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Update on Annex 1 of the EU GMP Guide

by Doris Borchert, PhD

The 27th PTS GMP Conference took place face-to-face and in parallel digitally from 30.11. to 01.12.2021 in Mainz, Germany. The hybrid event was broadcast live from the Atrium Hotel in Mainz, where most of the speakers were present in person.

The presentation by Rico Schulze, Saxon State Ministry for Social Affairs and Social Cohesion, on the revision status and publication of **Annex 1 to the EU GMP Guideline** was particularly eagerly awaited. It is now almost 10 years since the initial proposal for a complete revision. More than 6000 individual comments had to be processed by the working group after the publication of the first draft in December 2017. Not only this workload, but also Brexit-related personnel changes and the relocation of the EMA resulted in a second draft not being on the table until the beginning of 2020. However, even this version did not only meet with approval from the parties involved – more than 1000 further comments, classified as substantial, were received. The focus was clearly on sections 4 "Premises" and 8 "Production and specific technologies". Thus, a third draft went to authorities and involved parties in October 2021 – and again there were numerous critical objections. The decision-making process scheduled for the end of November 2021 was therefore replaced by a further examination of the content by January 2022. So that this scenario does not become a never-ending story, the last draft is only to be distributed to the members of the GMP/GDP Inspectors Working Group. The disputed points can then only be accepted or rejected, but no longer commented on. The decision-making process is to take place by circulation. **Adoption, according to Rico Schulze, is expected in spring 2022. An implementation period of 6-12 months is under discussion, possibly up to 3 years for critical issues.**

So much for facts and figures. But what is it actually about in terms of content? What makes the coordination process so difficult?

A far-reaching change is the **scope of application**, which in future will include sterile medicinal products as well as sterile active substances, excipients and primary packaging materials. Following the general trend, the application of **quality risk management (QRM)** is also required in the new Annex 1. This results in many "soft" formulations, the design of which is left to the user. The core element of the new Annex 1 is the **contamination control strategy (CCS)**, which affects almost all areas. For example, RABS and isolator systems are to replace human intervention in critical zones in future – exceptions must be justified! Barrier technologies will thus become indispensable.

With regard to classification, (re)qualification and monitoring, the aim was to harmonise ISO and GMP requirements as far as possible. Flow visualisation will be required in all cleanroom classes in the future; separate airlocks for cleanroom class B are desirable.

Section 8 "Production and specific technologies", which is the most comprehensive, contains many process-dependent requirements that are supplemented by descriptions and explanations – which is definitely to be seen as positive. Integrity and leakage tests for filters and closed systems form a focal point. In this section in particular, however,

there are still points for discussion, e.g. on the validation of closure techniques, on the performance of integrity tests of final containers and on the sterilisation of freeze-drying systems. The question of whether and how filters should be tested for integrity BEFORE use (Pre-Use-Post-Sterilisation-Integrity-Testing, PUPSIT) has also not yet been conclusively clarified.

There is also news in **section 9 "Viable and non-viable environmental and process monitoring"**. Thus, microorganisms detected in Grade A and Grade B should be identified to species level and their potential impact on each affected product batch as well as the overall state of control should be evaluated. This procedure is also recommended for Grade C and D areas. Fortunately, the aseptic process simulation (APS) is better regulated than before and now contains clear guidelines for implementation. However, there are still question marks and concerns in this section as well, e.g. with regard to the European "special solution" for monitoring in Grade A cleanrooms, where particles ≥ 5 µm are still relevant.

Even if some questions have not yet been finally clarified, one thing seems certain: The new Annex 1 will lead to an adaptation of similar documents of the WHO, PIC/S and PDA and thus have a global impact. It is also clear that the new requirements and their implementation will demand intensive training measures both in the industry and at the authorities.

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