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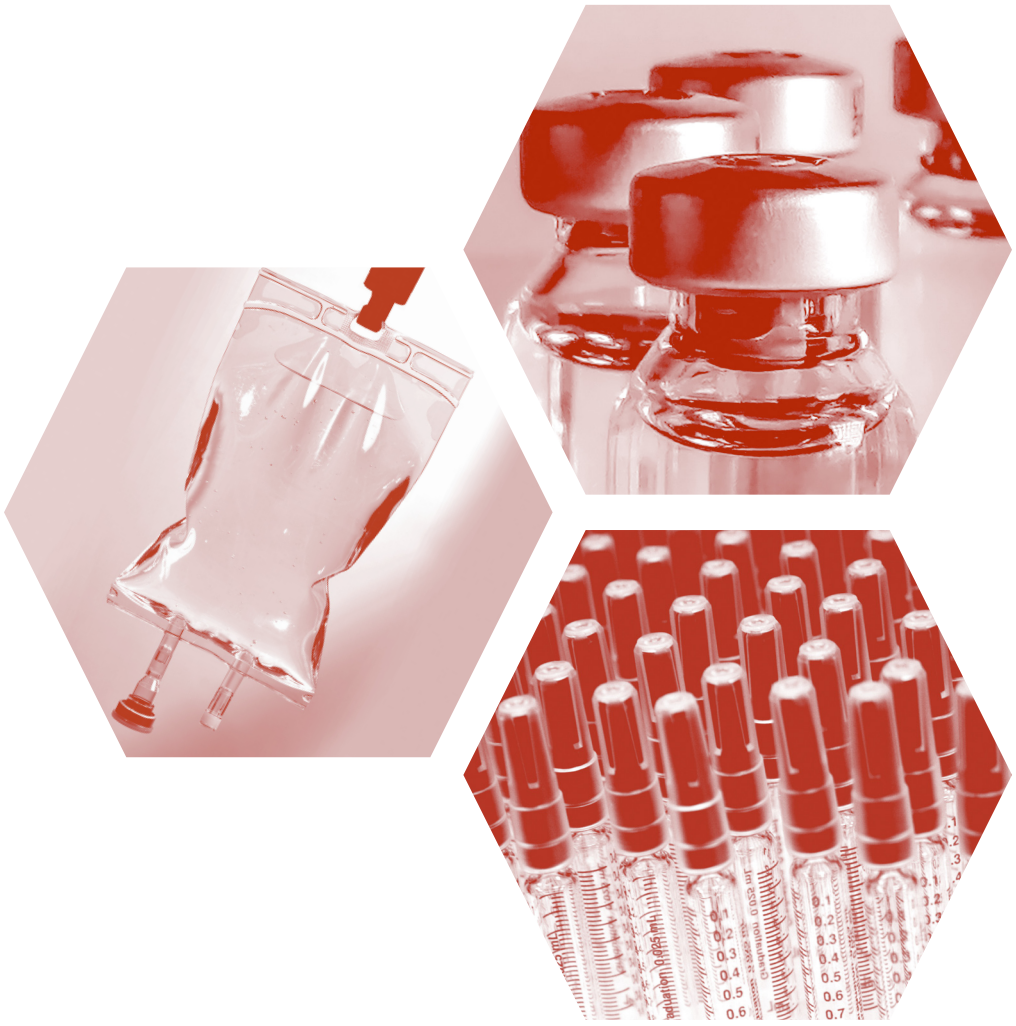
Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (Intravenous, Subcutaneous, and Intramuscular)



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Submitted to the PQRI Development Technical Committee, PQRI Steering Committee and US Food and Drug Administration by the PQRI PODP Leachables and Extractables Working Group

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Forward

Leachables in drug products that originate from the components used in packaging, delivery and manufacturing systems can compromise the quality of drug products and impact patient safety. The materials of construction associated with these components should be assessed for suitability in early drug development phases based on extractable profiles and correlated to potential and confirmed leachables. In 1999 the PQRI Leachables and Extractables (L&E) Working Group was established with the goal of reducing leachable uncertainty in Orally Inhaled and Nasal Drug Products (OINDP), using a science and risked based approach. The Working Group was made up of highly experienced scientists including toxicologists, analytical chemists, and others, from industry, government, and academia. The culmination of these efforts resulted in E&L recommendations to the USFDA. "Safety Thresholds and Best Practices for Extractable and Leachables in OINDP" was published in 2006 and since has been recognized by FDA and global regulatory authorities.

In 2008 the Parenteral and Ophthalmic Drug Product (PODP) L&E Working Group was formed to extrapolate the OINDP risked–based approach for evaluation and safety qualification of extractables and leachables in PODP. Specific factors associated with parenteral and ophthalmic drug products were considered that included patient population, dose, duration, and additional product-dependent characteristics. The PODP L&E Working Group conducted and evaluated the results of extraction studies on polymeric materials and evaluated a database of over 600 potential leachables using existing toxicological qualification approaches to justify thresholds for PODP. The proposed PODP identification and qualification thresholds were published in a 2013 manuscript followed by workshops. Subsequently, recommendations for "Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (PDP)," was thoroughly examined and consideration was given to factors related to new modalities. After rigorous review from industry and regulators a consensus was reached.

This document describes recommendations for E&L assessments of small volume, large volume parenterals and prefilled syringes with additional considerations for biological products. The field of biological products is rapidly advancing and with unique risks to product quality and patient safety. Study designs for E&L will consider intended use and regulatory jurisdiction and should be discussed early with the Regulatory Agency to understand proper application of the analytical evaluation threshold (AET), extraction concentrations, solvents, exposure conditions and analysis. There are unique considerations for ophthalmic drug products (ODP), and safety thresholds do not apply. Because of the unique considerations for ophthalmic drug products, extractables and leachables assessments are described in a separate manuscript entitled, "Principles for Management of Extractables and Leachables in Ophthalmic Drug Products." PDA Journal of Pharmaceutical Science and Technology February 2022, pdajpst.2022.012744. DOI: https://doi.org/10.5731/pdajpst.2022.012744. Parenteral products administered by the intrathecal, intra-cerebroventricular, intra-articular, epidural, and perineural routes are out of scope. The PDP recommendations were the result of understanding a broad range of E&L applications over several years of building consensus with leaders in scientific and regulatory community. The views expressed in these documents are not necessarily those of individual companies or US Food and Drug Administration.

Contributions of individuals from the core team, extended teams, reviewers and advisors are sincerely appreciated. The members of the PODP L&E Working Group acknowledges the Product Quality Research Institute and its member organizations for providing this forum to make this collaboration possible. We also would like to recognize the dedicated scientists in volunteer laboratories that provided the essential data to make the reccomendations possible.

The Working Group hopes that the recommendations contained in this document will serve to guide the pharmaceutical development process for PDP and facilitate the approval and manufacture of safe, effective, and quality medicines.

On behalf of the PQRI PODP L&E WG

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