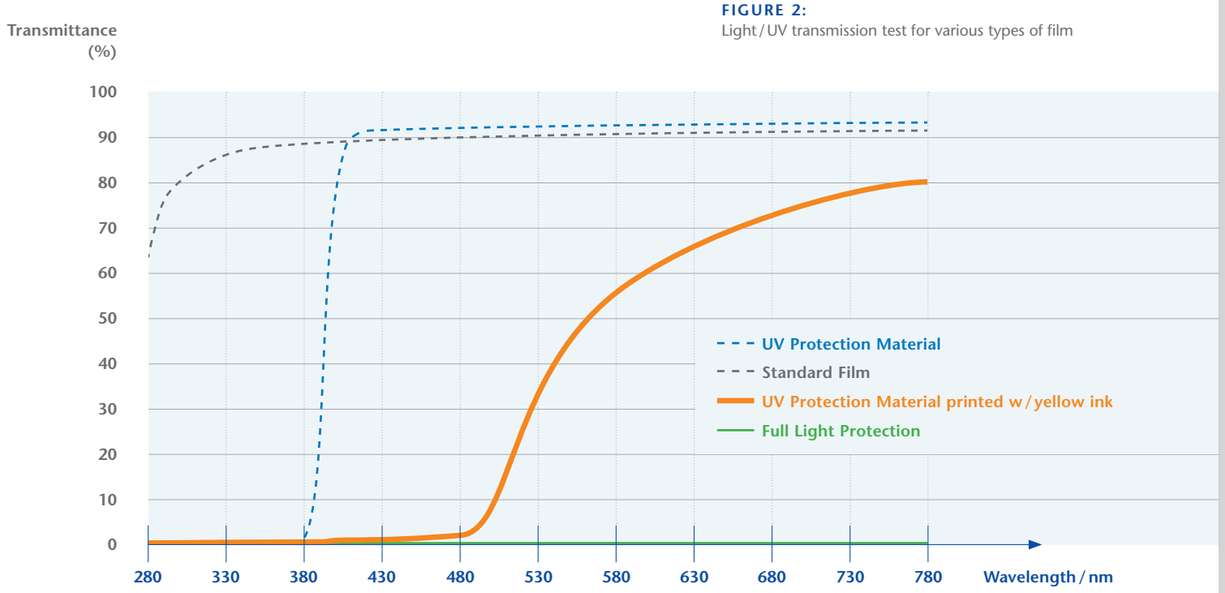
80 days. This period of time is more than twice as long as for the syringe without extra barrier protection. These initial results show that barrier labels have the potential to significantly reduce oxygen permeation and therefore might be an interesting option for drugs that are oxygen-sensitive but do not require a 100-percent gas barrier. The key advantage of this approach is the possibility to add the barrier functionality by means of a functional label without additional needs for process changes, high capital expenditures or modifications of the primary packaging. To increase the effect and adjust the barrier level to specific customer-driven use cases, further analyses are still required.

ADDITION OF UV AND LIGHT PROTECTION TO COC SYRINGES USING FUNCTIONAL LABELS

Ultraviolet as well as visible light can have a serious effect on light-sensitive drugs. One way to protect the drug is by choosing primary packaging of colored glass (amber glass). Colored glass, however, makes an inspection of substances difficult or even impossible. Especially for biologics and biosimilars, visual inspections with unadulterated results are indispensable in order to identify discoloration, turbidity or particles. Therefore, primary containers made of fully transparent materials are preferred for biological formulations. In a new approach, labels made of UV and light barrier films were used to add specific UV und light protection to transparent containers. In order to enable a full true-color inspection, the labels can be provided with a re-sealable inspection window, which allows for easy examination of the substances through the transparent primary container.

Various barrier films were tested for suitability as label material, printability, compatibility with pressure-sensitive adhesives and effectiveness as additional UV and light protection. In a transmission test, it was found that the test samples selected as suitable films demonstrated the possibility of providing a defined protection level (Figure 2).

FIGURE 2:
Light / UV transmission test for various types of film



In this graph, the translucence of a standard transparent film (gray curve), a transparent UV protection film (blue curve), a semi-opaque yellow printed UV protection film (orange curve) and a fully opaque film (green curve) are displayed.

A standard transparent PET film shows a high light transmission rate even in the ultraviolet light (< 380 nm) range and therefore does not provide a relevant protection level. The transparent UV protection film tested shows very low translucence in the UV range (< 1 %) with a sharp threshold at 380 nm. The yellow printed semi-transparent film provided significant protection against UV and blue light (< 480 nm) and the totally opaque film blocked the entire light spectrum tested. This test showed that using a UV protection film optionally combined with color printing allows for a tailored protection level against ultraviolet and visible light. These results can now be used to develop customized label concepts for pre-filled syringes adding extra UV and light protection according to specific use cases.

ADDITION OF TAMPER-EVIDENT FEATURES TO COC SYRINGES USING FUNCTIONAL LABELS

The sealing of a primary container is a valuable step in proving the integrity of the closure of primary packaging up until the point of use, visibly exposing a potential tampering attempt or preventing the re-use of a primary container in the context of product counterfeiting. Functional labels are a practical and efficient means of adding a tamper-evident feature to the syringe whenever this function is required. There are various options available for sealing a syringe with a label. Figure 3 shows a solution for a 5 ml SCHOTT TOPPAC® syringe. In this example, the main label reaches up to the primary closure. An adapter (Figure 4), which is snapped onto the primary closure, levels the diameter-difference between the primary closure and the syringe body to make labeling possible up to the top. A perforation within the label will result in a defined partial destruction of the label, which clearly indicates the first removal of the cap.

FIGURE 3:
The label with integrated perforation extends to the adapter and is irreversibly destroyed when opening the syringe cap. The adapter and primary closure are interlocked, thus preventing additional waste.

SUMMARY AND OUTLOOK

The joint approach and test results show that matching pre-filled syringes made of Cyclic Olefin Copolymer with functional labels can result in enhanced pharmaceutical containers with additional features. The study found that the barrier properties of the Cyclic Olefin Copolymer syringe tested combined with label concepts featuring a low migration profile result in no migration of chemical components emanating from the label. Moreover, through the use of tailored label solutions, a Cyclic Olefin Copolymer syringe can be enhanced with an oxygen barrier, UV protection or a first-opening indicator. Hence, pharmaceutical labeling offers a solution to provide more than just the required information on the primary container. SCHOTT and Schreiner MediPharm are exploring further steps to solve pharmaceutical packaging challenges by means of solutions that can be integrated easily and in a modular approach.

FIGURE 4:
Adapter is snapped onto the primary closure to compensate for the difference in diameter of the primary closure and the syringe body

The study found that the barrier properties of the COC syringe tested combined with label concepts featuring a low migration profile result in no migration of chemical components emanating from the label. Moreover, through the use of tailored label solutions, a COC syringe can be enhanced with an oxygen barrier, UV protection or a first-opening indicator.

For more information, please visit:
schott.com/pharma

SCHOTT AG, Pharmaceutical Systems
Hattenbergstr. 10
55122 Mainz, Germany

phone: +49 (0) 6131/66-1589
mailto: pharmaceutical_packaging@schott.com
http://www.schott.com/pharma

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