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Leachables and Extractables Handbook: Safety Evaluation, Qualification, and Best Practices-Applied to Inhalation Drug Products. Hoboken, New Jersey: John Wiley & Sons, Inc, 2012. 683 pp. $125.00
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The well-known proverb "Don't judge a book by its cover" is, at first glance, confirmed by Leachables and Extractables Handbook: Safety Evaluation, Qualification, and Best Practices Applied to Inhalation Drug Products. The eye-catching phrase, "Leachables and Extractables Handbook" is designed on the cover to attract attention; however, "Inhalation Drug Products," which is in smaller print and at the end of the long title, identifies the focus and the primary audience for the book. Nonetheless, the book contains information appropriate for toxicologists who are required to conduct toxicological analyses and make risk assessments of trace materials and chemicals associated with manufacturing, transporting, using, and disposing of chemicals not directly associated with medical devices that are specifically used for inhalation therapeutics. The editorial liberty exercised by the editors and publishers for the book's title is not only justified but commendable since human health risk assessments for leachables and extractables span a wide variety of circumstances and products which toxicologists are required to address.

The 4 editors of handbook solicited 49 authors who wrote 21 chapters and 4 appendixes. The 21 chapters are segregated into 2 parts. The first part entitled "Development of Safety Thresholds, Safety Evaluation, and Qualification of Extractables and Leachables in Orally Inhaled and Nasal Drug Products," consists of 9 chapters and constitutes approximately 23% of the handbook. The second part titled, "Best Practices for Evaluation and Management of Extractables and Leachables in Orally Inhaled and Nasal Drug Products" comprises approximately 69% of the handbook. The remaining 8% of the handbook is devoted to 4 appendixes.

The chapters in both part I and part II have the same basic structure: a brief introduction section or paragraph, the body of the subject material, a concluding section which is, in most cases, a combination of a summary and conclusion and finally a reference list. The sections within the chapters are numbered with appropriately numbered subtopics so as to give the chapters a cohesive outline structure. Unfortunately, the chapters do not have a numbered outline section at the beginning of the chapter and consequently, the reader must search through the chapter, page by page to understand the scope of the chapter's content rather than being able to view the breadth of the treatment at a glance.

The 9 chapters that comprise part I lay the foundation for the handbook's value found in part II. Chapter I gives an overview by describing the issues associated with leachables and extractables in orally inhaled and nasal therapeutic delivery systems and how the handbook will address them. The second chapter describes, in a broad way, how and why materials are established as suitable for

respiratory delivery devices. Chapters 3 to 7 lay out, principally for non-toxicologists, the hazard determination and risk assessment processes. Chapters 8 and 9 describe how the hazard determination, quantification of potential toxicants and then ultimately the risk assessment steps fit into the regulatory framework. Part I, with it component chapters, is an excellent foundation for the substance of the handbook which is contained in part II.

The 12 chapters in part II along with the 4 appendixes constitute the substance and hence the value of the handbook. Factual material, techniques, and suggested procedures are brought to life with copious examples that are identified in case studies. Two complete chapters, one on sulfur-cured elastomer and the other on polypropylene extractables, are case studies, and the chapter on sulfur-cured elastomer contains additional case studies within the chapter that embellish the overriding case study that is the topic of the chapter. One gets the impression that the authors have a sense of anticipation for what the readers would want to ask, perhaps because they have asked the same questions in their past experiences.

Chapter 18 "Development, Optimization, and Validation of Methods for Routine Testing" is noteworthy for several reasons. The 57 page chapter with 2 case studies is a road map for quality assurance/quality control for leachables and extractables to be sure but it can also serve as a framework for the practicing toxicologist to identify potentially troublesome chemicals after the drug product is made. In addition, the toxicologist will be able to assess the level of attention he or she should give to chemicals derived from the container and delivery system in the context of the risk assessment of the active ingredients of the drug. In another words, the toxicologist can elevate a risk assessment of a drug to a risk assessment of a product, that is, active ingredient plus its container and delivery system. Chapter 18 provides an opportunity for a practicing toxicologist to add value to his or her risk assessment.

For all of its value, the handbook has 2 flaws. While not fatal, the flaws can make the handbook difficult, and at times, punishing to use. Furthermore, these flaws of omission limit the value of the handbook's content when, in fact, the principles articulated in the book have application beyond the limited audience of those associated only with developing and providing toxicological support and human health risk assessments for inhalation drug products.

The first flaw is that the book does not have a list of abbreviations where a reader can go to translate an unfamiliar acronym and the authors were prolific with their use of acronyms. For example, on page 64: "The AET is officially defined by PQRI ... [for] OINDP ...." A reader unfamiliar with the jargon in the sentence will require several minutes to locate the translation of the acronyms in the text. Using acronyms is necessary but the bludgeoning experience for the reader can be mitigated with an abbreviation list. The second flaw is that the chapters lack an outline at the beginning of each chapter indicating what topics are covered in the chapter so that the reader, with one quick glance, can focus his or her search and determine whether a particular issue is covered in the chapter without thumbing through the entire chapter.

While the editors and authors acquired their experiences from inhalation products for writing the handbook, the approach, process, and methods for assessing human health risks for leachable chemicals from product container and delivery systems is universal. The product can be an inhalation drug, a liquid drug formulation, a solution for injection, or even a food product. Previously published information provides validation for the handbook's content. While the

principles and approaches have been validated in peer-reviewed scientific journals, the journal articles do not serve as a substitute for the handbook. All toxicologists can and should judge *Leachables and Extractables Handbook: Safety Evaluation, Qualification, and Best Practices Applied to Inhalation Drug Products* by its cover and the complete title with special attention to the phrase "applied to." The value of the handbook for all toxicologists is based on the fact that it is a framework for addressing human health risks for packaged products without limitation to inhaled drug products.

References

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