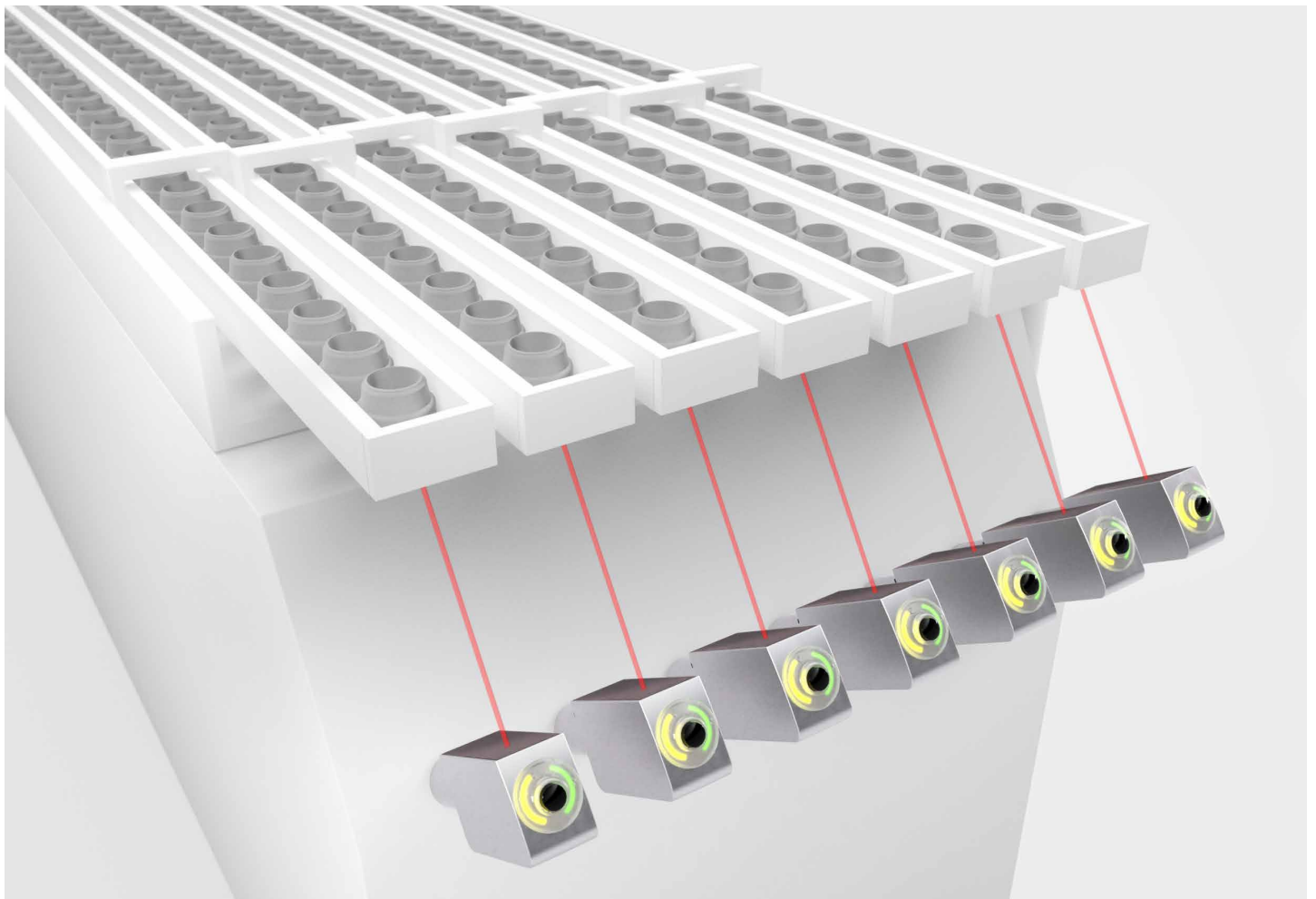


Pharma Guideline GMP, Annex 1

Placing of sensors

White Paper
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Packaging machines for sterile medicine and pharmaceutical products with modern sensors according to updated GMP directive

The updated EU GMP Directive (Annex 1, EU GMP Volume 4¹) introduced stricter requirements for the manufacture and packaging of sterile medicinal products and medical devices, effective from the end of August 2024, with the aim of preventing any possible contamination. This no longer applies only to parts that come into direct or indirect contact with the product. It now also covers all components that may interrupt “first air,” such as sensors positioned above sterile components.

¹The Rules Governing Medicinal Products in the European Union - Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 1 Manufacture of Sterile Medicinal Products.

Quelle: https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en

Sterilization now includes parts that interrupt the “first air”

Annex 1 addresses the topic of “first air” for the first time: Filtered air should reach the pharmaceutical product and any machine parts that come into contact with the product without interruption, because any interruption by components can pose a contamination risk. Components that interrupt the air flow must therefore be removed or, if this is not feasible, designed in such a way that they can be removed and autoclaved. Previously, decontamination was considered sufficient for sensors and reflectors installed in a way that interrupted first air. This included superficial cleaning using disinfectants or H₂O₂ vapor (vaporized hydrogen peroxide, VHP). Annex 1 “Manufacture of Sterile Medicinal Products Guideline” requires that these components also be treated with validated, penetrative sterilization methods (e.g., autoclaving).

Specifically, this means:**1. Sterilization is handled more strictly**

Not every disinfection or decontamination counts as sterilization. Decontamination by means of disinfection or H₂O₂ cleaning to reduce microorganisms is not sufficient. Instead, sterile procedures are required (no detectable living microorganisms present). Indirect contact parts and contact parts that interrupt first air must be treated as direct parts if they are part of the critical sterile environment.

**2. Mandatory penetrative sterilization of all contact parts and components that interrupt first air**

Not only parts that come into direct and indirect contact with the product should be sterilized. This now also applies to components that interrupt first air. This means indirect contact parts that can disrupt airflow, including any components positioned above sterile parts and products, such as sensors. An exception is possible if a risk analysis within the framework of the Contamination Control Strategy (CCS) proves that cleaning or decontamination are sufficient and there is no risk of contamination.

**3. Higher requirements for the sterilization method**

Sterilization must be validated. For indirect contact and parts that interrupt first air, the procedure must be equivalent to the methods accepted for direct parts – penetrative sterilization methods such as moist heat (for example autoclaving), dry heat, gamma radiation, or ethylene oxide, are suitable. Direct and indirect contact parts as well as components that interrupt the first air are classified as “critical surfaces” according to Annex 1 and must therefore be sterilized. Surface decontamination, VHP-based methods, or steam disinfection are only permitted if evidence or risk analyses prove that these methods are sufficient. VHP-based methods are generally considered decontamination rather than sterilization, especially for closed or hard-to-reach surfaces.

**4. More comprehensive risk analysis and documentation**

It must be documented why and how indirect contact parts are sterilized. The risk assessment must show how critical the contact is and what influence it has on product sterility. In addition, the requirements for control and monitoring are increasing – especially during maintenance or servicing.

Direct vs. indirect contact:
What does this mean for sensor systems?

Sensors and reflectors in sterile processes differ depending on their installation position:

Contact type	Definition	Examples (sensors)	Requirement according to Annex 1	Typical sterilization method
Direct contact	Component physically touches the product.	Level sensor in product line, sensor on filling needle	Must always be sterilized.	Penetrative sterilization (e.g. autoclave, steam [SIP], moist/dry heat)
Indirect contact	Component itself does not come into contact with the product, but touches components that later come into contact with the product (e.g. stopper plugs).		Must always be sterilized.	Penetrative sterilization (e.g. autoclave, steam [SIP], moist/dry heat)
Interrupting first air	Component does not come into direct contact with the product but is located in the “first air” intake path and may pose a contamination risk to overall sterility through air, particles, droplets, or proximity to open product surfaces (e.g. stopper plugs).	Sensor or reflector directly above the product/object	Must be sterilized or treated with a validated alternative method (comprehensive risk analysis required).	Penetrative sterilization or validated alternative (e.g., VHP only with verification)

In short, this means that Annex 1 now also requires validated sterilization or a thorough risk analysis demonstrating that an alternative treatment is sufficient for components with direct or indirect contact or that interrupt first air.

Which sensor types are suitable for sterile environments

Depending on the sensor type used, different challenges and opportunities arise with regard to the new sterilization requirements of Annex 1. Overview:

Ultrasonic sensors and retro-reflective sensors:

Detect the fill level of liquids or solids, or detect objects such as stopper plugs, caps, or closures in containers.

→ If these sensors are installed above the product (as is usually the case), for example as a reflector or ultrasonic sensor, they are considered contact parts that interrupt first air. They are often not designed to withstand the high temperatures (typically above 120 °C during autoclaving) and stresses of penetrative sterilization, making them generally unsuitable under the new requirements.

Optical sensors based on ToF (Time-of-Flight):

Detect objects reliably and without contact, even at long operating ranges and with different colors.

→ Can be mounted on the side or underneath, thus avoiding direct or indirect contact or interruption of the “first air.” The sensors are a good alternative for circumventing the high requirements of “no direct or indirect product contact.”

Small sizes are generally recommended – this is becoming even more important under the new requirements.

Sensors with measurement value evaluation are also becoming increasingly important, as they record and deliver measurement values that go beyond pure switching functions. This offers additional options for process monitoring and documentation and meets the increased requirements for control and verification.

Solutions: Hygienic time-of-flight sensor systems in response to Annex 1



Optical sensors with ToF technology:

If these sensors are mounted on the side, below the product, or at large angles, and there is therefore no direct or indirect contact with products and no interruption of the “first air,” the sterilization requirement for these sensors according to Annex 1 does not apply. This is made possible by ToF technology: It offers a long operating range in a small housing and a high tolerance for reliable detection at large installation angles. In addition, the sensors’ hygienic stainless steel housings allow conventional cleaning and disinfection of the surfaces.



Compact designs:

The 53C and 55C sensor series in stainless steel housings (without ToF) are particularly compact and can be integrated into systems with high hygiene requirements, even where space is limited. The 33C series in hygienic design and the 35C series in robust wash-down design are also available in stainless steel housings (without ToF). In addition, Leuze also offers the new ODT53CL1-2M or ODT55CL1-2M sensor with ToF technology, which combines all requirements (stainless steel, long operating range, small housing, angle tolerance).



Measurement value evaluation and IO-Link:

Many Leuze sensors have IO-Link interfaces that enable simple parameterization, diagnostic data evaluation and predictive maintenance. In this way, they support seamless process monitoring and documentation – a clear advantage in terms of the EU GMP Directive, Annex 1 requirements. The optical distance sensors output a measurement value via IO-Link.



Advantages at a glance – Leuze sensor systems for the EU GMP Directive, Annex 1

- Developed for use in hygienic environments
- ToF sensor systems offer an alternative approach to meeting the increased requirements of EU GMP Directive, Annex 1.
- Flexible installation outside critical areas thanks to small housing and long operating range
- Compact designs for tight installation situations
- Simple integration and seamless process monitoring

Conclusion

The updated Annex 1 requirements pose clear challenges for manufacturers and packagers of sterile medicinal products and medical devices: Sensors and reflectors in the first air interruption area must also be either reliably sterilized or designed and installed in such a way that they do not pose a risk to the overall sterility of products. Sensor solutions from Leuze – hygienic, flexibly mountable stainless steel sensors – enable safe, efficient, and compliant implementation of the new requirements. This allows you to meet the current Annex 1 requirements safely and efficiently.

Would you like to make your system or sensor system compliant with Annex 1?

Get personalized advice now: Contact our experts to secure a customized solution for maximum process reliability and compliance.



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