Evaluation of the Chemical Compatibility of Plastic Contact Materials and Pharmaceutical Products; Safety Considerations Related to Extractables and Leachables

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ABSTRACT: A review is provided on the general topic of the compatibility of plastic materials with pharmaceutical products, with specific emphasis on the safety aspects associated with extractables and leachables related to such plastic materials. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 96:2566–2581, 2007

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INTRODUCTION

Plastic materials are widely used in medical products, such as containers, packaging systems, sets, transfer tubing, manufacturing systems and aids and devices. The unique physiochemical nature of the material utilized provides the necessary and desirable performance characteristics. A number of medical products involve plastic constructs whose primary purpose is the storage, packaging, delivery, generation and/or transport of items that are used either directly or indirectly by patients to produce a desirable therapeutic outcome. Additionally, such plastic constructs may be used for the same purposes with precursors of the therapeutic materials. Less frequently, such plastic constructs themselves may provide the therapeutic benefit. While an important performance characteristic of plastics used in medical applications is chemical inertness, interactions between a plastic material and the pharmaceutical product it contacts are well documented. Instances in which such an interaction can impact the medical product, from either an efficacy and/or safety perspective, have also been reported. As a recent example, the leaching of a vulcanizing agent from uncoated stoppers used in pre-filled syringes has been proposed as a mechanism contributing to adverse clinical events associated with EPREX®.[1]

As outlined in relevant regulatory policies, procedures, and guidelines, any contact between a plastic construct and therapeutic agent is an opportunity for that agent to be changed as a result of that contact. The purpose of a construct's chemical compatibility evaluation is to assess the magnitude, if any, of such changes.

DIMENSIONS OF COMPATABILITY ASSESSMENT

A complete compatibility assessment considers numerous potential outcomes of the product/construct interaction, as illustrated in Figure 1. In the most general sense, specific aspects of a compatibility assessment address either the issues of product efficacy (does the product per-

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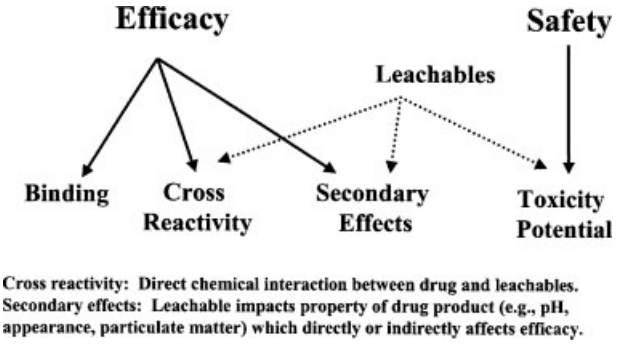

Figure 1. Dimensions of compatibility assessment.

form in a manner consistent with its labeling and indication) or product safety (does the product produce an unanticipated and adverse user response). Considering efficacy, while drug binding (loss of ingredient from the product due to its uptake by the plastic construct) is the most typically documented efficacy-impacting interaction, other types of interactions are possible and significant. For example, cross-reactivity refers to the situation in which a specific leached substance and a product ingredient interact chemically, resulting in the ingredient's decomposition and/or inactivation. This interaction may be direct or indirect, for example, via a catalytic action. Additionally, it is noted that efficacy does not solely reflect a product's ability to deliver its specified therapeutic dose. Secondary effects reflect those instances where a property of the leachable itself has an impact on the chemical or physical characteristics of the drug product. Examples of such secondary effects include (1) an acidic or basic leachable whose accumulation pushes a product outside of its pH specification, (2) a leachable which causes the formation of particulate matter, and (c) a leachable whose accumulation has an adverse spectral effect (e.g., discoloration, high UV absorbance). In the extreme situation, the secondary effect may not be manifested in an undesirable drug product but rather as an undesirable plastic construct, which may lose its ability to perform its desired function due to the product/construct interaction.

In general, the literature associated with compatibility assessment can be divided into three categories: (1) regulatory guidance, (2) strategies and tactics to meet the requirements, and (3) case studies. This review will consider the requirements for compatibility in a general sense and then will focus specifically on the area of assessing the safety implications of extractables and leachables in terms of strategies, tactics and case studies.

REGULATORY GUIDANCE FOR COMPATIBILITY ASSESSMENTS

As one might expect, the requirements for compatibility assessments are contained within the context of legislation and its associated regulations. Relevant regulatory guidance in terms of such evaluations is considered as follows.

Container Closure Systems for Packaging Human Drugs and Biologicals

The Federal Food, Drug and Cosmetic Act (the Act) mandates the need for adequate information related to packaging materials. Section 501 (a)(3) of the Act states that a drug is deemed to be adulterated "if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health. . .". In response to this Mandate, the Federal Food and Drug Administration (FDA) published its "Guidance for Industry: Container Closure Systems for Packaging of Human Drugs and Biologics" in 1999.[2] This document is intended to provide guidance on general principles for submitting information on packaging materials used for human drugs and biologics. In general, that Guidance did not suggest specific test methods and acceptance criteria, nor did it suggest comprehensive lists of tests. Rather it suggests that such details should be determined based on good scientific principles. The Guidance specifies that every packaging system should be shown to be suitable for its intended use, where suitability includes the expectations that (a) the system should be composed of materials that are considered safe for use with the dosage form and route of administration and (b) packaging components will not interact sufficiently to cause unacceptable changes in the quality of either the dosage form or the packaging component. The guidance notes that packaging components should be constructed of materials that will not leach harmful or undesirable amounts of substances to which the patient will be exposed when being treated with the drug product. For a drug product such as an injection, inhalation, ophthalmic or transdermal, a comprehensive assessment is appropriate. Such an assessment involves two parts: an extraction study on the packaging component to determine which chemical species