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FLEXIBLE INSPECTION OF PREFILLED SYRINGES

With the advent of new and highly potent drugs, the market for prefilled syringes is growing continuously. These devices pose special challenges to the inspection process. They require both particle and cosmetic inspection for an increasingly large number of items. Here, Joachim Baczewski, President of Bosch Packaging Technology K.K. in Japan, and Global Responsible for Inspection Technology, describes how leading equipment manufacturers such as Bosch Packaging enable pharma companies to achieve target product quality with flexible processes, by offering a combination of innovative inspection systems for prefilled syringes and other containers

Due to an increase of chronic diseases such as diabetes and cancer, a rising number of patients require injectable drugs for self-administration. Prefilled syringes enable highly accurate dosing and decrease the exposure to potent products while, at the same time, they significantly reduce the danger of dosing errors and contribute to overall patient safety. As a result, the market for prefilled syringes is set for further growth. According to a recent market report,¹ worldwide production of prefilled syringes will almost double again by 2020.

TARGETING THE HIGHEST QUALITY STANDARDS

Since any container defect or change in the drugs' structure poses a serious threat to patient safety and product quality, both prefilled syringes and medicines necessitate thorough inspection. Subsequently, pharmaceutical manufacturers require sophisticated and versatile inspection technologies to meet the highest quality levels at all times. These technologies are used either for the detection of product-related contamination, container defects, leakages or all of them.

Product contamination implies the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter into or onto a raw material, intermediate, or API during production, sampling, packaging, storage or transport.² Cosmetic container defects, on the other hand, can occur during handling, either by human intervention or by incorrectly set-up machinery. Leakages of containers or closures might entail microbial ingress and reduced shelf life. To ensure that no contaminated products can enter the market and reach the patient, highly accurate inspection is required.

Inspection technologies range from manual and semi-automated through to fully automated, high-speed machines. When performing manual inspection, each syringe is inspected with fluorescent light against a black and white background. As manual systems remain subject to human errors and do not offer the speed required for larger batches, they are mainly used for customised applications and stability surveys. Semi-automated inspection systems can achieve more accuracy and reduce the need for manual handling. Automatic feeding, sorting and discharging functions enable inspectors to focus entirely on the quality control of prefilled syringes.



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AUTOMATED INSPECTION FOR FAST, HIGHLY ACCURATE RESULTS

Automated particle inspection systems have their origins in the 1970s. One of the original automated inspection principles is the Static Division (SD) system, which was developed by Eisai Machinery (now part of Bosch Packaging Technology). The SD (Figure 1) system derives its name from the ability to differentiate static from moving objects. It transmits light through the solution within the container onto an optical SD sensor. The prefilled syringe is rotated and then suddenly stopped and the liquid continues to rotate in the immobile container. Foreign particles moving inside the liquid block a portion of the transmitted light and cast a shadow, which is detected by the SD sensor.

Automated camera-based systems are used for both particle and cosmetic inspection and are either based on complementary metal oxide semiconductors (CMOS) or on charge coupled device (CCD) sensor technology, and are used in area or line scan cameras. Combined with specially designed optics and lighting such as LED (Figure 2), camera-based systems also ensure highly accurate inspection of product defects such as particles stuck to the sidewall, fill levels and product color, as well as container flaws such as cracks in syringe flanges. The latest CMOS-based systems even identify particles inside medium to highly viscous products, oils and suspensions. During rotation, the cameras take a sequence of images. These images are compared and analysed via sophisticated algorithms. The system identifies target defects while ensuring a low false reject rate. Product-specific parameters determine whether the syringe is rejected or accepted.

POWERFUL COMBINATIONS

The fully automated inspection series AIM 8000 (Figure 3) aims at high detection rates, even for suspensions and viscous products, and detects particles floating inside the liquid or sticking to the syringe's plunger stopper. A combination of transmitted and reflected light furthermore enables manufacturers to simultaneously detect light and dark colored particles on the same inspection station, thus leading to

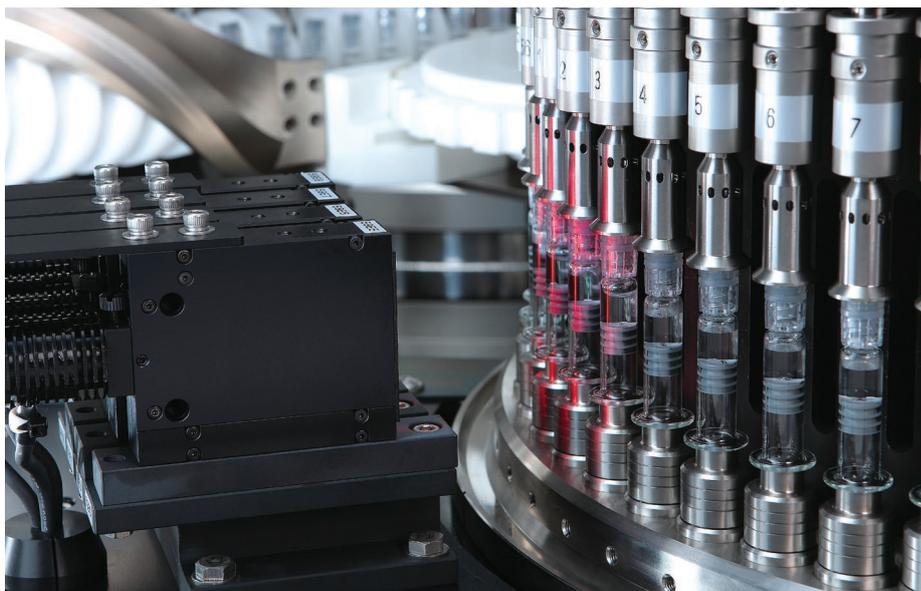


Figure 1: For 40 years, the SD technology keeps improving to meet the most challenging customers' requirements.

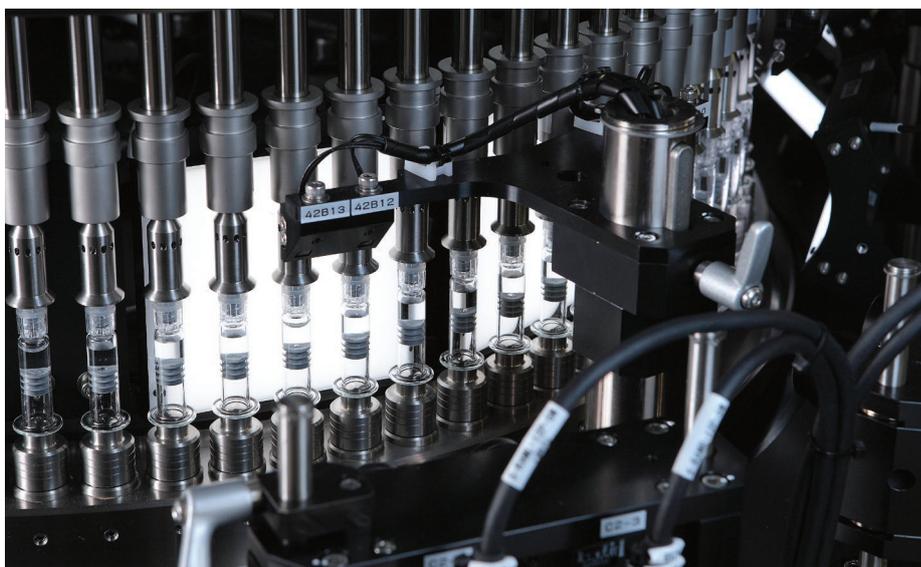


Figure 2: Inspection system with LED lighting.

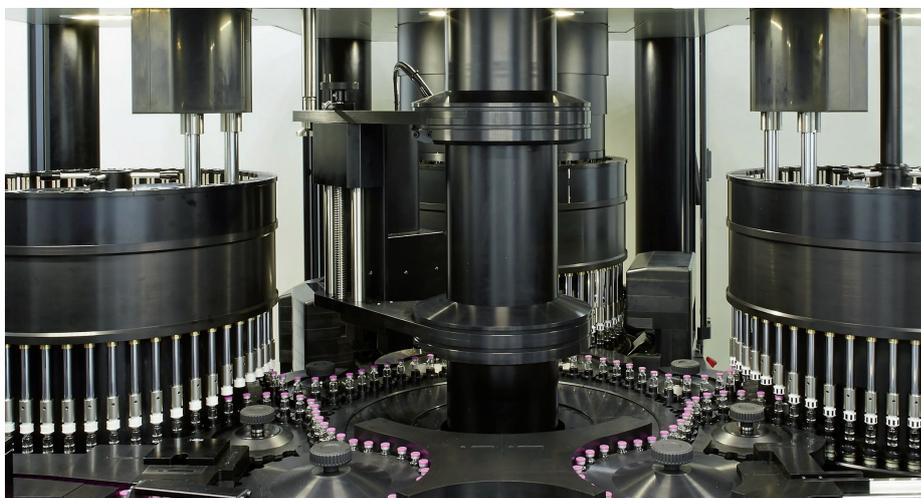


Figure 3: The AIM 8000 series is the most versatile inspection platform allowing rapid customisation to each customer's requirement.

significant space savings compared to the usage of two separate stations for each of the inspection methods. The latest pre-spin technology caters to the special inspection requirements of prefilled syringes by removing bubbles from the plunger stopper at elevated speeds. Moreover, the machine allows cosmetic inspection of a large number of syringe items, such as the needle shield, shoulder, or flange.

To meet the industry's rapidly changing requirements further, the AIM 8000 series offers a hybrid approach by integrating

ilised products and medicines filled under vacuum or purged with gas. Vacuum leak detection (VLD), in turn, measures vacuum or pressure decay in a dedicated chamber.

CONSIDERATIONS FOR THE EFFECTIVE USE OF INSPECTION EQUIPMENT

Utilising state-of-the-art technologies starts by thoroughly testing the inspection methods with product samples before choosing the equipment. After the instal-

"CCI methods allow pharmaceutical manufacturers to detect sterility breaches prior to product contamination, and prove to be less time-consuming than most commonly used sterility testing methods"

both SD and camera-based inspection technology in one flexible platform. This enables pharmaceutical manufacturers to adapt their inspection processes to their individual production and product needs beyond the conventional scope. Next to prefilled syringes, this equipment is also designed for the inspection of other containers such as vials, ampoules and cartridges, offering flexibility to manufacturers. The modular design facilitates the expansion of existing systems by integrating additional inspection units or adding an extra inspection module. In addition, Container Closure Integrity (CCI) testing via high-voltage leak detection or headspace analysis can be integrated into the AIM 8000 platform on request.

CCI has steadily moved up the agenda in recent years.³ Studies show that prefilled syringes are also prone to CCI defects, which might be even more hazardous than particles when they lead to a change in the API. CCI methods allow pharmaceutical manufacturers to detect sterility breaches prior to product contamination, and prove to be less time-consuming than most commonly used sterility testing methods. State-of-the-art inspection platforms are able to incorporate tailored CCI testing systems for prefilled syringes. For instance, high-voltage leak detection (HVLD) measures the electrical resistance of the syringes with conductive solutions. Headspace analysis (HSA) measures the quantity of light passing through the headspace region via laser spectroscopy, and is applicable to lyoph-

lization of the equipment, operator qualification and training, as well as regular maintenance of the equipment by competent service personnel, is required. Retrofitting additional inspection equipment and adapting it to new products and/or inspection requirements, as well as complete system modernisations should also be considered as key factors for the selection of the ideal inspection equipment.

The above is especially true for the inspection of prefilled syringes with their various inspection criteria and steps. Assuring the highest quality and lowest false-reject rates throughout the lifespan of this machinery will not only bring quality benefits to patients but also economical benefits to pharmaceutical producers.

Paying close attention to the requirements for prefilled syringes, Bosch offers an extensive portfolio of dedicated inspection equipment ranging from manual to fully automated high-speed systems. A special focus is set on the combination of different technologies for particle and cosmetic inspection, as well as CCI. As a competent partner to the industry, Bosch also supports pharmaceutical producers in improving their entire production process, for instance by integrating inspection equipment into complex production and packaging lines. Highly qualified scientists and engineers at Bosch ensure that Bosch is the ideal partner for all inspection requirements, including the rapidly expanding market for prefilled syringes.

REFERENCES

1. *Smithers Rapra*, "The Future of Alliances and Partnerships in the Pre-Filled Syringes Market to 2020", cited August 12, 2015. Available from <http://www.smithersrapra.com/products/market-reports/the-future-of-alliances-and-partnerships-in-the-pr>
2. http://www.gmp-compliance.org/elements/PDF/19_Glossary_GMP2020.pdf
3. *Akers MJ*, "Sterile Drug Products: Formulation, Packaging, Manufacturing and Quality", 2010, p. 455.

ABOUT BOSCH PACKAGING TECHNOLOGY – PRODUCT DIVISION PHARMA

Bosch Packaging Technology – Product Division Pharma is one of the leading providers of process technology and packaging solutions for the pharmaceutical industry. The portfolio includes single units, complete lines and integrated systems for the manufacturing and processing of liquid and solid pharmaceuticals. It also includes process technology, primary packaging, inspection technology for different application fields and packaging types. Secondary packaging with qualification and validation, software solutions for track and trace and technical customer service are also available.

The following product brands are part of the Bosch portfolio for the pharmaceutical industry: Hüttlin, Klenzaid, Manesty, Moeller&Devicon, Pharmatec, SBM Schoeller-Bleckmann Medizintechnik, Sigpack and Valicare. For more information, please visit www.boschpackaging.com.

ABOUT BOSCH PACKAGING TECHNOLOGY

Based in Waiblingen near Stuttgart, Germany, and employing 6,100 associates, the Bosch Packaging Technology division is one of the leading suppliers of process and packaging technology. At over 30 locations in more than 15 countries worldwide, a highly-qualified workforce develops and produces complete solutions for the pharmaceuticals, food, and confectionery industries. These solutions are complemented by a comprehensive after-sales service portfolio. A global service and sales network provides customers with local points of contact.

Innovative Automated Inspection of pre-filled syringes with AIM 8000 series



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Bosch offers complete lines for pre-filled syringes from a single source – from water treatment, filling, closing and inspection to assembly and labeling, as well as secondary packaging. As an essential part of these lines, Bosch provides innovative inspection technologies, which ensure final product quality and contribute to patient safety.

Long-term inspection experience

As a leading manufacturer of inspection machines, Bosch offers equipment for both liquid and solid dosage forms. The first automated inspection machine was developed by Eisai Machinery (now part of Bosch Packaging Technology) in 1975. Over the years, more than 1200 machines have been installed by Bosch in more than 50 countries and have set the standard for automated inspection.

Versatile AIM 8000 series

The AIM 8000 series is the highly versatile and flexible inspection platform, allowing rapid customization according to each customer's requirements:

- ▶ Up to 600 containers/min
- ▶ Wide diameter and container height ranges
- ▶ For syringes, cartridges, vials, ampoules

Inspection for particles

- ▶ Camera-based technology for particles in all liquids (with optimized performance for high viscosity media and suspensions)
- ▶ Light transmission based SD (Static Division) technology for particles in low to medium viscosity liquids and liquid fill levels

The characteristics of the products to be inspected and the inspection requirements determine the inspection methodology.

Inspection for cosmetic defects

- ▶ Camera-based technology for lyophilized products, cosmetic container defects and liquid fill levels

Inspection for Container Closure Integrity (CCI)

- ▶ CCI testing by high-voltage leak detection and headspace analysis

Advanced inspection solutions

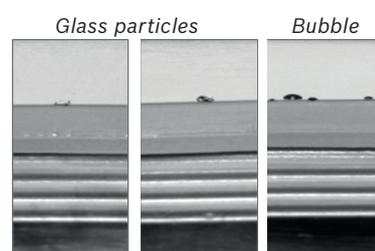
Pre-filled syringes pose special challenges to the inspection process. They must be inspected to detect floating and in-liquid particles, as well as particles on the stopper and siliconized walls. Moreover they require cosmetic inspection of a large number of items (for example luer lock, flange and needle).

The AIM 8000 series is especially suited for these complex inspection tasks. An example is the two-step approach to remove the influence of



AIM 8000 series

air bubbles on inspection results. First, the pre-spin system of the AIM 8000 helps to remove air bubbles from the liquid and the stopper. Second, a sophisticated imaging processing method is applied to distinguish particles from remaining air bubbles. Each AIM 8000 is a complete system that ensures low false rejects and highest performance levels; with an approach that is easy to set-up and easy to validate. Thanks to the optimal combination of the latest CMOS camera and SD technologies, as well as CCI testing modules, the AIM 8000 series offers a customizable high-end solution to meet the most challenging inspection requirements for pre-filled syringes.



Particles/Bubbles on stopper

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