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Extractable and Leachable Studies of Parenteral Infusion and Transfusion Products

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Overview

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- Fresenius Kabi and Products.
- Extractable and Leachable Study Designs.
- Extractable and Leachable Test Guidelines.
- Analyses of Extractable and Leachables.
- Case Study: Extractable/Leachable Study of A Pre-filled Syringe (PFS) Product.
- Risk Assessments of Extractables and Leachables.
- Summary.

Fresenius Kabi

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- A global company, 34,000 employees, part of Fresenius Group. Global Headquarters: **Bad Homburg, Germany**.
- North American Headquarter: **Lake Zurich, IL, USA**. Two Divisions: Pharmaceutical and Medical Devices.

Pharmaceutical Division Products:

- ✓ Parenteral and enteral nutrition.
- ✓ Intravenous drugs (Oncology, Anesthetics and anti-infective, etc.)

Medical Device Division Products:

- ✓ Instrument (pump) and disposables (filter, bags, tubing) for blood collection / separation used for transfusion medicine and cell therapies.
- ✓ Blood components: treatment of surgical and cancer patients, and people with life threatening conditions.

Fresenius Kabi Pharmaceutical and Medical Device Products

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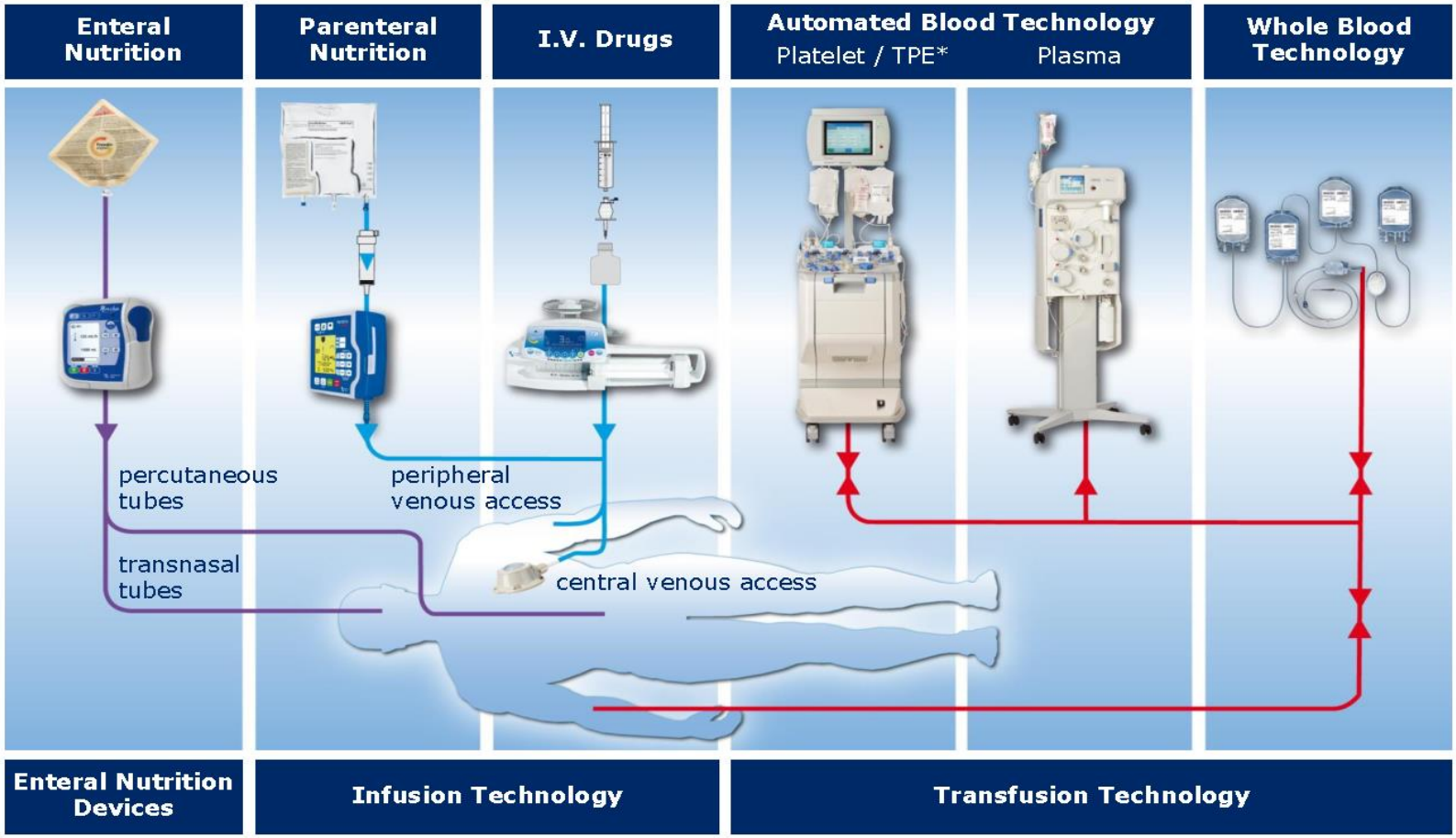

A wide range of medical grade material (sheeting, filter, tubing, port, vial and stopper, syringe barrel plunger etc.) is used and needs to be qualified.

Extractable/Leachable Study Designs

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- **Extractable study**:

  Extraction Solvents: Polarities/propensities bracket actual clinical use conditions.

  Extraction Conditions: Reasonably exaggerated compared to actual uses (temp, duration, part surface area/extract solvent volume ratio):

  - ✓ *To maximize extraction rate and extractable amount.*
  - ✓ *Provide information for potential leachables.*
  - ✓ *Provide information for preliminary health risk assessment.*

- **Leachable study:**

  Extraction conditions: Same as (or simulate to) the actual clinical uses.

  - ✓ *Performed at the end of shelf-life and accelerated leachable /stability studies.*
  - ✓ *Leachables need definite health risk assessments.*

- **Simulation Study:**

  Extraction conditions: Moderately exaggerated conditions compared to actual clinical use. It May be used to predict possible leachable compounds/levels during long term storage of medical products.

Extractable / Leachable Tests

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- **Bulk Properties Tests:**

  pH, UV and TOC.

- **Broad Scope Screening Tests for Organics:**

  1. Inorganic elements: ICP/MS.
  2. Volatile organics: Headspace GC/MS (EI & CI)
  3. Semi-volatiles: Direct GC/MS (EI & CI)
  4. Polar Compounds with derivatizable groups: Derivatized GC/MS (EI & CI).
  5. Non-volatile Compounds: Waters Acquity UPLC/UV/MS (Q-TOF Premier and Xevo G2 Q-TOF /MS with APGC).

- **Elemental Analysis**

  ICP/MS.

E/L Testing Guidelines

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- **Extractable and Leachable Study - Parts of biocompatibility study**
- **ISO 14791 Application of Risk Management to Medical device.**
- **ISO 10993 Biological Evaluation of Medical Devices. 20 Parts.**
- **Mandated by US FDA.**

- **USP Extractable /Leachable(E/L) Chapters Related to Plastic Material and Systems:**

  <87> Biological Reactivity in Vitro

  <88> Biological Reactivity in Vivo

  <381> Elastomeric Closures for Injections.

  <660> Containers - Glass

E/L Testing Guidelines

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<661> Containers – Plastics.

- **<661.1> Plastic Materials of Constructions.**
- **<661.2> Packing Systems for Pharmaceutical Uses.**
- **<661.3> Manufacture System.**
- **<661.4> Device**

⟨1661⟩ Evaluation of Plastic Packaging Systems and Their Material of Construction With Respect to Their User Safety Impact.

<662> Containers – Metals

<665> Polymer Components and Systems Used in the Manufacturing of Pharmaceutical and Biopharmaceutical Drug Products .

<1665> Plastic Components and Systems Used to Manufacture.

<1663> Assessment of Drug Product Extractables .

<1664> Assessment of Drug Product Leachables .

E/L Testing Guidelines

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- **European Pharmacopeia Testing (EP)**

3.1.1.1 Sheeting for Blood Containers **PVC**

3.1.1.2 Tubing for Blood Sets **PVC**

3.1.3 Sheeting for Containers-**Polyolefin**

3.1.4 **PE** without additives containers for parenteral/ophthalmic preps.

3.1.14 Sheeting for Parenteral Containers, **PVC**

3.2.1 **Glass** Containers for pharmaceutical Use

3.2.2.1 **Plastic** Containers for Aqueous Solutions for Infusion

3.2.3 **Sterile Plastic** Containers for Blood & Blood Components

3.2.4 Empty Sterile Containers of **Plasticized PVC** for Blood Containing Anticoagulant.

3.2.6 **Sets for Transfusion** of Blood/Blood Components.

3.2.8 Sterile single-use **Plastic syringe**.

3.2.9 **Rubber** Closures

Extractable Study Designs

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- **Possible Extraction Solvents:**
  1. pH 2 HCl Solution
  2. pH 3.5 formate buffer
  3. Water (*not buffered. Extractable accumulation may change due to the pH change of the matrix arising of the leaching process*).
  4. Phosphate Buffered Saline (PBS), pH ≈7.4 *(mimic nonreactive inorganic salts)*
  5. PBS/Alcohol Mixture. Alcohol *provides some lipophilic characteristics and increase solubility of some organic compounds.*
  5. pH 9 phosphate buffer
  6. pH 10 NaOH Solution
  7. Alcohols
  8. Hexane

Extractable Study Designs (con't)

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- **Material Amount: (ISO 10993-12)**

  -Desired minimum surface-to-volume ratio:**6.0 cm^2/mL** (thickness < 0.5 mm).

  -Desired minimum surface-to-volume ratio: **3.0 cm^2/mL** (thickness :0.5 mm-1.0 m).

  Normally is exaggerated compared to actual applications.

- **Extraction Temperature:**
  - Elevated temperatures.
  - The highest temperature should be lower than the Glass Transition temperatures of polymeric material. Otherwise the extractable profile may be changed.

Toxicological Evaluations of E/L Compounds

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- **Guidelines**:

✓**ICH Q3C Impurities: Guideline for Residual Solvents**

(Used for volatile organic solvents as E/L compounds).

✓ **ICH M7 Assessment and Control of DNA Reactive (mutagenic) Impurities in Pharmaceutical to Limit Potential Carcinogenic Risk.**

(used for other organic compounds)

Note:"*Applications of this guideline (M7) to leachables associated with drug product packaging is not intended, but the safety risk assessment principles outlined in this guideline for limiting potential carcinogenic risk can be used if warranted".*

✓**USP Elemental Impurity Chapter <233> and ICH Q3D**

(for inorganic elements).

Analytical Evaluation Thresholds (AET) for Extractables and Leachables

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- **What is AET ?**

✓ The concentration threshold at or above which an analytical chemist should identify a particular extractable and/or leachable and report it for potential toxicological assessment.

✓ The AET may be used as a guide for the minimum sensitivity required for the extractable/leachables method(s).

✓ AET is calculated based on Permitted Daily Exposure (PDE), Maximum Daily Dose (MDD), the container / material surface area ratio and extract solvent volume.

ICH M7 for Toxicological Evaluations & AET Calculations

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Important Assumptions:

1. The cancer risk (or toxicological risk) increases as a function of cumulative dose.
2. Cancer risk (or toxicological risk) of a continuous low dose over a lifetime would be equivalent to the cancer risk associated with an identical cumulative exposure averaged over a shorter duration (Less than life time (LTL)).

Duration of treatment	< 1 Month	> 1-12 Month	> 1-10 Year	> 10 Year-lifetime
Daily intake (µg/day)	120	20	10	1.5

Note: Not applicable to metals, sensitizer, material causing fever, large molecules and nanomaterials.

Toxicological Evaluations, ICH Q3D and USP 233 for Elemental Extractables / Leachables

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Element	Target Class	PDE (µg/day)
Cd	1	2
Pb	1	5
As	1	15
Hg	1	3
Co	2A	5
V	2A	10
Ni	2A	20
Tl	2B	8
Au	2B	100
Pd	2B	10
Ir	2B	10
Os	2B	10
Rh	2B	10
Ru	2B	10
Se	2B	80
Ag	2B	10
Pt	2B	10
Li	3	250
Sb	3	90
Ba	3	700
Mo	3	1500
Cu	3	300
Sn	3	600
Cr	3	1100

Case Study: Extractable Study of PFS (barrel, plunger and tip cap)

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IV Drug Formulation:

-pH: near neutral.

-No organic solvent and surfactant in the formulation.

-Target storage conditions: ambient conditions for two years

Extractable Study for Material (6 cm^2 /mL):

1) 20 Syringe Barrels

2) 98 Syringe Plungers

3) 126 Tip Caps

Extraction at (55 °C, 14 days, with agitation) with 150 mL Solvents:

- pH 3.5 formate
- pH 9 Phosphate
- Dulbecco's Phosphate Buffered Saline (PBS)
- Water/Ethanol (v/v) 50/50

Case Study: Extractable Study of PFS Parts (con't)

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AET Calculations:

- Inorganic Element Extractable AET:

  TTC =Permissible Daily Exposure (PDE) / (max. no. of syringes/day); max no. of syringes/day = MDD /(amount/syringe).

  AET = TTC x [(no. parts)/(volume of extract solvent)] x CT (0.3) x UF (0.5)

- Organic Extractable AET:

  AET (µg/mL) = TTC x (no. of parts / extraction volume)

  Plunger extract: **24 ppm**

  Tip Cap extract: **30 ppm**

  Glass Barrel extract: **4.8 ppm**

Case Study: Extractable Study of PFS Parts. Inorganic Elemental AET

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Element	Target Class	PDE (µg/day)	AET (ppm) in Extracts		
			Plunger	Tip Cap	Glass Barrel
Cd	1	2	0.12	0.15	0.024
Pb	1	5	0.29	0.38	0.060
As	1	15	0.88	1.13	0.180
Hg	1	3	0.18	0.23	0.036
Co	2A	5	0.29	0.38	0.060
V	2A	10	0.59	0.76	0.120
Ni	2A	20	1.18	1.51	0.240
Tl	2B	8	0.47	0.61	0.096
Au	2B	100	5.88	7.56	1.20
Pd	2B	10	0.59	0.76	0.12
Ir	2B	10	0.59	0.76	0.12
Os	2B	10	0.59	0.76	0.12
Rh	2B	10	0.59	0.76	0.12
Ru	2B	10	0.59	0.76	0.12
Se	2B	80	4.70	6.05	0.96
Ag	2B	10	0.59	0.76	0.12
Pt	2B	10	0.59	0.76	0.12
Li	3	250	14.7	18.9	3.00
Sb	3	90	5.29	6.80	1.08
Ba	3	700	41.2	52.9	8.40
Mo	3	1500	88.2	113	18.0
Cu	3	300	17.6	22.7	3.60
Sn	3	600	35.3	45.4	7.20
Cr	3	1100	64.7	83.2	13.2

Case Study: Extractable Study of PFS Parts, Inorganic Elemental AET

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Element	Target Class	PDE (µg/day)	AET (ppm) in Extracts		
			Plunger	Tip Cap	Glass Barrel
B	N/A	1000	58.8	75.6	12.0
Mn	N/A	250	14.7	18.9	3.00
Fe	N/A	1300	76.4	98.3	15.6
Zn	N/A	1300	76.4	98.3	15.6
Al	N/A	5000	294	378	60.0
W	N/A	3000	176	227	36.0
Ti	N/A	1500	88.2	113	18.0
Ca	N/A	178,500	10496	13495	2142
Mg	N/A	25,000	1470	1890	300
Bi	N/A	1500	88.2	113	18.0
Be	N/A	1500	88.2	113	18.0
Sr	N/A	360	21.2	27.2	4.32
Zr	N/A	1500	88.2	113	18.0

Extractable Study of PFS Parts (con't)

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- **Extractable Study Results**:

-Inorganic Elemental

The concentrations of all elements, except Al in pH 3 formate extract of the glass barrel, were well below AET.

-Organic Extractables

- HS GC/MS detected no volatile extractable above AET for the solid syringe parts (barrel, plunger and tip cap) and extract solutions.

-GC/MS detected palmitic acid and a possibly an aromatic alkyl alcohol/acid in PBS/50% ethanol extract of tip cap.

No other extractable above AET in other extract solutions was detected.

Extractable Study of A PFS Parts (con't)

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- Non-Volatile organic extractable:

  - **UPLC/MS Analyses**

    50/50 Water/ethanol extract solvent of Tip cap extract most of the extractables above AET:

    - A couple of phthalates.
    - A couple of aromatic amine and/or amide compounds.
    - A couple of compounds contain aromatic and carboxyl groups.
    - Several polymer degradation products.

    A common fatty acid was detected in both tip cap and plunger extracts of PBS/50% ethanol but <AETs.

  - **UPLC/UV Analyses**:

    No extractable at or above AET was detected in extract solutions.

Extractable Study of A PFS Parts (con't)

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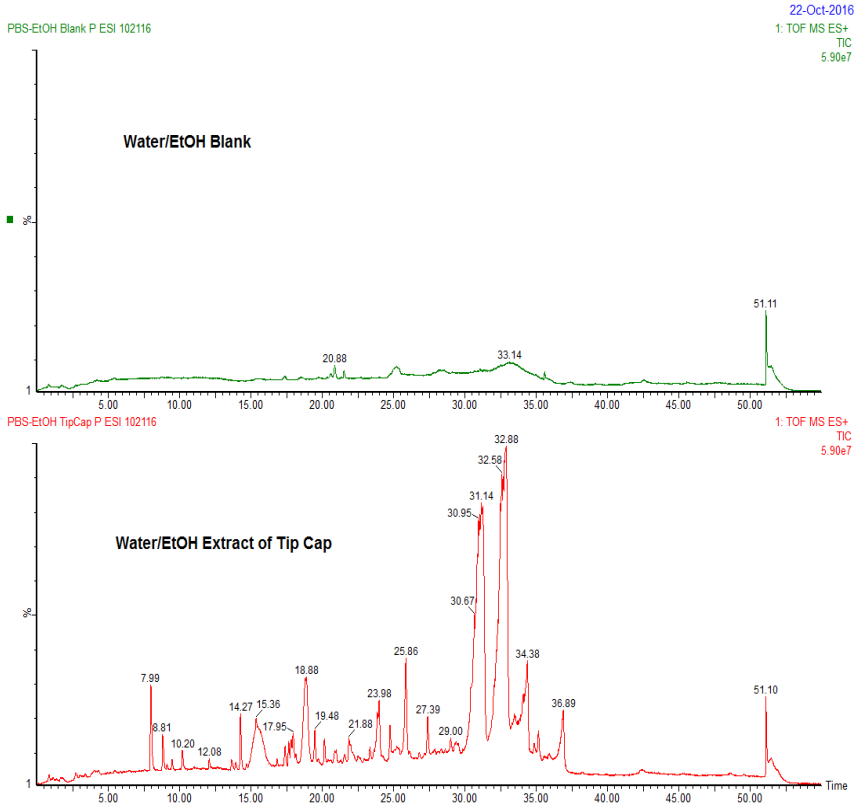
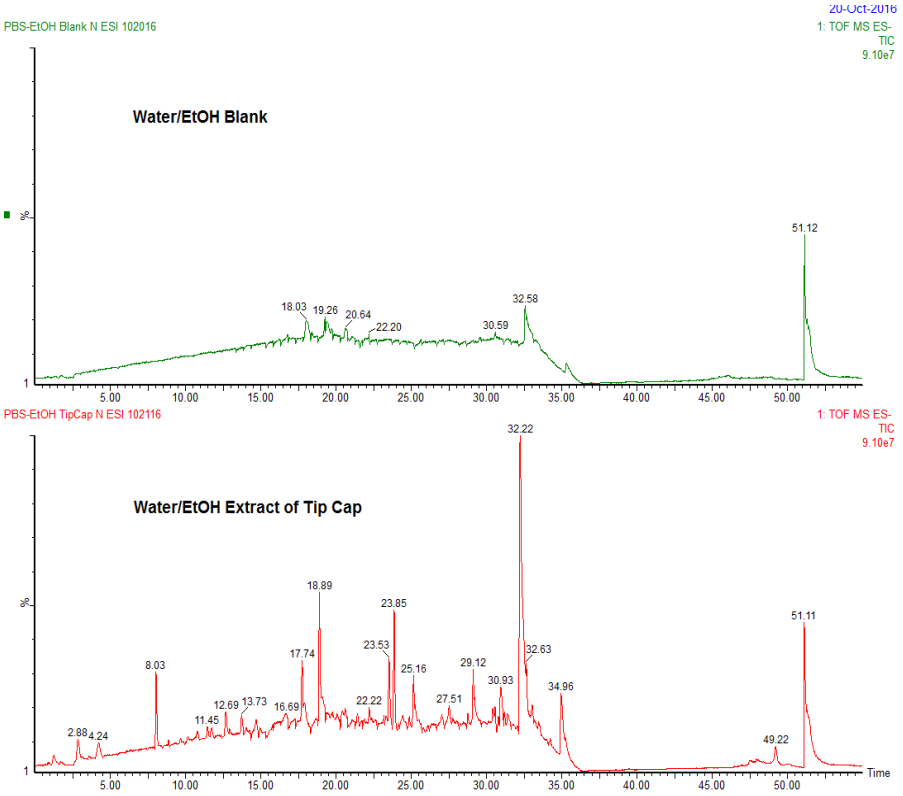
- **UPLC/MS Chromatogram of 50/50 Water/ Ethanol Extract of A Tip Cap**

Positive ESI



Negative ESI



Leachable Simulation Study of A PFS

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- Purpose:

  To predict possible leachable compounds/level during the long term product storage in a shorter time.

- Study Design:

  - Extraction Solvent: PFS formulation.
  - Extraction Conditions:
    - Use 50 of 3 mL PFS (filled with IV formulation).
    - Store in an orbital shaker horizontally with shaking (55 °C/14 days).
    - Pool the 50 syringe extracts (150 mL) after 14 days for testing.

Inorganic Leachable AET of A PFS

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Element	Target Class	PDE (µg/day)	AET (ppm)
Cd	1	2	0.06
Pb	1	5	0.15
As	1	15	0.45
Hg	1	3	0.09
Co	2A	5	0.15
V	2A	10	0.30
Ni	2A	20	0.60
Tl	2B	8	0.24
Au	2B	100	3.00
Pd	2B	10	0.30
Ir	2B	10	0.30
Os	2B	10	0.30
Rh	2B	10	0.30
Ru	2B	10	0.30
Se	2B	80	2.4
Ag	2B	10	0.30
Pt	2B	10	0.30
Li	3	250	7.5
Sb	3	90	2.7
Ba	3	700	21.0
Mo	3	1500	45.0
Cu	3	300	9.0
Sn	3	600	18.0
Cr	3	1100	33.0

Inorganic Leachable AET of A PFS

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Element	Target Class	PDE (µg/day)	AET (ppm)
B	N/A	1000	30.0
Mn	N/A	250	7.50
Fe	N/A	1300	39.0
Zn	N/A	1300	39.0
Al	N/A	5000	150
W	N/A	3000	90.0
Ti	N/A	1500	45.0
Ca	N/A	178,500	5355
Mg	N/A	25,000	750
Bi	N/A	1500	45.0
Be	N/A	1500	45.0
Sr	N/A	360	10.8
Zr	N/A	1500	45.0

AET = ((PDE) / (no. of syringe /day))/(extraction volume) x CF x UF

CF= Control Threshold (ICH Q3D) as a conservative adjustment factor:**0.3**.

UF= Uncertainty factor is used for the variability of semi-quantitative analyses which is estimated accurate to within ± 50%.

PDE of Cd:2 µg / day. *1 µg /mL = 1 ppm. 1 ppm = 1000 ppb*.

AET (ppb)=((2 µg/day)/[(5 mg/ day) x (1 syringe / 3 mg)] x [(1 syringe / 3 mL)] x 0.3 x 0.5 =0.06 µg/mL =**0.06 ppm**.

Leachable Simulation Study of A PFS (con't).

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Organic Leachable AET Determination:

- Maximum Daily Dose (MDD):**5 mg**.
- Drug total dosing days < **30 days** for a patient.
- Syringe fill volume: **3 mL**. Drug conc. :**1 mg/mL**. Drug in one syringe:**3 mg**.
- TTC for **organic leachables**:

  TTC = (acceptable daily intake) x (maximum no. of syringes used in one day)

  TTC = (120 µg/day) / ((5 mg/day) / (3 mg / syringe))

  = 72 µg/syringe = 72 µg/3 mL =24 µg/mL = **24 ppm**

- Apply a conservative factor of 2, **AET** is **12 ppm** (24 ppm/2).

Simulation Study Results and Next Steps

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- ✓No elemental leachable was detected with concentration ≥ AET or even 1/3 AET.
- ✓HS GC/MS, GC/MS and UPLC/MS/UV did not detect any organic leachable with concentration ≥ AET. In fact, ≤ 1 ppm.
- ✓The extractable study and simulation study results are being reviewed.
- ✓If extractable and simulation studies found that the concentrations of extractable & leachable are significantly below the AET (or acceptable toxicological levels. ISO-10993-17), not performing leachable testing may be justified. *Otherwise proceed to step (next slide)*.

Toxicological Assessments of Extractables / Leachables

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- Propose chemicals to be monitored in the leachable studies. The chemical selections are based on:
  1. Probability of presence and concentration in product formulation under intended use conditions.
  2. Toxicity and impact on the product.
  3. Ability to represent a compound class.
  4. Regulatory or historical precedence.
  5. Availability of authentic standards.
  6. Feasibility of detections of the leachables in the drug solution matrix.

- Perform Analytical Method(s) Validation for selected compounds (ISO 10993-18): Accuracy, Precision, Specificity, LOD, LOQ, Linearity, Range, Ruggedness and Robustness.

Summary

- Extractable/leachable testing processes for medical device parts and pharmaceutical containers are developed and they are compliant to applicable guidelines and risk-management based.
- Appropriate determinations of AET in E/L studies are important and they are scientifically based and derived based on regulatory guidelines.
- The risk assessments of E/L compounds are based on extractable study, simulation study results, the material characteristics, intended uses and considerations of effects on health of donors and patients.
- The processes have been successful for supporting new product development and material changes that meet regulatory requirements and protect the health of patients and donors.