// The **Contamination Control Strategy** (CCS) – What are its implications for your **processes**? ///

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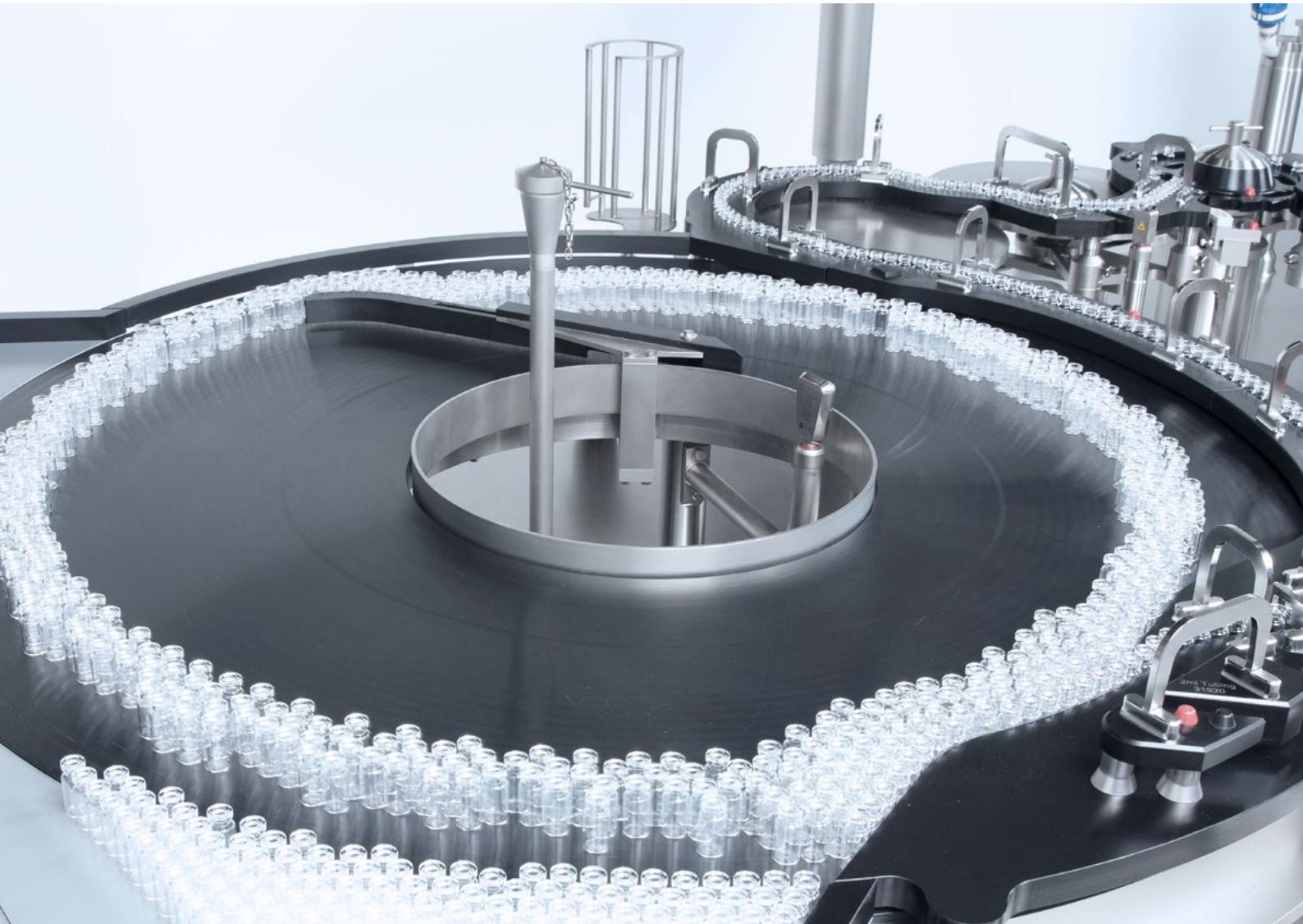
Exploring a new addition to Annex 1: the **Contamination Control Strategy** (CCS) What are its implications for your processes?

After five years of revision, the latest version of Annex 1 to the European GMP Guideline will come into effect on August 25, 2023. The key revision requirements include creating a Contamination Control Strategy (CCS) and consistently applying Quality Risk Management (QRM) principles [1]. The focal point of this article will be the CCS.

The CCS is an interdisciplinary tool, combining inspection measures and contamination sources throughout production, from supplier qualification and quality control to packaging and transport, within a single document. The CCS will initially be created by an interdisciplinary team of experts from the fields of science and technology under the guidance of an author or CCS champion. It is a living, dynamic document subject to periodical updating. The aim is to minimize the risk of contamination [1],[2].



In a GxP-compliant production process, there are pre-existing usable documents that need to be combined and supplemented to ensure the proper functioning of the CCS. The goal of the CCS is to consistently enhance production and inspection methods over time. This is achieved by analyzing data (including trend and root cause analysis) collected from environmental and process monitoring and implementing improvement actions derived from this analysis [1]. Any factors affecting product quality are recorded, analyzed and evaluated [3]. For this reason, a review of the CCS will be a key aspect of many audits.

In the following, we will show you what implementing a CCS means for your pharmaceutical production process and how Bausch+Ströbel can support you in this process:

Equipment

New machines, as well as existing machines, are required to meet the specifications as defined in the revised version of Annex 1. A transition period is currently in effect until August 23, 2023, by which time businesses are required to ensure their machines are in conformity. In certain instances, the new regulations require the implementation of building modifications [4]. The following is an excerpt outlining possible requirements that might require adjustments to machine equipment:

+ No interruption in the supply of first air (especially over pharmaceutical product or primary packaging materials) caused by technical installations → Uniform Distribution of Air Flow (UDAF) with a homogeneous air velocity from 0.36 to 0.54 m/s in the working position, or a documented exemption supported by scientific evidence in the CCS.
+ Strict zonal separation (e.g. between machine base and machine work top, or between machine modules).
+ No continuous feedthrough between different zones (e.g. via conveyor belts), with the exception of depyrogenation tunnels.
+ Sterilizability of directly or indirectly product-contacting parts. Isolated H_2O_2 or VHP treatment is insufficient.
+ Product-contacting components must be designed and sized in such a way that they can be cleaned and steam-sterilized.
+ Glove ports must be factored into risk management. Cleanroom class A gloves should be sterilized using a validated method and bio-decontaminated before each production cycle.
+ Special requirements for the design of airlocks and pass-through hatches, such as effective purging with filtered air.
+ Where possible, the operator should be removed from the production environment. The use of RABS and isolators is recommended. Annex 1 contains a special section outlining requirements for the barrier technology. These include the minimum requirements, glove integrity testing, and decontamination or disinfection of the system [1].
+ It is recommended that, whenever possible, use be made of Rapid Transfer Ports that allow effective bio-decontamination. Use should also be made of “No-touch” unpacking units, attached directly to a RABS or an isolator.

Environmental & **Process** Monitoring

Environmental monitoring is a key component of the CCS, monitoring a variety of contamination sources, such as microorganisms, particulates, and pyrogens.

The new version of Annex 1 envisages that the environmental monitoring strategy will be informed by historical data, process knowledge, and a risk-based approach [1]. It is recommended that viable particles undergo continuous environmental monitoring, and that air flow patterns and complex gas flow paths be taken into consideration. For the filling operation at the core of the aseptic process, it is, therefore, crucial to make this evidence-based decision: Where do particle counters and microbial air samplers need to be placed to ensure the greatest process reliability and avoid unnecessary costs?

Bausch+Ströbel has, in accordance with section 9.4 of Annex 1, conducted studies that validate (critical) control points for the modules of a filling line with scientific data. The positions of particle counters as well as active and passive microbial air samplers were calculated based on airflow simulations and the resulting steric loads. Technical factors affecting First Air flow were also considered.

In a systematic approach, a hazard analysis was conducted for the individual operation modes within a specific machine type using Hazard Analysis Critical Control Points (HACCPs). The effectiveness of an Environmental Monitoring Program depends on the correct identification of Critical Control Points (CCPs) during risk assessment 5. Each control point is assigned an ID. The Risk Priority Number (RPN) was calculated by multiplying severity by occurrence and detection. Table 1 shows that different control points could be evaluated using a different RPN.

Thus, it was possible to identify especially critical control points from the data. Irrespective of the process details, the scientific-data-based studies offer a potential approach to developing a CCS strategy.

Environmental Air Monitoring points results

Machine type/ Modules	Description	Cleanroom class	Process recorded by monitoring	ID	RPZ
DDMXXX*	Delidding of the tub and automated transfer to the discharge plate using robot arms.	A	Delidding of the tub with a heating frame and temporarily holding the opened tub at the ready.	A1	192
			Transfer of open containers using robot arms.	A2	160
			Transfer of open vials using robot arms.	A3	160

Table 1: Control points within machine type DDMXXX, excerpt from the evaluation of an entire filling line
*Information withheld for reasons of confidentiality

Summary

Creating a CCS requires scientific data and experience. Collaborating with Bausch+Ströbel offers real added value, especially in the chapters “Equipment” and “Environmental & Process Monitoring”: We can provide you with a scientifically based strategy for meeting the requirements set out in the new version of Annex 1. Please feel free to contact us for further information.

References **August 2023**

1 Euopean Commission. The 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. https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf.

2 Krebsbach T, ed. Sterilherstellung in der pharmazeutischen Industrie: Aseptische Herstellung und terminale Sterilisation. Aulendorf: Editio Cantor Verlag; 2023.

3 Dr. Florian Blauert. EU GMP – Annex 1 Die Änderungen im Überblick. https://j-k-consulting.de/en/0201/02/15/eu-gmp-annex-1-die-aenderungen-im-ueberblick/. Accessed June 5, 2023.

4 Sebastien Trichot JL. Impact of Annex 1 revision on new vial filling line at Sanofi Pasteur Marcy-l'Étoile. https://www.a3p.org/en/impact-of-annex-1-revision-on-new-vial-filling-line-at-sanofi-pasteur-marcy-letoile/.

5 PDA. Contamination Control Strategy Development in Pharmaceutical Manufacturing: Contamination Control Strategy Development in Pharmaceutical Manufacturing.

Questions? Let's talk!

If you would like more information about this topic please feel free to contact us.

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