MINI-REVIEW

On Developing a Process for Conducting Extractable–Leachable Assessment of Components Used for Storage of Biopharmaceuticals

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ABSTRACT: Extractables and leachables are product-related impurities that result from product contact with components such as gaskets, stoppers, storage bags, cartridges, and prefilled syringes that are used for processing, storage, and/or delivery of biopharmaceuticals. These impurities are a concern for patients due to potential effects on product quality and safety. It is possible that such an impurity could directly impact the patient or indirectly impact the patient by interacting with the protein therapeutics and forming protein adducts. Adducts and leachables may or may not be detected as product-related impurities in routine stability indicating assays depending on the rigor of the analytical program. The need for the development of a thorough and holistic extractable and leachable program based on risk assessment, review of existing literature, and consolidation of industry best practices is discussed. Standardizing component use within an organization enables streamlining of the extractable–leachable program. Our strategy for an extractable–leachable program is divided into different stages, each stage detailing the activities and the department within the organization that is responsible for execution of these activities. The roles and responsibilities of the key stakeholders are identified. The integration of analytical activities with health-based risk-assessment information into the design of an extractable–leachable program is highlighted. © 2009 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:2209–2218, 2010

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INTRODUCTION

Extractables are a class of compounds released from a component under aggressive treatment conditions; those that exceed what a component may endure during normal use (e.g., extended time, increased

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temperature and ionic strength, pH extremes). Leachables are a class of compounds that emanate from a component into the drug substance or drug product under normal conditions and are typically a subset of extractables. Wang and Chien[1] extensively reviewed the kinetics models and factors that affect leaching phenomena in 1984. Leaching typically occurs upon migration of dissolved solute through the polymer matrix. The rate of leaching is diffusion controlled, and the amount of leachable is in proportion to the square root of time. The diffusion of organic substances in polymer matrix is also governed by activation energy that is in the range of 10–13 kcal/mol, thus one can expect the rate to double for every 10°C increase in temperature.[2,3] On the other hand, leaching of plasticizer from polyvinyl chloride (PVC) bags follows a linear relationship with time because the plasticizer is present in large concentration and encounters a nontortuous path by which the leaching substance can diffuse. Early efforts to detect extractables or leachables have employed UV spectroscopy or other nonspecific methodologies. A pioneering work on identifying extractables in a biotechnology product was conducted using LC in series with electrospray MS. In this study, butylated hydroxy toluene (BHT) and a polymer species were identified as extractables when acetonitrile was used as the extraction medium. However, these substances were not found in the drug product when extracted with the protein formulation or buffer formulation.[4]

In recent years the Eprex® case has had a major impact on the regulatory scrutiny related to extractables and leachables. There were 175 cases of epoetin-associated pure red-cell aplasia (PRCA) reported for Eprex® between 1998 and 2004. Most of these cases involved patients with chronic kidney disease who had received subcutaneous injections of epoetin.[5] The phenolic derivatives that leached from the rubber stopper, used in prefilled syringes, into the formulation were postulated to be a causative agent for the immunogenic response observed.[6–8] It was proposed that the presence of polysorbate 80, the stabilizer employed to replace human serum albumin in the second-generation drug product formulation, induced the leaching of these phenolic derivatives.[8,9] Although a clear association between the presence of these leachables and the incidence of PRCA could not be demonstrated, the decrease in instances of PRCA did coincide with the change in the stopper configuration from the original uncoated stopper to the current Teflon-coated stopper.[5,7] The incidences of Eprex®-related PRCA dropped significantly after additional changes were applied to storage and handling and the route of administration was changed from subcutaneous (SC) to intravenous (IV) route. Another factor that was identified as a potential cause for the immunogenicity was modification of epoetin when associated with polysorbate micelles.[10] In a recent study, Mueller et al.[11] investigated the "immunogenicity potential" of extractables and leachables from three drug product stoppers using dendritic cell models. Activation of dendritic cells was monitored by analyzing the expression levels of the costimulatory molecule CD86. The stoppers evaluated in this investigation included the PH 4106 stopper reported to be a component of the Eprex® prefilled syringe. This investigation suggested that it is not the extractables and leachables from these different stoppers that lead to an increase in the dendritic readout. Instead, the hydrolytic breakdown product of polysorbate 80, oleic acid, as well as other follow-up products were identified as plausible factors responsible for the increase in the dendritic activation. Other factors such as leached silicone oil, a lubricant used in the prefilled syringe, have also been considered as potential causes for increase in immunogencity.[9]

Novel drug-delivery technologies such as prefilled syringes and pen-injector systems have also necessitated scrutiny of leachables as new materials are introduced to product contact. These devices consist of components such as plungers, stoppers, lined seals, and needles, each having the potential to leach chemicals into the drug product formulation.[12–14] Additionally, these components utilize lubricants such as a silicone oil to coat the internal surface of the syringe barrel to ease motion of the plunger. Silicone oil is also applied to the exteriors of the hypodermic needle to ease movement through the epidermis during subcutaneous injections. Thirumangalathu et al.[15] have demonstrated that the biophysical stability of monoclonal antibodies (MAbs) is adversely impacted by the presence of silicone oil in formulations. The presence of silicone oil at levels above 0.5% (w/v) was also shown to increase aggregation under accelerated conditions for four model proteins: ribonuclease A, lysozyme, bovine serum albumin, and concanavalin A.[16] Studies with MAbs incubated in the presence of silicone oil have shown that the protein adsorbs as a monolayer to the surface of the silicone oil particle. The combination of silicone oil and agitation stress was also shown to lead to protein aggregation.[15] Contamination of drug product caused by leaching of silicone oil has also been implicated as a factor responsible for aggregation of insulin in disposable plastic syringes.[17–19] Prefilled syringe manufacture requires use of a heated tungsten rod to obtain a needle bore on the syringe. The tungsten wires are known to vaporize and erode during use, depositing a layer of tungsten along the needle bore that comes in contact with the product.[20] Bee et al.[13] demonstrated that the formation of soluble tungsten polyanions in formulations at