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Technical Challenges and Considerations for Complex LVP Drug Products

24th – 25th March 2021

Dr. Mike D Hodgson, Senior Manager (Pharma) & Baxter Global E&L Lead

Extractables/Leachables

Technical Challenges & Considerations for Different Product Types

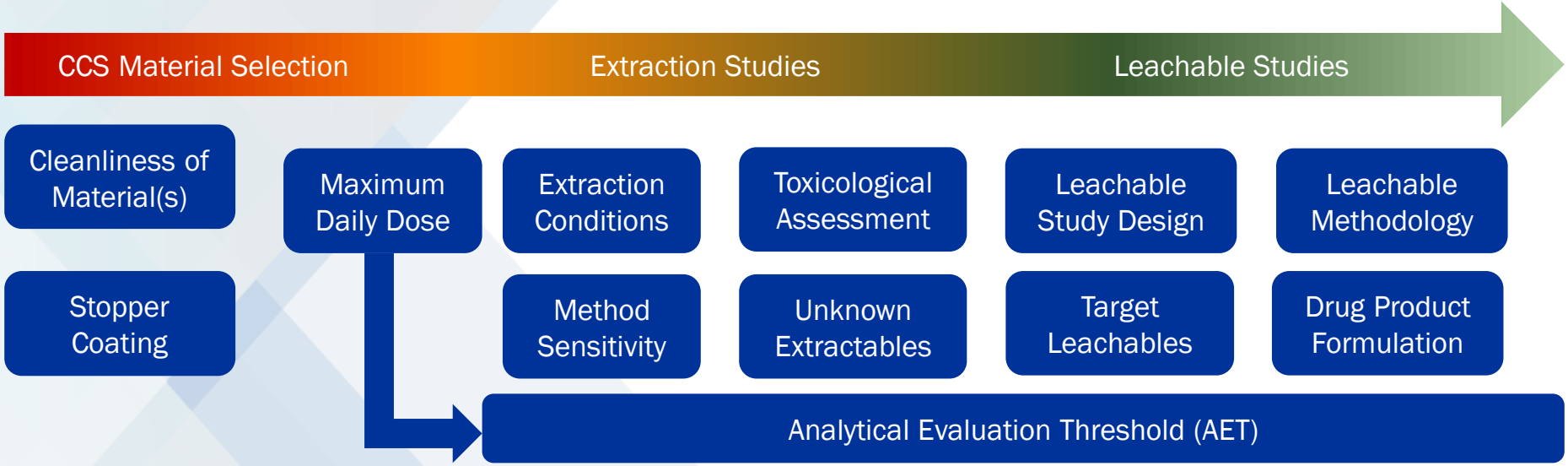
- Metered Dose Inhalers (MDIs)
  - *Exhaustive extraction studies*
  - *Complex leachable profiles*
  - *Implementation of a control strategy*
- Topicals/Ointments/Creams
  - *Formulation*
  - *Extractable study design*
  - *Leachable strategy/methodology*
- Large Volume Parenteral
  - *Poorly defined MDDs*
  - *Ultra-trace level method sensitivity*
  - *Increased chance of unknowns*

One Size Does **NOT** Fit All!

Take Home: Each dosage form has its unique set of challenges. It is NOT appropriate to apply the same generic approach to a variety of product types

Parenteral Drug Products

Schematic of Critical E&L Activities



Take Home: The Analytical Evaluation Threshold (AET) is a critical input when designing a strategy that addresses the toxicological risk associated with patient exposure to leachables originating from a Container Closure System or manufacturing process used for parenteral (IV) drug products

Large Volume Parenteral (LVP) Drug Products

Analytical Challenges

- The PQRI PDP working group released an update (9th Sept 2020) proposing a Safety Concern Threshold (SCT) of **1.5 µg/day** regardless of treatment duration (acute/chronic) or daily dose volume (SVP/LVP).

- The SCT is used to calculate the AET. It is derived using the Maximum Daily Dose (MDD) of a drug product and expressed in analytically meaningful units; µg/mL, µg/stopper etc

- Since the AET is related to the Maximum Daily Dose (MDD) of a given drug product, the higher the MDD (mL per day), the lower the AET.

- The lower the AET, the greater the analytical challenge. In some cases, aligning with the AET is beyond even the latest state of the art instrumentation

Take Home: The higher the MDD (mL), the lower the AET and the greater the analytical challenge

Large Volume Parenteral (LVP) Drug Products

Challenges Associated with Defining the MDD of Some LVP drug products/IV fluids

Sodium Chloride Injection, USP in VIAFLEX Plastic Container:

Product Labelling: The choice of product, dosage, volume, rate, and duration of administration is dependent upon the age, weight and clinical condition of the patient and concomitant therapy, and administration should be determined by a physician experienced in intravenous fluid therapy.

In practice, the dose of sodium chloride is highly variable and dependent on patient needs. For example, in hypovolemic shock an initial rapid infusion of several liters of fluid, followed by additional boluses if needed, maintenance fluid therapy, and fluid as a diluent in medications can result in massive volumes of sodium chloride administered in a 24-hour period.

Take Home: The MDD (mL) of some products cannot be defined resulting in the need for clinical expertise and assumptions to be made.

Large Volume Parenteral (LVP) Drug Products

Impact of Multiple Vial Sizes and Drug Product Strengths on the AET

- Parenteral drug products supplied in smaller vials (1 – 10mL) can have large maximum daily dose volumes
- Multiple strengths and sizes complicate the AET derivation process
- If there is reason to believe that the patient would require the MDD, should the AET be based on a situation that is worst case but clinically impractical (low AET) or one that is a typical clinical practice (higher AET)

Drug Product Strength (mg/mL)	Vial Fill Volume (mL)	MDD (mL)	MDD (Vials)	AET (µg/vial)
2	1	100	100	0.02
2	5	100	20	0.30
2	10	100	10	0.15
5	1	40	40	0.60
5	2	40	20	0.30

Take Home: Some parenteral drug products have multiple AETs. Discussion with the regulatory authorities or someone with clinical expertise is a necessary step to balance practicalities with risk and clinical benefit.

Extractable/Leachable Study Methodology

Method Sensitivity – Realistic Expectations

Analytical "Screening" Method Sensitivity: Even the latest state-of-the-art analytical instrumentation and accompanying sample preparation techniques are unable to achieve the sensitivity requirements to align with the PQRI PDP working group's recommendations (1.5µg/day) for some high daily dosing LVP drug products.

For example; an LVP drug product with Maximum Daily Dose of 5L would require method sensitivity in the region of 300ng/L (300 parts per trillion) based on PQRI PDPs recommended SCT

SCT (µg/day)	MDD (mL)	AET (µg/L)
1.5	10	150
1.5	25	60
1.5	50	30
1.5	75	20
1.5	100	15
1.5	500	3.0
1.5	750	2.0
1.5	1000	1.5
1.5	2500	0.6
1.5	5000	0.3

Take Home: Instrument/Method Sensitivity Guidance:

Achievable with state-of-the-art instruments (non-specific, screening)
Possible, but dependent on sample & sample preparation (non-specific, screening)
Feasible if the analyte is **known** and the method is **highly optimized** (specific, targeted)

Extractable Study Methodology

Method Sensitivity – Definition and Variation

- **Performance of Instrumentation (Vendor to Vendor)** – Minor differences
- **Sample Preparation** – Can impact overall sensitivity of the method. Common techniques used include Static Headspace (Volatiles) & liq/liq extraction (Semi-Volatiles)
- **Choice of Internal Standard** – Varies from one organization to another. Depending on the compound selected and its Response Factor (RF), this can result in an over-estimation or under-estimation of sensitivity
- **Defining the Sensitivity of a Screening Method** – Various approaches
  - *Concentration of the Internal Standard*
  - *Lowest estimated compound detected, with a s/n > 10 using the RF of the Internal Standard*
  - *Mean theoretical Limit of Detection (LOD) determined for a diverse range analytes*

Take Home: The sensitivity of an extractable study method varies from one compound to another. It is therefore only possible to estimate the “true” sensitivity of an extractable method.

Extractable Study Methodology

Extraction Conditions – Simulation vs Aggressive?

- The advantage of replicating the interaction (time, temperature, nature, solvent) between the Container Closure System (CCS) and drug product solution is that it is a greater indicator of risk.
- **Time/Temperature** – The temperature a drug product is exposed to rarely exceeds 40°C. Model the extraction time using 40°C and the long-term storage conditions and shelf-life.
- **Nature of Extraction** – Immersing stoppers in a solvent system is not always representative of the interaction with the drug product when they are seated in the vial; for example, it doesn't establish how effective a barrier coating/film applied to stoppers on the drug contacting surfaces is at minimizing leaching
- **Solvent Choice** – A solvent that mimics the bulk properties of the drug product is more predictive of leachables than a hexane or IPA extract – most LVP drug products are predominantly aqueous.

Take Home: Be clear on the intent of the extractable study and select conditions with that intent in mind; predict leachable profile (patient risk) or chemically characterize a material or CCS

Toxicological Risk Assessment

Impact of AET on the toxicological risk assessment process and outcome

Extractable/Leachable Compound Identification Challenges: Even the latest state-of-the-art analytical instrumentation (High Resolution Mass Spectrometers) coupled with mass spectral libraries and structural elucidation techniques cannot readily identify **all** compounds at such low levels.

- Some extractables (e.g. rubber oligomers) are generated during the manufacture of the material or component. Not all of these are commercially available, and the reaction mechanisms/structure are incredibly difficult to predict
- Other structural elucidation tools, such as preparative LC and NMR, are not an option at such low levels.
- For those extractables or leachables that cannot be identified, it is NOT possible to assess patient risk using the analytical data.
- Additional biocompatibility data (*in vivo/in vitro*) on extracts justified as being representative of the leachable profile in the drug product could facilitate establishing patient risk vs clinical benefit

Take Home: It is unrealistic to expect an analytical chemist to be able to identify every extractable or leachable compound at ultra-trace levels. Recognizing the *role in vivo in vitro* biocompatibility data and other forms of supplier compliance (i.e. USP<661) can play in supporting the safety of the packaging system is critical for success.

Large Volume Parenteral (LVP) Drug Products

Leachable Studies – Risk-Based Considerations

Drug Product Matrix Interferences: Can inhibit sensitivity so if the AET is very low, a simulation study is likely a better option.

Non-Specific vs Targeted Methods: If the outcome of the toxicological assessment on the extractable profile indicates negligible risk, consider the benefits of a non-specific leachable method to address the risk (leachables > AET) associated with leachables originating from the manufacturing process AND container closure system

Timepoints/Batches/Storage Conditions: If the outcome of the toxicological assessment on the extractable profile indicates negligible risk, consider the benefits of including multiple batches, timepoints and storage conditions into the leachable study. Resource investment (i.e. extent of leachable testing) should be commensurate with the perceived toxicological risk

Large Volume Parenteral (LVP) Drug Products

Opportunities for Alignment & Industry Standardization

Definition of Sensitivity: *Recognize the sensitivity of a screening method applied to extractable studies (solvent system) or leachable studies (drug product) is **ONLY** an estimate when comparing against the AET.*

Consider standardizing the process to estimate the sensitivity of extractable screening methods (HSGCMS, GCMS & LCMS) towards a diverse range of compounds to level the playing field.

Maximum Daily Dose: *Recognize that some LVP drug products have, either no MDD, or one that is so high that it is not possible to align with an SCT of 1.5µg/day. Consider the practical benefits vs risk by capping the MDD at 2L in line with ICH Q3D (Elemental Impurities)*

Unidentifiable Extractables/Leachables:

1) *Recognize that an analytical chemist does not have a "magic" instrument that can detect and identify all potential extractable/leachable compounds at the AET for some high dosing drug products, and*
2) *Receptive to discussing/agreeing solutions to this challenge to ensure the level of patient risk is understood to the best of our knowledge using current state-of-the-art instrumentation and balanced with the clinical benefit of the product.*

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Thank You for Your Attention!

Questions???