COMPATIBILITY OF PHARMACEUTICAL PRODUCTS AND CONTACT MATERIALS

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Safety Considerations Associated with Extractables and Leachables

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To My Family,
In case you were wondering, this is where all that time went.

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PREFACE

I think it was at the 2005 Extractables and Leachables Forum, sponsored by the PDA, where someone said those fateful words, "Someone ought to write a book about this stuff". Having never understood the thin line that separates wisdom from folly, pragmatism from naïveté, and diversion from torment, I thought the idea had sufficient merit that I would give it a shot. In retrospect, I am not sure whether this kind of thinking is a strong recommendation for this book or not.

There is an old and respected saying that goes "but first do no harm". This statement is the essence of how leachables and extractables relate to therapeutic products. In order for a therapeutic product to be effectively utilized to achieve the desirable goal of improving the human condition, it must be manufactured, packaged, stored, and administered. Systems that perform these functions are thus a necessary, important, and beneficial contributor to therapeutic practice. An ideal system would perform its required function (the positive benefit) without interacting with the therapeutic product (the potentially negative harm). Alas, the development of systems that are truly inert remains a goal, as opposed to an accomplishment, of modern material science. Interactions between systems and products are well known and documented. It is incumbent on the producers and users of such systems to demonstrate that any interaction occurring between a system and a therapeutic product has no meaningful effect on the composition of that product.

While regulations and standard practices have been developed to accomplish the task of demonstrating "no impact", such regulations and practices are either general, high level, or strategic in nature and/or are part of a fragmented general literature on the topic of system–product compatibility. Members of the regulatory and industrial communities who find it necessary to assess system–product interactions struggle mightily to develop, implement, and report effective, efficient, standardized, and scientifically sound strategies and tactics for performing such compatibility assessments.

This juxtaposition establishes the driving force behind this book. This book attempted to answer two major questions; What do we have to do? and When do we have to do it? It looks at the multiple aspects of both safety assessment and therapeutic product development and notes that if safety assessment and product development were to start at the same time, there are logical time connections between the two. That is, both safety assessment and product development activities are facilitated if these two processes are performed in an orderly manner and furthermore are linked in terms of timing. Thus, for example, the right time to evaluate, screen, and identify materials to be used for systems to manufacture, store, or deliver therapeutic products is in the early stages of the development of the therapeutic product. Similarly, the right time to validate an analytical method for the purpose of monitoring leachables over shelf-life is when the therapeutic product is well into its development.

A few words about the construction of this book are relevant. The book is loosely constructed around a timeline that delineates the major activities associated with the safety assessment of extractables and leachables. The reader is introduced to general concepts in Chapters 1 and 2. Chapter 1 serves to introduce the topic of the safety assessment of extractables and leachables and provides an overview of pertinent regulations. Chapter 2 defines the nomenclature that is used in the book and hopefully facilitates understanding and order in the general scientific community. As is the case with many endeavors that involve complex generalities and subtle nuances, being able to fall back on a clear and common language is a key to moving forward. Chapter 3 defines the product life cycle and establishes the link between activities that occur during a product's life cycle and the major activities associated with safety assessments of extractables and leachables. As such, Chapter 3 provides the structure upon which the remainder of the book is based. Chapter 3 answers the questions noted previously (what to do and when to do it) in a general sense while the following chapters address individual activities in much greater detail.

Before one has a system or construct that contacts a therapeutic product, there is a set of materials that the construct is made of. It is reasonable to assume that these materials were chosen for use in the construct based on sound reasoning, which presumably includes a consideration of their extractables characteristics. Chapter 4 considers the processes of material characterization and the utilization of characterization information in the material screening process. The utility of compendial testing is considered, a framework for constructive interactions between vendors and users of materials in terms of extractables information is defined and specific tactics for material characterization studies are discussed and illustrated with case studies.

A construct that is made up of appropriate materials and is made by an appropriate manufacturing process undergoes significant testing from the time it is first proposed as a prototype, through its development and optimization, and finally to the time it is launched as a part of an approved final product. At some time in this process, the construct, and its associated therapeutic product, must undergo a leachables assessment to support the product's registration. It is reasonable to anticipate that one of the product requirements would be that the construct "contributes safe levels of leachables to the therapeutic product". Such a leachables assessment should (must) be performed on the final construct, manufactured by the final production process, and contacted by the finalized therapeutic product. If there are no extractables and leachables activities that occur between material selection and final product testing, then one has not practiced effective risk management because one has essentially "bet the farm" on obtaining a "clean bill of health" as a result of the leachables testing. Additionally, there are certain things that need to be in place (e.g., a list of target leachables and validated test methods) in order to perform the leachables assessment. Thus the next section of the text deals with Construct Qualification, which includes performing a preliminary, product simulating extraction study and toxicological assessment (Chapter 5) and doing the assay work required to "gear up" for a leachables study (Chapter 6). The points made in both Chapters 5 and 6 are illustrated via several case studies.

In qualifying a construct, one has either established that the probable safety risk associated with utilization of the construct with a therapeutic product is low, in which case the product development activity continues toward completion (i.e., marketing of the product), or that the probable safety risk is high, in which case product development is "sidetracked" as a strategy is developed to mitigate, reduce, or eliminate the risk. However, it is clear that qualifying and validating a

construct are two completely different situations. Construct validation is thus the next segment of a product's life cycle that is considered in the book. The term validation can be generally defined as the process by which a system is demonstrated to meets its performance requirements. In the context of safety assessment, construct validation is accomplished in that study that definitely establishes the levels of construct-related leachables present in the therapeutic product. In the language of the European Guidelines for Plastic Immediate Packaging Materials, this study is termed a migration study. Chapter 7 deals with the details associated with the migration study and the toxicological interpretation of the generated data. This chapter also considers in detail how one might handle "disasters" that can occur in a migration study, for example, the sudden appearance of a "new" leachable or unanticipated trends in leachables data.

Clearly, the whole process of safety assessment is directed toward submitting the information to a regulatory agency for the purpose of securing approval to market. Chapter 8 considers the content and construction of the extractables–leachables portion of a product registration dossier, specifically with respect to the Common Technical Document. Chapter 9 provides some practical insights on how one might handle the dossier-related questions that might be received from the product's regulatory reviewer.

Once the product has been approved and is "in the field", it must be supported and maintained during its (hopefully) long, impactful, and profitable market lifetime. Chapter 10 considers critical aspects of Product Maintenance (from an extractables and leachables perspective), including ongoing quality control, change control, and disaster management.

Eventually, the product has "had its run" and is withdrawn (retired) from the field. Chapter 11 briefly considers the utilization and disposition of the E&L information that has been accumulated over the product's useful lifetime.

Chapter 12 provides an opportunity to address specific issues related to extractables and leachables. It starts with a discussion of the efforts to develop and standardize methods and methodologies to address extractables and process related impurities from plastic-based manufacturing systems (i.e., the so-called single-use, or disposable, manufacturing systems). It continues with a discussion of the Best Demonstrated Practices that were established by a PQRI Working Group for performing extractables and leachables assessment for container closure systems encountered in inhalation drug products. It contains a brief synopsis of suitability for use consideration for container closures other

than safety. It summarizes the practical considerations that are relevant in terms of deciding what resources are required in performing E&L assessments and where those resources might exist. Finally, it provides this author with the opportunity to look forward into the near future and speculate on what developments in E&L assessments are out there just over the horizon.

Lastly, an Appendix provides information such as name, CAS registry number, chemical formula and molecular weight for extractables and/or leachables that have been reported in the literature.

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One readily notes my affiliation with the Baxter International Inc. It is possible that a reader could note that affiliation and conclude that "all the practices, specifically stated and implied in this book, are utilized at Baxter" or that "this book reflects the policies and procedures, tactics and strategies utilized by Baxter to develop, assess and register their products". This is not the case and any such inferences are inaccurate and incorrect. In fact, the information contained within this

book reflects input from a number of companies, organizations and individuals who are actively engaged in the process of compatibility assessment and, to the best of my knowledge, the sum total of the concepts, methodologies, strategies, tactics, recommendations, and suggestions contained in this book are not practiced by any single organization, including, but not limited to Baxter.

PART A

GENERAL CONCEPTS

1

INTRODUCTION

GENERAL DISCUSSION

Materials such as plastics, glasses, and metals, are widely used in medical constructs, for example, containers, packaging systems, sets, transfer and transport systems, manufacturing systems–facilities, and devices. The physiochemical nature of these materials provides medical products with their necessary and desirable performance characteristics. A number of medical products involve constructs (objects constructed in whole or in part from materials) whose primary purpose is the generation, production, transport, storage, and/or delivery of therapeutic products that are used either directly or indirectly by patients to produce a desirable therapeutic outcome. Additionally, such constructs may be used for the same purposes with precursors of the therapeutic product. Less frequently, such constructs themselves may provide the therapeutic benefit.

While an important performance characteristic of materials (or systems) used in medical applications is chemical inertness, interactions between a material (or system) and the pharmaceutical product it contacts are well documented. Such interactions may include sorption (binding), the uptake of product components by the material, or

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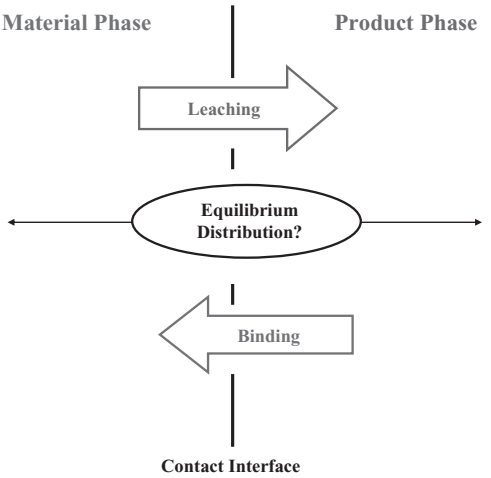

Fig. 1.1. Interactions between a therapeutic product and a material (plastic) phase. Such interactions include leaching, the migration of material-related components into the product, and binding the sorption of product ingredients by the material. Both processes impact the drug product's final composition at its time of use and thus its safety and/or efficacy. *Note*: the arrows denote the direction of solute movement. The oval represents a solute molecule, which can end up in either phase at equilibrium.

leaching the release of material-related components to the product (Fig. 1.1). Instances in which such an interaction can impact the therapeutic product, from either an efficacy and/or safety perspective, also have been reported. As a recent example, the leaching of a vulcanizing agent from uncoated stoppers used in prefilled syringes has been proposed as a mechanism contributing to adverse clinical events associated with EPREX®.[1] Other recent examples of leachables exerting an undesirable influence on therapeutic products have also been documented.[2,3] These recent examples augment a long history of instances where the safety or efficacy of a therapeutic product has been compromised by its interaction with a construct.

As outlined in relevant regulatory policies, procedures, and guidelines, any contact between a construct and therapeutic substance, which may or may not be a finished drug product, is an opportunity for that substance to be changed as a result of that contact. The purpose of a construct's compatibility evaluation is to assess the magnitude, if any, of such a change. By convention, if little or no change occurs, then it is concluded that the construct and the therapeutic substance are compatible. A complete compatibility assessment considers numerous potential outcomes of the construct–substance interaction, as illustrated