U.S. Food and Drug Administration
Protecting and Promoting Public Health

Regulatory Perspective on Safety Qualification of Extractables and Leachables

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PQRI Workshop on Thresholds and Best Practices for Parenteral and Ophthal
Drug Products (PODP)

Risk-based Approach in Evaluating E&L

- **Safety considerations** (e.g., toxicity, immunogenicity, etc.)
- **Efficacy considerations** (e.g., L interacting wit a product → loss of activity; L may induce development of neutralizing activity via NAb formation)
- **Quality considerations** (e.g., impact on the manufacturing process, product stability, etc.

Safety considerations

- **Toxicity (e.g., acute, chronic, synergistic, additive, carcinogeni endocrine dysregulation, etc.)**
- **Adjuvant effects:**
  - **Adjuvants are substances that increase the activity of the immune system without having any specific antigenic effect**
  - **In contrast to vaccines where adjuvant effect is a desired effect, th may be a serious safety concern for therapeutic proteins**
  - **May promote development of anti-drug antibodies**
    - **A decrease or loss of efficacy due to development of neutralizing**
    - **May be life-threatening if NAbs are developed against a non-redu endogenous protein (e.g., erythropoietin - anemia/PRCA; thrombo - thrombocytopenia)**
    - **Altering the PK of the drug**
  - **May promote non-specific inflammation**

Safety considerations (cont.)

- Drug dose, mode and frequency of administration (e.g., SC vs. IV, life-time dosing and chronic exposure)
- Prior clinical exposure to leachables may enhance sensitivity in case of re-exposure
- Therapeutic necessity of the drug (higher levels m be tolerated if drug is considered a part of essenti therapy)

Manufacturing considerations

- Place in the process stream (e.g., upstream vs. downstream; typically risks are greater as production moves closer to the finished product)
- Type of the processed/stored material (e.g., purification buffe final product)
- Storage temperature (e.g., freezing vs. 2-8 C)
- Surface-to-volume ratio
- Contact time
- Type of polymeric material (e.g., PVC at risk for leaching di(2-ethylhexyl)phthalate, which is linked to various toxicities)
- Formulation/choice of excipients; (e.g., liquid vs. lyophilized; phosphate buffer)
- Risks often assessed on a case-by-case basis

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