

Editor's Comments:

The USP has launched an initiative that will modernize pharmacy compounding of sterile products. A critical part of this effort will be a requirement for more comprehensive microbial assessment of compounded parenterals prior to release.

Your attention is drawn to two new books that are valuable contributions to our industry. Kevin Williams, a scientist at Eli Lilly & Co., has authored the most useful and comprehensive text to date on the parenteral aspects of endotoxins and LAL testing. For the microbiological laboratory in the pharmaceutical setting, Richard Prince has edited a uniquely structured and comprehensive text. A brief description of each book is presented.

J. F. Cooper

USP Hosts Compounding Pharmacy Stakeholders Forum

The USP held a forum in Rockville on August 21, 2001, to gather input from pharmacy professionals and other stakeholders regarding future USP initiatives. The purpose of the forum was to outline ways the USP could support optimal compounding practices. The history of USP involvement is summarized in a recent *Pharmacopeial Forum*. (Okeke C, *et al.* History and background information on USP's activities in compounding pharmacy practices. **2001**; *PF* 27(5):3169-71) A follow-up open conference is under consideration.

In order to implement the FDA Modernization Act of 1997 (FDAMA), the FDA convened expert advisory committees to advise the FDA on regulatory activities. The FDA received a setback when the Court of Appeals for the 9th Circuit ruled that the pharmacy compounding section of FDAMA was unconstitutional. Last year, an interesting and widely circulated position paper from the FDA attempted to define 'difficult-to-compound products,' those that would need microbial assessment before release.

We can expect the USP to take several positive steps. There will be an accelerated effort to develop more monographs for sterile bulk products and excipients, and perhaps, compounding monographs for critical medications. The <1206> sterile compounding chapter may also be moved from the informational to required pharmacopeial status and expanded to include neonatal, pediatric, geriatric and terminally ill patients. Educational programs will be needed to train pharmacists and chemists in suitable LAL technology.

BOOK REVIEW: *Endotoxins*
by Kevin Williams . Marcel Dekker. 2001

Although described as a revision of Pearson's text *Pyrogens*, 1985, I found this to be essentially a new book because of the extensive upgrades as well as new material. The work is scholarly and appeals to a broad audience, from academia to industry. Williams often maintains attention with interesting anecdotes and appropriate wit. The text is well illustrated to support important concepts. This book should be a familiar reference for anyone seriously interested in endotoxin research or testing. Investigators will find that the body of knowledge concerning endotoxin is well referenced.

The first part of the book concerns pyrogens with the greatest emphasis appropriately placed on endotoxin. The book opens with an interesting account of how the nature of pyrogens and endotoxins was revealed and how the development of intravenous (IV) therapy and our understanding of pyrogens intermingled. The enormous host responses, induced by as little as nanogram quantities of endotoxin, are described in detail. The next two chapters focus on the character of endotoxin. After discussing toxins in general, the author substantiates his conclusion that the ubiquity, potency, stability and likelihood of contamination by endotoxin make it the only significant pyrogen encountered in traditional sterile products.

The use of the metaphor to describe endotoxin standards is priceless; see the beginning of Chapter 8. The discussion of structure, function and activity of endotoxin helps one understand the fickle nature of endotoxin standards and how they cause certain types of LAL interference conditions. When proteins are removed from endotoxin, the term lipopolysaccharide (LPS) applies. The purification process renders LPS less soluble

than endotoxin in an aqueous environment. The biological properties and LAL activity of endotoxin are strongly influenced by external factors such as temperature, vortex mixing, pH, concentration of bivalent cations of Mg and Ca, salt concentration and presence of surface-active agents. The critical factor in variable activity is the aggregation state of endotoxin or LPS. Evidence indicates that LPS must be highly disaggregated to be most active, but small units of molecules exist rather than monomers. The aggregate of endotoxin encountered in LVPs and device extracts will have a molecular weight of approximately 10^6 daltons in the absence of significant levels of divalent cations and surface-active agents.

The discussions of non-endotoxin pyrogens and host response to pyrogens are of keen interest to biotechnology. A modern definition of pyrogen would be an exogenous agent that activates the complex host (cytokine) system. Microbial-derived pyrogens are not seen in traditional drug production, but they may survive the manufacturing process for biologicals. It is a solemn reminder that LAL methods may not be entirely sufficient to screen for contaminants that may arise from production of biologicals from living organisms in culture media.

The second section concerns LAL discovery, reagent properties, test methods and applications. The author reviews advantages and disadvantages of all LAL methods and concludes that kinetic LAL will continue to supplant gel tests because of the efficiency of these methods and their ability to extrapolate endotoxin results over a wide range.

Chapter 11 describes how to develop a LAL method for a new chemical entity and complete a validation report. In the process, ways to identify and resolve interference methods are explained. Appendices to this chapter present a number of useful forms, a

copy of the FDA's LAL test guideline, as amended in 1991, and a copy of the new harmonized BET, 2nd supplement to USP 24. There is a review of automation including kinetic LAL testing and robotics. Automation is presented as a means for controlling test variability caused by the method, product, LAL reagent, analyst behavior and accessories. In arguing the merits of polynomial versus linear regression analyses for kinetic methods, the author overlooked a risk of using polynomial regression. Whereas enhancement in linear regression alerts one to weakness of the low concentration endotoxin standards, polynomial regression ignores this warning and may allow background noise in some wells to be calculated as failures, especially if values are corrected for dilution. Speaking from personal experience at Lilly, Williams provides a candid discussion of the advantages and pitfalls of LAL methods by robotic devices.

Another topic addresses GMP issues. A systematic way is proposed to set corporate endotoxin limits for excipients and bulk materials; however, a more simple approach using safety factors may be equally effective. There are excellent discussions of contamination control and validation procedures for water and other components needed for aseptic processing. Finally, there is a vision for prospective pyrogen tests and therapeutic approaches to Gram-negative sepsis.

BOOK REVIEW: *Microbiology in Pharmaceutical Manufacturing*
Richard Prince, Editor. PDA and Davis Horwood International Publishing. 2001

This new pharmaceutical text covers a broad range of topics that are critical to the evolving parenteral drug and device industries. The book is unique in that subjects move logically from basic science, to applied technological

solutions, to aseptic processing, to laboratory testing, to quality control and regulatory compliance. The authors are an impressive group of leaders in our industry.

The first section addresses basics in pharmaceutical microbiology. The second section explores the technological advances that are designed to mitigate or prevent adventitious contamination in the manufacturing setting. These chapters describe current as well as emerging technologies for the pharmaceutical microbiological lab for conducting tests and detecting microbes.

The third section addresses the heart of aseptic processing; that is, the complex of environmental systems and controls that are critical in order to successfully manufacture parenteral drugs. Chapters relevant to the microbiology lab include designing a contamination control program, validation master plan, validation of sterilization processes, microbial concerns in water systems and sterilizing filtration.

The fourth section discusses microbiological laboratory sampling, testing and data management. Topics include statistical sampling plans, microbial limits test systems, endotoxin test systems and a chapter on managing discrepant microbiological data and results. The endotoxins chapter is an overview of the technology, and serves as a practical guide to testing a broad spectrum of starting materials and final products.

Additional, informative sections address a management view of pharmaceutical quality systems and regulatory compliance. The depth, scope and timeliness of this book sets it apart from earlier texts.