

Regulatory Perspective on Safety Qualification of Extractables and Leachables

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Risk-based Approach in Evaluating E&L

- **Safety considerations** (e.g., toxicity, immunogenicity, etc.)
- **Efficacy considerations** (e.g., L interacting with 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.)



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Safety considerations

- Toxicity (e.g., acute, chronic, synergistic, additive, carcinogenic, 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, there 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 antibodies
 - ❖ May be life-threatening if NABs are developed against a non-redundant endogenous protein (e.g., erythropoietin - anemia/PRCA; thrombopoietin - thrombocytopenia)
 - ❖ Altering the PK of the drug
 - May promote non-specific inflammation



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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 may be tolerated if drug is considered a part of essential therapy)**



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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 buffer 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)

• Disks often accessed on a case-by-case basis

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