INTRODUCTION

This book is intended to provide a background to the quality control (QC) microbiology function from the perspective of the laboratory, and particularly from that of the laboratory manager. While it mentions interesting topics such as aseptic processing, gowning certification, environmental monitoring and so on, these are not discussed in sufficient depth to provide mastery of the subject. The focus of this book is on the role of the QC microbiology laboratory in the pharmaceutical manufacturing environment.

In this, *Pharmaceutical Quality Control Microbiology: Guidebook to the Basics,* is different from many in the field of pharmaceutical microbiology. Books with "pharmaceutical microbiology" in their titles seem to come in two main varieties.

In the first, the editor calls upon his associates and friends to write chapters on specific topics, and then hounds them with increasing enthusiasm as their deadlines slip. The chapter authors feel the responsibility to write detailed and lengthy chapters on a relatively narrow topic and are reluctant to release a less than perfect work. Finally this dynamic is resolved and the book is released with excellent chapters on different topics stitched together in a book that is several hundred pages long with strong, in-depth coverage of many different and relevant topics. This is not that kind of book — it is not a reference book in any normal sense as no attempt has been made to provide detailed, scholarly, literature support for all key points, let alone trying for comprehensive coverage of pharmaceutical microbiology as a scientific discipline.

The second main type of "pharma micro" book is the introductory text written by an academician. I have nothing against academicians — given a perfect world I would love to be one myself (the grass being always greener). However, pharma QC microbiology frequently comes down to successfully performing lab testing under the constant pressures of time and budget constraints, sometimes inexplicable regulatory expectations, all the while reporting to management who have no background in your field. This is not a situation that can be readily described without living the experience. Therefore the descriptions of life in the lab tend to be somewhat idealized when compared to the actuality of the experience.

This book is directed at concerns in the laboratory. I have had the honor of working for several excellent companies who valued the role of the microbiology lab. As a consultant, I have had several clients who felt the same way, and several others who felt differently. Unfortunately, on a day-to-day basis some companies seem to view the QC microbiology function as you might a slightly dotty aunt. I mean this in that it is not important so much as to what she is doing (on the whole) as it is that she does not embarrass the family. No one wants the microbiology representative to speak up in a project team meeting — it is virtually never good news. The microbiology representative is most likely preparing to describe a new "opportunity" with a recently filled batch that needs to be discussed, or some interesting situation with significant quality improvement potential which has been identified by environmental monitoring*. In any event, many companies tend to view microbiology as a necessary evil that must be tolerated. A frequent corollary of this viewpoint is that much of the unpleasantness emanating from the microbiology lab would be resolved if it was only led by a good, firm manager. Therefore the microbiology unit will frequently serve as the "proving grounds" for up and coming formulators, analytical chemists, or liberal arts majors who need management experience. After all, how hard can microbiology be?

The results from this approach are predictable. In 2006, over 36% of Food and Drug Administration (FDA) Form 483 and Warning Letter citations (of 818 total) fell into the categories of in-process sampling and testing, lab controls, or testing and release or personnel qualifications. 59% of recalls in that year included citations of lack of sterility assurance, microbial contamination of nonsterile product or non-sterility (of 215 recalls) (McCormick, 2006). Granted, not all of these were the result of a technically weak microbiology group, but a strong subject matter expert (SME) on site would not have hurt matters at all.

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* Intelligent lab workers quickly figure out the problems inherent in being perceived as "negative" or even worse "not a team player". I even figured it out after a few years. Problems are best described as "opportunities for improvement" or some other silly euphemism.

So what *is* the point of writing this book? I hope to find an audience in several diverse populations. First, for the new microbiologist going into the pharmaceutical, medical device or cosmetics industries this book is meant as a "heads-up", a look at what is in store. University microbiology courses are a dying effort. Bacteriology courses even more so. What is offered for microbiology in most campuses seems to be primarily recombinant DNA — the most common result seen by the hiring manager is that gene jockeys are generated even in programs that have the word "microbiology" in their letterhead. No one seems to be teaching basic lab hygiene, the use of the autoclave, fundamental lab practices and aseptic technique. Sadly, it is the rare college graduate who has the basic skills needed for work in the QC microbiology lab. This book is directed to you. Do not expect an industrial quality control lab to resemble movie versions of the research lab, or even what your professors might have told you went on in industry. Be prepared to learn all sorts of pedestrian tasks, such as equipment operation, plating, extraordinary documentation skills, and so on. The microbiology lab is a fun, clean job where you are surrounded by intelligent, usually entertaining, and motivated people. Enjoy them. The function itself comes into contact with every product and most of the processes going on in your company. You will not find a function that provides a better learning experience in your company — this can serve you well in the future, even if you leave the lab to seek promotion. Pay attention, get along with as many people as possible, and use the time to decide if you want to work at an honest living or go into sales and marketing (or worse, consulting).

The second audience I hope to reach is the newly-promoted manager of a microbiology laboratory who might not be comfortable in microbiology. Although I believe this manager is likely to face some significant challenges in the near future, the microbiologically-naive manager can be effective. Your motivation is obvious. Any time your lab generates a failing result on a sterility test (or any other product release or stability test) your life becomes interesting for a couple of months. It is best to make sure that the cause of that result is not ultimately determined as due to poor scientific execution of the testing under your direction*. This book is not going to turn you into a microbiologist, but perhaps it can give you some direction in how to think about some of these tests, and the operation of the lab, to minimize the lab-induced errors. I have also tried to provide some relevant (and easy to find†) articles and book chapters for further reading on various topics. For some help in the near and short-term, immediately focus on:

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* A few of these lab-induced results over a period become a CLS (career limiting situation). The common response of upper management to frequent lab issues is to give someone else a shot at leading the micro group. That is how you got the position in the first place, isn't it?

† Well, perhaps the 1939 reference on the concentration exponent is not going to be the easiest to locate, but we can consider that the exception to prove the rule.

- Understanding the critical nature of culture media and how to document its adequacy.

- Getting control of your culture maintenance and inoculum preparation procedures, and understanding how your specific practices may directly influence test results.

- Somehow finding time in between meetings to get some hands-on experience on the bench tests. Lack of knowledge of assay limitations will lead to overinterpretation of data or failure to recognize absurd data.

- Understanding appropriate biosafety techniques — novices usually institute excessively restrictive practices (usually over-utilization of biosafety hoods) to overcome poor lab technique.

- Becoming familiar with the theory behind your laboratory tests in terms of the limitations of the data and appropriate control on assays. Failure here will lead to ineffective investigation of microbiological data deviations.

This book will not be the final word on these topics for you. I hope it will provide some insight from my experiences, but you need to study both the science and the practice of microbiology to effectively lead this technical function. Microbiology is not easy and it is not something you can learn exclusively from a book. Find some time to get to the bench.

Finally, this book is directed to upper management. Microbiology is a technical field that requires years of study and practice to learn (if indeed the learning ever really ends). It is difficult to find competent scientists who can lead a lab, but even the most brilliant scientist in one field is not necessarily the best choice to lead another scientific discipline. New workers must be trained in good laboratory practice by their supervisors — this training is better done by those who have years of microbiology lab experience. There are fundamental biosafety issues involved in dealing with infectious agents. It is the responsibility of your lab head to establish adequate containment procedures to protect lab workers. In addition, the successful execution of microbiology testing requires experienced leadership providing effective guidance in terms of training and procedures to avoid repeated test failures and unnecessary investigations. Finally, while there is a real need to minimize overheads and to speed up product release, I hope that this treatment of the microbiology function will help management understand the trade-off between well-controlled and well-executed tests on the one hand, and uncertain microbiology data with the opportunity to conduct many investigations into unforeseen results on the other.

This book is not meant as an exhaustive treatise on the role of microbiology in support of manufacturing. Those books mentioned above would be much better for review of the details, but who reads 600-page textbooks? Specific chapters in these books are referenced at the end of each chapter for convenience in answering specific questions. This book is meant to provide the flavor of the microbiology function (at least from my, admittedly subjective, perspective — I *like* microbiology), and some guidance on lab and testing concerns that might help minimize unfortunate lab-induced situations. In addition to these reference books I would also recommend several internet resources:*

- The PMFList — an email list devoted to industrial microbiology. Information at *http://www.microbiol.org/pmflist.htm*.
- The PSDGList — an email list devoted to pharmaceutical stability study issues. Information at *http://www.microbiol.org/psdglist.htm*.
- The PMF Newsletter — information and archives available through *http://www.microbiologyforum.org*.
- The Rapid Microbiology User's Group (RMUG) post newsletters and information available at *http://www.rapidmicro.org*.
- The PDA's PharmSciTech discussion group — an email list devoted to pharmaceutical issues of all kinds. Information available at *http://www.pharmweb.net/pwmirror/pwg/pharmwebg2.html*.

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I hope you find this book useful.

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REFERENCE

McCormick, D. (2006). Poor OOS Review Lead Causes of FDA Citations. *Pharm Technol*. **30**(12):18.