EUROPEAN SOCIETY OF ONCOLOGY PHARMACY

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To whom it may concerne

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Dear Ladies and Gentlemen

We are happy to answer the question of the proper and professional review of individual recipes in central production areas within the pharmacies. The requirements for these manufacturing areas serve the safety of the patients and are to be carried out according to the principles of good manufacturing practice. Nonetheless, they differ from the batch processes of industrial production because they are individual recipes that are not checked by reference samples, but by the validation of the aseptic manufacturing process.
Today we are happy to give you some information about these techniques and are at your disposal for further questions.

The validation provides documented evidence that procedures, processes, operations or systems meet the previously specified requirements in practical use. The requirement of the European Pharmacopoeia [(Ph.Eur., Chapter 5.1.1.): "*Sterility is the absence of viable microorganisms. The sterility of a preparation cannot be ensured by testing; Sterility must be guaranteed through the use of a suitable and validated manufacturing process*. "] Became mandatory for all pharmacies by prescription. The questions about the type and scope of the microbiological validation are now the points to be clarified.
For production under aseptic conditions, the European Pharmacopoeia (also in Chapter 5.1.1) defines in the section "Production under aseptic conditions": "*The aim of a production under aseptic conditions, the sterility of a preparation composed of sterilized components is to be preserved [...]. In order to maintain the sterility of the components during production, special attention must be paid to the following points, among others: environment, personnel, critical surfaces, transfer steps. The process validation includes suitable tests of the aforementioned points*. "

Although the "sterility test" is in principle intended for all parenteral drugs, it can be replaced for the production of ready-to-use parenteral drugs by a full validation and close monitoring of the environment during the production process. In the commentary of the European Pharmacopoeia, Chapter 2.6.1 "Testing for sterility" states: "*The statement that testing for sterility is the only possibility for the authorities to check the sterility of a sample is also no longer applicable today. If there is any doubt about the sterility of a product, it is much more informative to review the manufacturer's process and validation data than to perform the sterility test*." This formulation also reveals the absolute necessity of comprehensive validation including close-knit environmental monitoring,

in order to be adequately safeguarded in the case of forensic questions regarding the microbiological safety of the aseptic manufacturing process used with parametric approval of the individual manufacturing processes.
Very good as well as detailed implementation instructions can be found in the EC guideline for good manufacturing practice (GMP) or in the associated appendix 1. European Pharmacopoeia expressly required for the manufacture of sterile pharmaceuticals.
Practical process proposals are described in the Quality Standards for the pharmaceutical-oncological Service (QuapoS) in the following under the item validation concept.

According to GMP recommendations, the validation of the aseptic process must include process simulation with culture media. The routine manufacturing steps should be largely simulated and include all critical successive manufacturing steps. All work processes that are known to occur during aseptic production as well as "worst case" situations must be mapped. The initial validation should be carried out with three successive simulation runs.

The validation is then repeated at regular intervals, taking into account experience gained and after significant changes to the process flow or equipment. Process simulations are normally to be provided twice a year (according to GMP). According to WHO and USP there is a contamination rate for aseptically manufactured parenteral drugs of 1: 1000 defined as the upper permissible limit. The validation for batch-related production that is customary in industry is not possible in the pharmacy for aseptic individual production of parenteral drugs due to the system, since in principle each individual preparation represents a produced batch. The manufacturing process must therefore be validated as such.

Sometimes the question was asked why infusion solutions not containing cytostatic agents are used for microbiological evaluation. The following should be considered. When producing cytostatics, the principle must always be followed, as safely as possible and as much as necessary.
On the one hand, there is no compelling need to use expensive cytostatics only for regular examination purposes and, moreover, to cause an additional workload through hazardous substances.
If, independently of regular, daily test production, which serves microbiological documentation purposes, a review for content and purity is to be carried out by supervisory authorities in order to check the accuracy of production by way of example, this does not mean that such a procedure for the daily validation of hygienic and aseptic manufacturing methodology is generally suitable.
Because microbiological validation is about checking the daily routine production, for which a suitable sensitive medium is required. Quite apart from the fact that certain cytostatics with antibiotic origin cannot be denied that there is a microbiological influence on cells that can influence the examination of hygiene, culture media as recommended in the pharmacopoeia are the means of choice for validating the control process.

Yours sincerely

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