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Book review

Environmental Monitoring for Cleanrooms and Controlled Environments, Anne Marie Dixon (Ed.). Drugs and the Pharmaceutical Sciences, Vol. 164. Informa Healthcare, New York, London. 230 pp., ISBN: 0-8247-2359-7.

In nine chapters the book ''Environmental Monitoring for Cleanrooms and Controlled Environments'' gives a state-of-the-art overview on current concepts and techniques in the environmental monitoring for cleanrooms and controlled environments.

In the first chapter the behavior of particles in a cleanroom is discussed by D.S. Ensor and K.F. Foarde. It should help to recognize potential particle size dependent sampling and measurement biases in all states of a cleanroom, e.g. as built, at-rest or operational. For the design of appropriate sampling and measurement techniques it is important to fully understand the role of the various sources of particles in a cleanroom as well as the particle mechanics in impactors.

R.A. Matthews discusses ''the Application of the New International Standards Organization (ISO) Cleanroom Standards''. After a short introduction into the history of the development of the ISO cleanroom standards he discusses the standards ISO 14644-1 up to ISO 14644-8. In the first of these eight guidelines the rules for the classification of air cleanliness are presented. A mathematical formula to be used to calculate the maximally accepted, size dependent number of particles in a given class of cleanliness is presented. In ISO 14644-2 ''Specifications for testing and monitoring to prove continued compliance with ISO 14644-1'' are discussed. The most comprehensive standard, ISO 14644-3, describes ''Test methods'' to be used in the monitoring of cleanrooms. ISO 14644-4 describes in detail the basic concepts for the design, construction and start-up of cleanrooms whereas ISO 14644-5 specifies the basic requirements for operating a cleanroom. It is very helpful that in ISO 14644-6 all of the common terms and definitions used in the other ISO standards are summarized as in a vocabulary. The ISO standard 14644-8 describes ''Separative Devices'' as clean air hoods, glove boxes and mini environments. The principles and basic metrology for a formal system to assess and control Biocontamination are summarized in two separate ISO standards, ISO 14698-1 and ISO 14698-2.

In Chapter 3, D. Brande discusses ''Cleanroom certification and Particulate Testing''. In four postulates he summarizes the prerequisites for a certification of a cleanroom. First postulate: ''Show that if particulate does enter the controlled environment, the particulate will be disposed of in a timely and efficient manner''. This is achieved by the control of the air changes/hour. Second postulate: ''We must demonstrate that no particles will enter the controlled environment as a result of construction''. This is achieved by room pressure differentials. Third postulate: ''You need to establish that no particulate can enter the controlled environment through the supply air system''. This results in controls of the filter integrity. The fourth postulate: ''In conclusion, you must show that the controlled environment can produce and maintain the desired room classification''. This has to be done for all three states of a cleanroom mentioned above.

In Chapter 4, B. Ljungqvist and B. Reinmüller describe the conditions and the efficiency of air sampling. They intensively discuss factors determining the d_{50}-value, the cutoff size, of air sampling devices. Information of the d_{50}-value is an important factor when selecting the appropriate equipment for a cleanroom. In addition to the active air sampling methods for the passive air sampling are discussed.

In Chapter 5, S. Sutton presents methods used in the ''Microbial Surface Monitoring''. In several tables he summarizes the levels provided in common references for the various classes of cleanrooms with respect to viable surfaces, personnel gowns and personnel gloves. In addition methods used in the microbial surface monitoring and their efficacy are presented.

In Chapter 6, A.M. Dixon, the editor of this book, deals with ''Process simulations (Media fills)''. Process simulation has at least two purposes: it demonstrates that the aseptic fill/finish process is capable of producing a sterile drug product and in addition it is used to qualify or certify aseptic processing personnel.

Before going into the details of the process of devising, executing and assessing media fills contamination sources, e.g. people, equipment and room environment, are discussed. Then the first step in establishing a media fill program is the drafting of a broad policy that may be in one of different forms, e.g. of a master plan or a validation protocol. ''This policy document should define the purpose of the program, a risk analysis, the frequency of routine revalidation, and nonroutine reasons for revalidation''. In a second step the detailed program is planned. Process

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parameters and criteria for intervention and acceptance criteria are defined. In addition a failure investigation plan and potential corrective actions are discussed.

Water is the most important raw material in the manufacture of most sterile products. Therefore, A.M. Dixon and K.Z. McCullough devoted Chapter 7 to ''Water monitoring''. They used the FDA document ''Guide to inspections of high purity water systems'' as a starting point for their considerations as this document provides information on the agency's expectations for the design and operation of systems that produce pharmaceutical grade water. The standards of the various qualities of pharmaceutical grade water are listed up, validation procedures, sampling techniques and routine monitoring as well as investigations in the case of failure are discussed.

Water for Injection (WFI) is sterile and has an endotoxin content under 0.25 EU/ml (EU = endotoxin unit). Bacterial endotoxin is a very potent pyrogen. Therefore, in Chapter 8, K.Z. McCullough deals only with ''Bacterial Endotoxin Testing (BET)''. First she discusses the legal requirements with respect to pyrogens. In a short list the most important properties of pyrogens/endotoxins are summarized and eventually compliance definitions and requirements are listed up. Special interest is paid to the hazard analysis and critical control point (HACCP) study. HACCP is defined as a ''process oriented approach to risk analysis, which focuses on prevention or reduction of risk through the proactive identification of critical points in the system''. Seven principles help to make a HACCP successful. They are discussed in detail. Based on the calculation of the endotoxin limits for small-volume parenteral drug products maximum endotoxin levels for the various critical control points (CCPs) are derived. In a separate section methods of depyrogenation and their validation are presented.

In Chapter 9, K.Z. McCullough and A. Zakzeski deal with the ''Fault tree analysis of the USP Sterility Test''. Sterility testing is considered as a ''necessary evil'' as ''the result of a sterility test gives little, if any, indication about sterility of a batch''. This statement is illustrated by an example. ''Statistical evaluations indicate ... if a 10,000-unit lot with a 0.1% contamination level was sterility tested using 20 units, there is a 98% chance that the batch would pass the test''. The authors come to the conclusion ''given these statistics, it is reasonable to assert the sterility is assured through careful process validation and control'' only. Nevertheless ''with the observation of an OOS (out of specification) result, we are obliged to determine the root cause(s) of any sterility test failure''. Decision trees for the various steps of this procedure help to design such an analysis.

In a summary this book can be recommended to all those being involved in the development, the manufacture and the control of sterile drug products. It is impressive how much harmonization was achieved in the last decade. As the book considers the results of this harmonization it gives a state-of-the-art overview on ''Environmental Monitoring for Cleanrooms and Controlled Environments''.

Prof. Dr. Ingfried Zimmermann *
Institut für Pharmazie und Lebensmittelchemie, Universität Würzburg, Würzburg, Germany
E-mail address: i.zimmermann@pharmazie.uni-wuerzburg.de

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* Tel.: +49 931 888 5471; fax: +49 931 888 4608.