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INSPECTION TECHNOLOGIES FOR GLASS SYRINGES

The quality demands for pharmaceutical glass syringes are high; quality levels for critical defects approach or even come below ppm rates. In practice, these standards are achieved with a combination of visual and camera-based inspection technologies. In this piece, Bernhard Hinsch, PhD, of Hinsch-Consulting (Hamburg, Germany), consultant to Gerresheimer, argues that both technologies deliver reliable results if all relevant input variables are known and a model of their interaction has been created, but even though the influence of individual visual inspection capacity can be minimised, camera-based inspections are the preferred solution. Today, suitable camera technology is available for the detection of practically all dimensional and the majority of cosmetic defects. Dr Hinsch introduces cross-functional quality management, which involves the development of process validation strategies and the elaboration of technical and organisational procedures to facilitate permanent compliance with the validated standards.

Pharmaceutical glass syringes have to satisfy increasingly high requirements of quality. In practice, the benchmarks for dimensional precision and cosmetic defects are below the customary Acceptable Quality Limits (AQL). To guarantee this level of quality, a range of prerequisites have to be met. The first prerequisite is a precise definition of the defect types that can occur and their causes. Based on this definition, it is possible to optimise the production processes and reduce the defect rate to the minimum. A combination of visual and automated inspection technologies is used to identify defective syringes. The objective of cross-functional quality management is to install and continuously optimise these technologies. It also involves the development of process validation strategies and the definition of technical and organisational procedures which facilitate permanent compliance with the validated standards.

> "In the future, new technologies will be capable of detecting defect types that are not identifiable at this time"

DEFINITION AND CATEGORISATION OF DEFECTS

Glass syringes can demonstrate a variety of defects that can be categorised according to various criteria. It is most practical to use

Figure 1: Characteristic glass defects in syringes: cracks, checks and scratches.

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a system of categorisation that is oriented on the impairment of glass integrity, because this permits a direct evaluation of the potential risk for physicians, nursing personnel and, most importantly, the patients themselves. According to PDA Technical Report 43 (TR 43), "*Identification & Classification of Nonconformities in Molded & Tubular Glass Containers for Pharmaceutical Manufacturing*", cracks pose the highest risk, followed by checks and then scratches (Figure 1).

A crack is defined as a discontinuity in the glass matrix which runs inside the glass and can influence the container's integrity. Accordingly, cracks are categorised as critical defects which can be associated with health risks and even have life endangering consequences for the patients using the defective products. Checks are discontinuities in the glass which demonstrably do not impair the syringe's integrity. Checks are categorised as major defects which can cause problems in the further processing or use of the product. Scratches are superficial or minor defects which do not impair the integrity of the glass. Cosmetic defects such as impurities, bubbles, air lines or (glass) particles are also categorised as minor defects.

PRODUCTION PROCESS, DEFECT CAUSE & PREVENTION

The glass syringe production process, described here using the example of prefillable syringes, can be divided into three main phases. The first phase is forming. It involves tube cutting and the multi-stage process of forming the shoulder, cone and finger flange, as well as syringe printing. In the second phase, the needle is mounted. Then, in the third phase, the syringe is washed, siliconised, sterilised and packaged (see Figure 2).

Cracks – the most serious defect – generally occur in the tube cutting process, the forming process or as a result of the glass not being properly annealed. Most cracks are caused by thermal force – either due to a thermal shock as a result of too high or low quantities of water being used in the tube cutting process, excessive temperature differences between the glass and tool in the forming process or mistakes in the annealing process. These cracks can be prevented by optimising the process parameters and by reducing the temperature differences during processing. Checks and scratches are generally caused by glass-glass contact

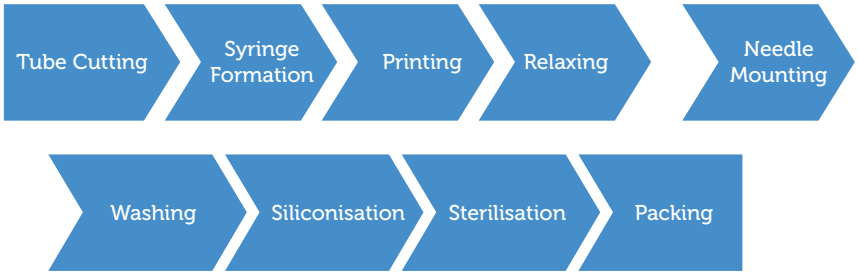

Figure 2: Simplified syringe production process.

or mechanical forces during processing. Effective measures to prevent these defects are therefore the avoidance of glass-glass or glass-metal contact and ensuring that the transport processes are as gentle as possible.

COMBINED VISUAL & CAMERA-BASED INSPECTION

The pharmaceutical industry's high quality requirements necessitate 100% inspections of glass syringes. In current specifications, the typical AQL is 0.01-0.065 for critical defects and 0.04-0.4 for major defects. To achieve the highest possible standard of safety, however, defect rates of ≤1 ppm for critical defects and ≤100 ppm for major defects are often demanded. From a quality management perspective, fully automated, camera-based inspection technology is preferential. At the present state of the art though, suitable inspection processes are not available for all defect types.

VISUAL INSPECTION PROCESS VALIDATION

In any reliable visual inspection process, an awareness of and control over all relevant input variables are essential, as is a viable model of their interaction. It is also important to remember that validation only applies to a defined input range. If there are too many input defects, the target output value will be exceeded. In addition to the false pass rate (FPR), the input defect rate has to be known and monitored. If it becomes too high, the production line has to be stopped for both economic and quality-related reasons so that the cause can be investigated.

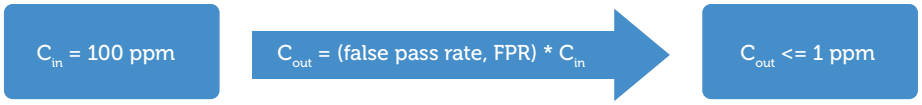

Figure 3: Validation of output quality in visual inspections.

In the validation process (Figure 3) it is essential to understand the visual inspection as a structured process with a known number of variables. Some of the input variables relate to the choice of personnel, who have to satisfy certain requirements of visual performance and concentration powers. The inspectors also have to be properly trained and attend regular refresher workshops to sustain the learning effect. Another group of input variables relate to the technical design of the inspection process. The main ones are light-related factors such as the colour and direction of

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In practice, manufacturers will continue to use a combination of automated and visual inspection technologies in the foreseeable future. The regulatory authorities require the submission of comprehensive process validation data obtained in case studies according to the quality by design (QbD) concept in the drug licensing process.

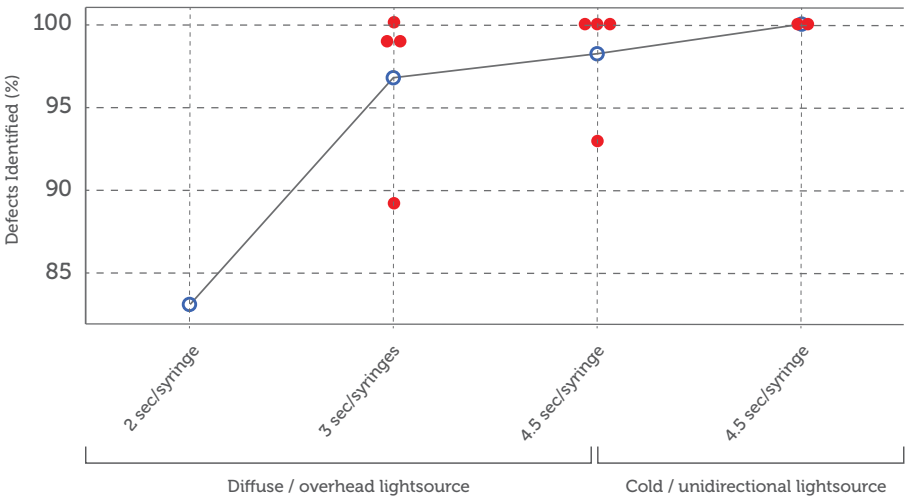

Figure 4: Results of a visual inspection efficiency study.

the inspection light source and the design of the surface on which the inspections are performed. A third group of input variables relate to the ergonomics of the inspection process. They include the design of the inspection workstation, whether the inspectors take enough breaks from their work and whether they are supported in the inspection process by visual timers such as changing light colour. This is particularly significant because the time taken to inspect each syringe has a high influence on visual inspection output quality.

An efficiency study showed the complex interactions of the individual input variables (Figure 4). The four people surveyed – two experienced and two less experienced inspectors – were given a number of syringes to inspect over a period of 40 minutes in a production environment. There were a known number of defective products in the batch of syringes, whereby the defect rate was deliberately set at the upper limit for typical defects. The defects themselves were very small in size to create challenging test conditions. The time variables in the study deviate from the actual time variables in the production environment.

The diagram shows the overall performance of the people surveyed with different inspection timeframes and conditions. One key survey finding is that the time spent on the inspection of each product is extremely significant. With a time allowed of 2 seconds per syringe, the performance of all the inspectors was weak and they identified less than 85% of the defective products. So, even the experienced inspectors do not perform adequately in unfavourable conditions. When the time allowed for inspection was increased to 3 and 4.5 seconds respectively, the results improved considerably. However, there was some drifting, which indicates the significance of individual visual performance. The number of defects identified by three out of the four inspectors improved substantially (though not completely identically) when the time allowed for inspection was increased to 3 seconds, while one inspector's performance deteriorated considerably. This difference in performance remained unchanged when the time allowed for inspection was increased to 4.5 seconds. In fact, it did not improve until another input variable was changed.

In the first three tests a diffuse overhead light source was used. Another test sequence was then performed with a cold light source and optical conductors that bundled the light axially into the syringe barrels, making cosmetic defects highly visible. Under these conditions all inspectors – even the inspector with lower visual performance – detected 100% of the defects.

Another significant result of the study, in addition to the need to allow an appropriate time for inspection of each product, is that the individual variability of test results could be effectively reversed by changing the test process structure. Another important consideration is that the results cannot be generalised. The inspection conditions for a product or product group have to be established on a case-by-case basis and depend on how easy or difficult product-specific defects are to identify.

Figure 5: Dimensional inspection of the syringe needle.

CAMERA-BASED INSPECTION PROCESS VALIDATION

Camera-based inspection systems to inspect the dimensions of syringes can achieve a resolution of up to 20 µm with defects of only 2 µm. They are therefore far superior to visual inspections, though not necessarily superior to mechanical inspection methods – e.g. use of calipers – for the inspection of complex three-dimensional geometries such as the shape of the finger flange. However, if the syringe is rotated during the camera inspection process, reliable results are achieved. The advantages of camera systems are particularly evident in the identification of bent needles which, if undetected, would cause pain to the person being injected (Figure 5).

Camera-based inspection systems perform far more complex tasks in the identification of cosmetic defects. Reliable identification is currently possible on an area of 0.1 mm^2 and this will be reduced to 0.03 mm^2 in the foreseeable future. As in visual inspections, camera-based inspections have to ensure a defect rate of <=1 ppm for critical defects. The automated systems can tolerate a far higher input defect rate than visual inspections. However, there is a limit for process validation purposes and the production line has to be stopped if the input defect rate gets too high. A reliable inspection can only be guaranteed if the false pass rate (FPR) and the input defect rate are known and continuously monitored.

A range of relevant input variables have to be taken into consideration in the validation process. One is the minimum size of the defect and an agreement has to be reached with the customer in this respect. A second typical defect characteristic is the contrast that it produces in the camera image, which is displayed as a greyscale difference. For example, impurities generally only create low contrasts, while defects in the glass matrix such as cracks create reflections if the light is traveling in the right direction, and therefore high contrasts. Here, too,

agreements are increasingly being reached with the customer on the lower limits for defect relevance in order to achieve transparent quality criteria that apply for both the customer and the manufacturer. Camera-specific identification limits and measuring inaccuracies exist with regard to defect size and contrast which have to be taken into account in the validation and in regular calibrations.

The third significant block of input variables, in addition to defect and camera characteristics, relate to inspection conditions. Firstly, all optical variables of the light sources used, such as luminosity, colour and direction, have to be optimally co-ordinated and kept constant. The direction of the camera, syringe and light source also have to be coordinated. The light should pass axially through the syringe to maximise defect visibility. Rotating the syringe permits the inspection of the entire surface area. Since some types of cracks will remain undetected if the camera is at a right angle to the light source, it makes sense to use a more acute inspection angle or work with two cameras.

In practice, camera validation involves six steps. The first step is to create a library of all defect types to be identified with both physical samples and photos of the defects. In the second step, the samples are used to create camera protocols and defect-specific algorithms for each defect. These algorithms can be very complex. Air lines in the glass create an interrupted pixel pattern whose individual elements would be below the relevance limit. This is where the algorithm comes in because it recognises the linear sequence of greyscale differences and adds them together into a relevant total length. The third step is the creation of samples which define the tolerances for each defect. Using tolerance samples, the corresponding tolerance parameters can be defined for the camera. In the fourth step the false pass rate is measured on the basis of the defined parameters. Sometimes, the parameters have to be adjusted to guarantee the required output quality. The fifth step is the definition of an upper limit for input defects which would trigger a production alarm. In the sixth and final step, the actual output quality is verified on the basis of a comprehensive performance qualification (PQ).

Figure 6 represents the dimensions of defect contrast and defect size, and it is possible to illustrate systematically the typical optical characteristics of cosmetic defects and their detectability with camera-based inspection systems. Defect that

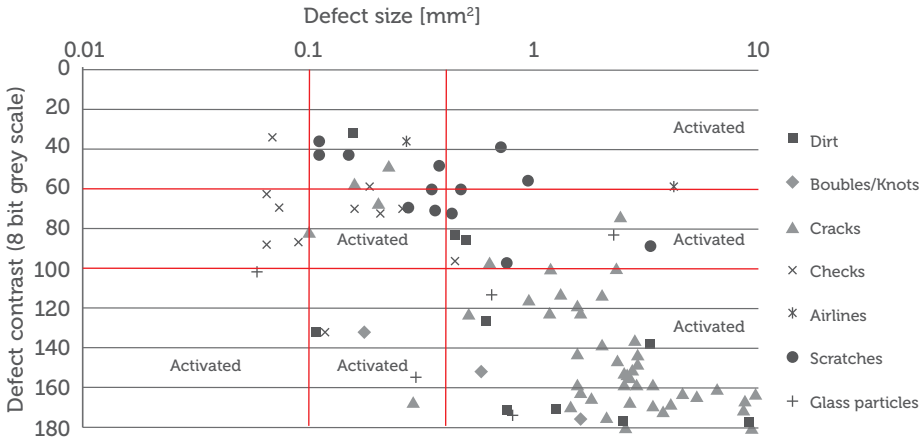

Figure 6: Typical distribution of cosmetic defects by size and contrast.

are small, low contrast and therefore difficult to detect are shown at the top left of the diagram while particularly large and high contrast defects which are easy to detect are shown at the bottom right. This makes it clear, for example, that scratches and checks are often difficult to identify in practice, while cracks (with very few exceptions) deliver large and high contrast defect patterns.

A system of inspection limits is defined in the diagram taking the camera system's power, the defect's level of criticality and the relevant quality agreement into account. Not only is a lower limit for size and contrast defined, but also a 3x3 matrix so that the defects can be recorded in a more differentiated way. To detect relevant defects, all fields with a defect size of more than 0.1 mm² and a defect contrast of over 1:60 are activated. The field with a defect size of above 0.4 mm² and a defect contrast of between 1:60 and 1:30 is also activated as the camera's measurement limit because relevant defects can still be detected in this range. For safety reasons, the segment of small, high-contrast defects at the bottom left is also activated, even though there are no defects shown there in this diagram. Fields in which defect detection is technically unfeasible or not necessary on the basis of the agreed quality criteria are not activated.

Camera-based systems for dimensional inspections are available for practically all relevant syringe dimensions. Gerresheimer AG performs automated camera inspections as standard on the syringe barrel, neck/shoulder, cone, finger flange and needle, as well as on the positioning of the closure. It also performs automated camera inspections for cosmetic defects in needle quality as standard. Cosmetic defect inspections of the syringe barrel, neck/shoulder, finger flange and printing can also be agreed. A cosmetic inspection of the closure can be performed by the supplier. Gerresheimer AG is currently working on concepts for inspecting the cone and siliconisation for cosmetic defects.

OUTLOOK

At the current time, both visual and camera-based technologies are used to inspect glass syringes. Despite their dependency on the individual inspectors' performance, visual inspections deliver the required output quality if the personnel are properly trained and the inspection conditions are appropriate and continuously monitored. However, camera-based inspection technology is more reliable if ppm or sub-ppm level defect rates have to be achieved. Here, too, knowledge and control of all relevant input processes are essential for validation. Gerresheimer AG has developed its own camera technology for the most important defect types. In the future, new technologies will be capable of detecting defect types that are not identifiable at this time.

"Camera-based inspection technology is more reliable if ppm or sub-ppm level defect rates have to be achieved"

Our comprehensive offering: RTF® syringe systems

- High-quality ready-to-fill syringes
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