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Book reviews

Joseph D. Nally (Ed.), Good Manufacturing Practices for Pharmaceuticals, sixth ed., Drugs and the Pharmaceutical Sciences (Vol. 169), Informa Healthcare, New York, London, 389 pp., ISBN 0-8493-3972-3

The fact that this book is now published in the sixth edition clearly demonstrates its importance for those being confronted with GMP regulations in one way or the other. Without any doubt this will also hold for the new edition as the world of Pharmaceutical GMP compliance has changed since the last edition was published five years ago.

The FDA has changed significantly during this period of time. The number of inspections decreased as well as the number of Warning letters has declined by 50% from 2000 to 2005. FDA has initiated a new framework for regulating manufacturing that supports e.g. risk-based regulation, quality-by-design, a quality systems approach and process analytical technology (PAT). In addition a number of The International Conference on Harmonization (ICH) standards was adopted.

This book comprises 24 chapters and three appendices. The chapters one through twelve cover the GMP regulations – subparts A to K. In each chapter the basic definitions used in the GMP regulations are highlighted by shadowed frames. These definitions are then followed by detailed explanations and comments on their implementation by the manufacturers or on their interpretation e.g. by inspectors. These chapters allow for an excellent understanding of what is intended by the various regulations. In each chapter internet addresses of relevant links are given as to allowing for an easy access to additional information and opening up a range of information much wider than the coverage of the book itself.

In Chapter 13 ''Repacking and Relabeling'' J.D. Nally discusses some circumstances under which repacking or relabeling is performed. There are no requirements demonstrating that stability and expiration time are the same as guaranteed by the manufacturer. The current regulations are insufficient to prevent from mislabeling. Recommendations are given what should be changed in order to comply with GMP. There are no good reasons for the dual standards in the manufacture of drug products on one hand and the repackaging and relabeling on the other hand.

In Chapter 14 ''Quality systems and Risk management approaches'' J. D. Nally and L.L. Nally discuss two recent FDA Guidance Documents on Quality System Approaches: ''Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations'' from September 2006 and ''Final Guidance and Compliance Program Guidance Manual for FDA Staff. Drug Manufacturing Inspections Program 7356.002''. The two guidance documents are a bridge between the 1978 GMP regulations characterized by test and control themes and the current concepts of quality systems being based on the insight that testing alone cannot be relied upon to ensure product quality. The risk management process is described in detail. It becomes clear that the application of risk management approaches makes good business sense and should benefit the company and the patient.

In Chapter 15 G. Bunn presents the CGMP regulations as applied during the manufacture of Clinical trials supplies (CTS). There is a need for some modification of the general regulations due to the fact that the overall development is still ongoing and that important information has to be gathered during this phase. He emphasizes that the most distinguishable difference between CTS and commercial is found in packaging records.

In Chapter 16 G. Bunn deals with questions and problems arising with ''Contracting and Outsourcing''. He points out that the expanded use of contractors for one or more developmental steps and, increasingly, for the entire process is one of the significant changes in the way pharmaceuticals are developed. In this context contractors have gained knowledge and experience over the last ten years enabling them to manage the requirements of several clients simultaneously. He lists up a series of reasons for an outsourcing, discusses various types of outsourcing and develops a flow diagram with criteria for the selection and maintenance of a contractor.

In a very short Chapter 17 on ''Active Pharmaceutical Ingredients (APIs)'' P.D. Celentano tries to provide guidance on current good manufacturing practices for the manufacturing of APIs and the current thinking of FDA.

In Chapter 18 I. Silverstein discusses ''Bulk Pharmaceutical Excipients GMPs''. The current good manufacturing practices (CGMP) regulations apply only to dosage forms and are to be used only as a general guide for excipient manufacture. In order to address issues concerning the manufacture of pharmaceutical excipients the International Pharmaceutical Excipients Council (IPEC) was formed as a global organization with associations in the bigger pharmaceutical markets. In 1995 this

organization published the IPEC Good Manufacturing Practices guide for Bulk Pharmaceutical Requirements. This guideline was organized according to the International Organization for Standardization ISO 9002:1994 guidelines. After various revisions the latest IPEC excipients GMP guideline was published in 2006 when the excipient quality system requirements were harmonized with those of the Pharmaceutical Quality Group. This guideline is now called IPED-PQG Good Manufacturing Practices for Pharmaceutical Excipients. Silverstein gives a short overview on this guideline. The Chapters 19 through 24 are written by J.D. Nally.

Chapter 19 is dealing with "Recalls, Warning Letters, Seizures and Injunctions: CGMP Enforcement Alternatives in the United States". He presents some statistical data on the frequency by which such measures were taken by the FDA during the last years.

In Chapter 20 on three pages in the context of "Controlled Substances Safeguards" a series of operational safeguards are listed up.

"The Inspection Procedure for Compliance in the United States" is the topic of Chapter 21. After the discussion of some legal problems which occurred in the context of inspections the author describes how an experienced inspector usually conducts the inspection. Another paragraph deals with special problems encountered by inspectors. He gives practical hints to be considered during GMP Inspections. He lists up a series of words which should be avoided and addresses issues the investigators/auditors like or dislike. He closes the chapter by listing up short summaries of FDA guidance documents being relevant to inspection procedures.

"FDA Pre-Approval-Inspections Investigations: The Road from Scale-Up and Post-Approval Changes to the Food and Drug Modernization Act" are the topic of Chapter 22. The author explains that largely as a result of the inclusion of falsified data in some approved new drug application (ANDA) submissions, FDA introduced the Pre-Approval Inspections/Investigations (PAI) Compliance Program in 1990. He lists up a series of conditions under which a PAI will be requested. References and suggested readings complete this list. The second part of this chapter deals with FDA's thinking on marketed new drugs without approved NDAS or ANDAS. In a short appendix an overview is given on FDA marketing approval requirements and categories of drugs that lack required FDA approval.

In Chapter 23 J.D. Nally gives an overview on "Worldwide Good Manufacturing Practices". He explains that the formalization of GMPs commenced in the 1960s. Besides the regulations in the US and the WHO GMPs for pharmaceutical products a series of regional requirements has appeared, among them the Pharmaceutical Inspection Convention (PIC), the general guidelines of the Association of South-East Asia Nations (ASEAN) GMP and the European Economic Community (EEC) guide to GMP for medicinal products.

These regional guidelines are similar in design and content. They model more of a quality management approach when compared with product testing and control prevalent in the US GMPs. Considering the internationality of the pharmaceutical business the author is presenting brief evaluations of some other GMPs followed in Europe, in Canada, and by WHO and highlighting major differences from the US GMPs.

In Chapter 24 the author presents some other quality standards and approaches to provide a broader picture of current quality philosophy and efforts that consider the business as a whole. After a brief discussion on historical reasons which lead to the development of quality management systems he gives a short overview on other systems like the ISO 9000, the Malcolm Baldrige National Quality Award (MBNQA) and the criteria for performance excellence and the Six Sigma Approaches. Again the chapter is completed by a number of Internet addresses to find more detailed information.

In Appendix A "Center for Drug Evaluation and Research: List of Guidance Documents" a comprehensive list of documents is presented showing FDA's current thinking on various topics related with GMP. The Internet Address for downloading the various documents is included.

Appendix B is a summary of the ICH Guidelines. Also in this case the home page for a quality index and links is given.

Appendix C eventually presents the FDA's Regulatory Affairs Compliance Policy guides. They explain the agency's policy on regulatory issues related to the FDA laws or regulations. As in the preceding chapters for further information Internet addresses are included.

The book "Good manufacturing Practices for Pharmaceuticals, Sixth edition" is not a simple introduction into the GMP regulations of the U.S. FDA. Of course he discusses primarily this issue but he always includes corresponding regulations from other regions. The inclusion of practical examples allows to understand the FDA's thinking on Current Good Manufacturing Practices. This helps to prevent major problems during the drug approval process. It will be very helpful especially for those who are confronted with CGMP for the first time. The inclusion of all the Internet addresses is a tremendous help for all working in the pharmaceutical business.

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