The Use of Scientifically-Justified Threshold Levels in the Safety Evaluation of Leachables for a Small Volume Parenteral Product

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Abstract

Contemporary parenteral drug products make use of the advantages that modern container closure systems and materials provide for technical and functional purposes as well as marketing/brand recognition. Despite the advantages, these systems also present the potential for contributing impurities to the formulated drug product in the form of leachables. As with any impurity, since leachables do not provide any therapeutic benefit to the patient using the drug, their presence only makes for concerns for safety as related to inadvertent exposure. As such, the drug developer has an obligation to demonstrate the biological safety of any leachable substances when the drug product is used as intended. Doing so can present numerous challenges to the scientist involved in the risk assessment evaluation, especially when the available information for the evaluation is limited in terms of the toxicological potential of any of the substances that emerge as leachables. In recognition of the obstacle that limited data presents, the PQRI Toxicology team has developed scientifically-justified threshold levels for safety evaluation of leachables from parenteral drug products. The application of those threshold levels when compound-specific data is either inadequate or unavailable is demonstrated in this example.

Introduction

A leachable study was conducted for a small volume intravenous drug product. The IV bags were composed of a multilayered plastic with tubing and connectors for both filling operations and administration of the drug product. Each component of the bag first underwent controlled extraction studies, and selected analytes were then targeted as potential leachables in the drug product. The drug product formulation is primarily aqueous, but contains a solubilizer due to the chemical properties of the active pharmaceutical ingredient. In addition to solubilizing the active ingredient, the formulation also results in the leaching of analytes which would not otherwise migrate into an aqueous product.

Experimental

Leachable testing was conducted on authentic drug product samples stored in the container closure system over 2 years at 25C, and over 6 months at 40C.

Analytical techniques consisted of both GC-FID and HPLC-UV.

Methods for sample preparation were developed and validated to achieve appropriate limits of detection, and included liquid-liquid extraction and concentration under nitrogen.

- The analytes reported are the maximum concentrations measured over the cited conditions and timeframe. Total daily doses were calculated based on highest concentration and the total daily volume delivered , based on the use conditions of the drug product.

Results and Discussion

Leachable	Genotoxic?	Sensitizer?	Dose (µg/day)
Aliphatic Saturated Acids			
Lauric Acid	No	No	65
Myristic Acid	No	No	110
Palmitic Acid	No	No	158
Stearic Acid	No	No	64
Aliphatic Monounsaturated Acids			
Palmitoleic Acid	No	No	96
Oleic Acid	No	No	189
Ester			
Tributyl Phosphate	No	No	25
Aliphatic Ketones			
3-Heptadecanone	No	No	158
3-Heneicosanone	No	No	98
Aliphatic Alkenes			
1-Octadecene	No	No	157
1-Eicosene	No	No	110
9- Octadecene	No	No	143
Antioxidant-Related			
Irganox 1520	No	Yes	3
Clarifying Agent			
Bis(3,4-dimethylbenzylidene) sorbitol	No	No	43

Results and Discussion

Application of proposed PQRI Thresholds

	Class 1	Class II	Class III
Level (µg/day)	150	5	1.5

- 14 leachables were identified and quantified from migration studies conducted with the drug product.
- No genotoxic compounds were identified as leachables.
- One compound (Irganox 1520) was classified as a sensitizer, however the inadvertent dose was below the proposed sensitization/irritation threshold of 5 µg/day. Therefore, no additional qualification was deemed necessary.
- Of the remaining 13 leachables that were not genotoxic or sensitizers, 9 were below the proposed PQRI general qualification threshold of 150 µg/day.
- An acceptable daily intake (ADI) was calculated for bis(3,4-dimethylbenzylidene) sorbitol using an ICH algorithm and reference to compound-specific toxicology data.

ADI = NOEL x Mass Adjustment/[F1 x F2 x F3 x F4 x F5]

ADI = 123 mg/kg/day (rat NOEL/13-week study) x 50 kg/5 x 10 x 5 x 1 x 1 = 24.6 mg/day ÷ 10 (change in route of administration) = 2.46 mg/day

- Four leachables that exceeded the general qualification threshold of 150 µg/day (i.e. palmitic acid, oleic acid, 3-heptadecanone, and 1-octadecene) would require additional justification of safety based on supporting data, as appropriate.

Conclusions

- Scientifically-justified threshold levels can be applied for the safety evaluation of leachable substances.
- Such applications will be dependent on:
  - The estimated daily dose of the leachable, which is a function of the concentration of the leachable in the drug product
  - The use conditions of the drug product.
  - And as a consequence, may differ for the same leachable, from product to product.

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