# E&L on combination devices

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PDA Parenteral Drug Association PDA TRAINING

Nelson Labs A Sotera Health company

# Outline

## Regulatory framework

Extractables studies according to ISO 10993-18

Other aspects to come to a study design

Case studies

Conclusions

# Regulatory framework – definition - USA

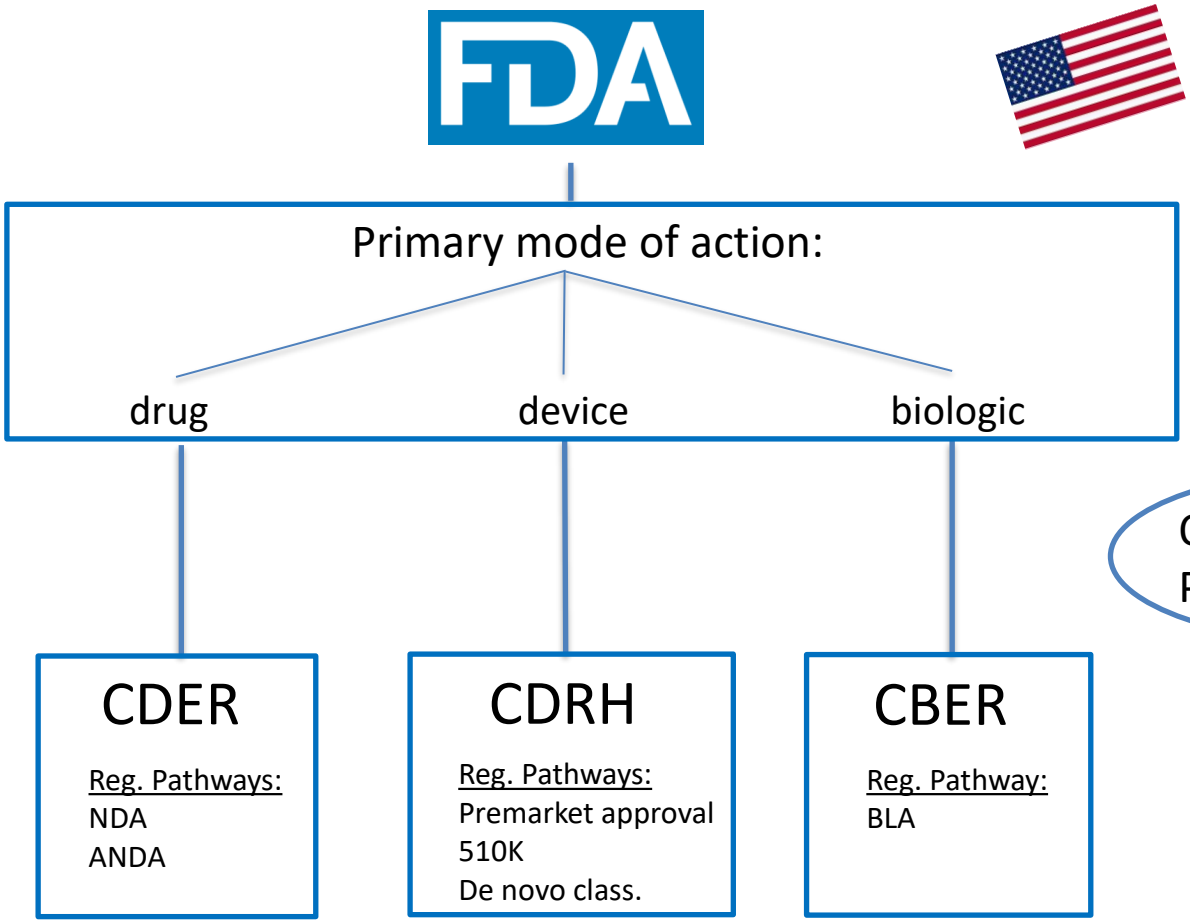


"A product comprised of two or more regulated components (i.e., drug/device, biologic/device, drug/device/biologic) that are physically, chemically, or otherwise combined or mixed" (FDA)

| Category | Description | Examples |
|---|---|---|
| Single-entity | Drug/device, biologic/device, drug/biologic, drug/device/biologic, combined to produce a single entity | Prefilled syringe with drug or biologic,<br>Insulin pen/pump,<br>Metered dose inhaler, Transdermal patch, Nasal spray,<br>Antimicrobial wound dressing, etc. |
| Co-packaged | Packaged together as a unit ('kit') | Drug/vaccine vial packaged with a syringe or transfer set, first aid or surgical kit containing an anesthetic drug, etc. |
| Cross-labeled | Sold separately but labled for use together | Drug/biological product (solution or lyo) recommending explicity which catheters to be used for drug administration in the IFU |

# Regulatory framework – USA






CDER: Center for Drug Evaluation and Research
CDRH: Center for Devices and Radiological Health
CBER: Center for Biologics Evaluation and Research

# Regulatory framework – Europe



No consistent definition of combination product!

Primary mode of action:

Drug/medicinal

**Medicinal combination product**

1. Drug-**Device**

Notified body → **Notified Body Opinion**

2. **Drug**-Device

EMA

no CE-mark

Device

**Medical device combination product**

1. **Drug**-Device

Competent authority

or

EMA → **CA or EMA opinion**

2. Drug-**Device**

Notified body

CE-mark

Approval by notified body

CE-mark

# Regulatory framework – guidance documents



- ISO 10993-18: chemical characterization of medical device materials within a risk management process
- Chemical Analysis for Biocompatibility Assessment of Medical Devices: Draft Guidance for Industry and Food and Drug Administration Stuff (Sep 2024) FDA draft
- Guidance for industry and FDA Staff: “Requesting FDA feedback in Combination Products”
- USP<1663> and USP<1664> on Extractables & leachables (pharmaceutical packaging AND DELIVERY SYSTEMS)
- PQRI documents (OINDP, PDP) and FDA guidance on ophthalmic drug products

# Regulatory framework – USA



## CDER

- **Extractables USP1663/ PQRI**
  - Controlled extractables study using model solvents
  - Device / components
- **Review Tox**
  - Select representative target compounds
  - (Q)SAR can contribute
- **Method optimization**
  - Optimize methods for the selected target compounds
- **Leachables/ simulation**
  - Leachables study using the final DP
  - Simulation study using a simulating solvent
- **Tox**
  - Full tox assessment of the leachables (if needed)

## CDRH

Presubmission !

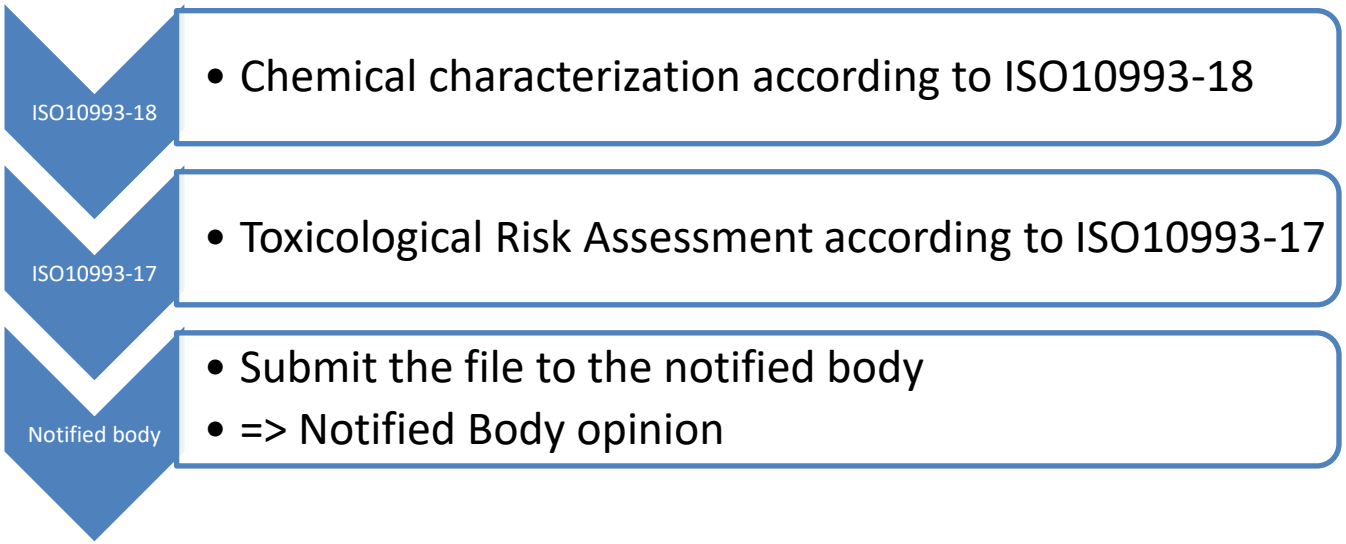
- **Extractables**
  - Chemical characterization (ISO10993-18), FDA draft
  - On placebo device? => case by case
- **Review Tox**
  - Full tox assessment of the extractables (ISO10993-17)
- **Method optimization**
  - Optimize methods for the selected target compounds (if needed)
- **Leachables/ simulation**
  - Simulation study using a simulating solvent or leachables study (if needed)
- **Tox**
  - Full tox assessment (if needed)

# Regulatory framework - EU

## Example of medicinal combination product

- **Step 1**: Medical Device Regulation

EU-MDR



# Regulatory framework - EU

## Example of medicinal combination product

- **Step 2**: Drug product

| | |
|---|---|
| USP<1663>/ PQRI | • Evaluate ISO10993-18 extraction conditions and results<br>• If needed, perform additional extractables testing |
| Review Tox | • Select representative target compounds<br>• (Q)SAR can contribute |
| Method optimization | • Optimize methods for the selected target compounds |
| Leachables simulation | • Leachables study using the final DP<br>• Simulation study using a simulating solvent |
| Tox | • Full tox assessment of the leachables |

# Outline

Regulatory framework

**Extractables studies according to ISO 10993-18**

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# Extractables studies according to ISO 10993-18

## Extraction solvents

- Extraction solvents:
  polar (UPW), non-polar (for e.g. hexane), semi-polar (for e.g. isopropanol, ethanol)

- Compatibility of solvents (colepalmer database, annex of ISO 10993-18, Nelson Labs solvent compatibility database,…)


FDA expects visual proof!

# Extractables studies according to ISO 10993-18

## Extraction ratio

**Table 1 — Standard surface areas and extract liquid volumes**

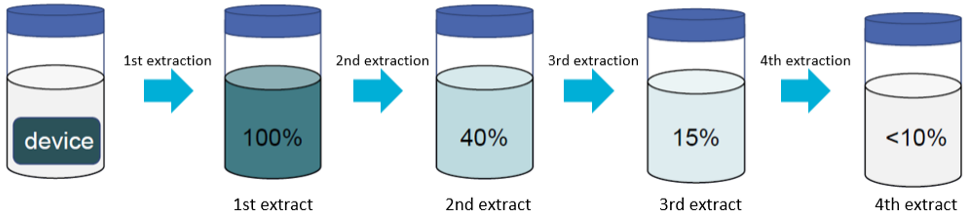
| Thickness[a] mm | Extraction ratio (surface area or mass/volume) ±10 % | Examples of forms of materials |
|---|---|---|
| <0,5 | 6 $cm^2$/ml | film, sheet, tubing wall |
| 0,5 to 1,0 | 3 $cm^2$/ml | tubing wall, slab, small moulded items |
| >1,0 | 3 $cm^2$/ml | larger moulded items |
| irregularly shaped solid devices | 0,2 g/ml | powder, pellets, foam, non-absorbent moulded items, porous high-density materials |
| irregularly shaped porous devices (low-density materials) | 0,1 g/ml | membranes, textiles |

Source: ISO 10993-12

# Extractables studies according to ISO 10993-18

## Extraction conditions

- Exhaustive conditions (UPW, hexane, ethanol)




- Exaggerated conditions (UPW, hexane, ethanol)

  72 h/50°C

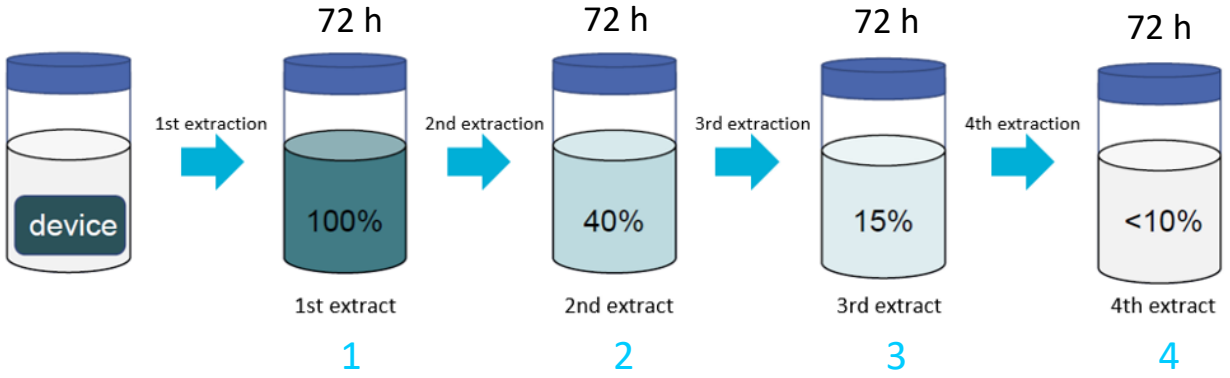
- Simulated use (adjust solvents based on real contact)

  t, T condition based on real use

In ISO 10993-18, but not in FDA draft guidance

# Extractables studies according to ISO 10993-18

## Extraction conditions: exhaustive extraction

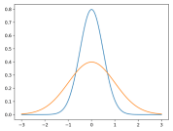



| Refresh solvent & analyze 1, 2, 3, 4 separately | Refresh solvent & pool 1, 2, 3, 4 extracts | Do not refresh solvent & perform 288h (=4 x 72h) extraction |
|---|---|---|
| +anticipate to saturation phenomena<br>+allows sensitive detection (~AET)<br>-expensive | + anticipate to saturation phenomena<br>+ less expensive<br>- Not always sufficient sensitivity (~AET) | + less expensive<br>+ allows sensitive detection (~AET)<br>- does not anticipate to saturation phenomena |

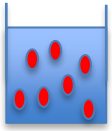
# Extractables studies in view of ISO 10993-18

## Replicates

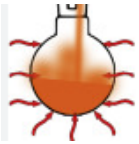

Deviations are possible:



Justification based on low variation in test articles composition



Multiple test items needed to create enough extract volume



Exhaustive/Exaggerated extractions already result in worst-case profiles

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# Aspects to come to a study design: toxicological thresholds

## Medical devices

| Product contact category | Limited contact (<24 h) | Prolonged (1 to 30 days) | Long-term/permanent (> 30 days) | | |
|---|---|---|---|---|---|
| Duration of body contact | ≤ 1 month | | 1-12 months | 1-10 years | > 10 years to lifetime |
| DBT (µg/day) for devices | 120 µg/day | | 20 µg/day | 10 µg/day | 1.5 µg/day |

TTC (ICHM7)

## Drug products

| Product contact category | Non-Chronical | | | chronical |
|---|---|---|---|---|
| Duration of DP administration | ≤ 1 month | 1-12 months | 1-10 years | > 10 years to lifetime |
| SCT (µg/day for parenteral drugs/biologics) | 1.5 (5 might be acceptable) µg/day | | | 1.5 µg/day |
| SCT (µg/day) for inhalation products | 0.15 µg/day | | | |

QT (PQRI)

SCT (PQRI)

# Practical approaches and considerations: analytical thresholds

Pharma: UF of 2 is typically acceptable (PQRI (OINDP), USP 1663)

$$AET = \frac{DBT \times \frac{A}{BC}}{UF}$$

Medical device (ISO10993-18): UF to be justified based on

- Based on In-house database:
  - Nelson Labs: GC/MS: 2; LC/MS: 5

$$UF = \frac{1}{1 - RSD}$$

- For HS-GC/MS use UF = 10
- Literature: frequent values are GC/MS: 4 and LC/MS: 10

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# Case study 1

Purpose:

- FDA-CDER
- Practical challenges with infusion devices
- Interesting observations with respect to E&L results

# Case study 1

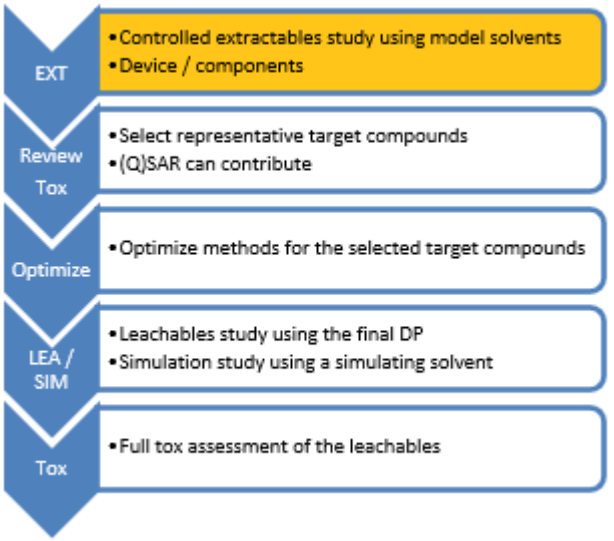
- Drug product: Aqueous and contains hormone, TRIS buffer, NaCl, m-Cresol – pH 6.5
- Delivery device:
  - Cassette: bromobutyl rubber, PC, SS, PE, PU and MABS
  - Infusion device: MABS, PTFE (connectors); PE and PU (inner & outer layer of tubing)
    - Flow rates: 1 – 100 µL/h
    - Max daily dose = 0.42 mL
    - Duration of administration: chronical therapy
    - Administration time with 1 device
      - Max 72 h

# Case study 1



- Solvent selection
  - water
  - 5% Isopropanol in water
- Time/temperature: 72 h / 40°C (> 37 °C)

USP 1663, PQRI




<u>Challenging aspects:</u>

- Simulation of the flow rate
  - Lowest flow-rate = worst case: 1 µL/h
    - 72h of pumping = 72 µL => too low
  - to deliver max daily dose of 420 µL, 17.5 µL/h flow rate required
  - 4 µL/h was selected as “practically feasible”
    - 288 µL of extract was generated per device after 72h
    - 12 re-usable pumps were provided
    - 24 runs were performed per solvent, each run used the 12 re-usable pumps simultaneously
    - Extract was diluted 10x afterwards

# Case study 1



# Case study 1



*Table 3: Calculation of the analytical evaluation threshold (AET)*

| | |
|---|---|
| Safety concern threshold (PQRI)) | 1.5 µg/day |
| Maximum daily dose volume (information provided by the sponsor) | 0.00042 L |
| Analytical Evaluation Threshold (AET) in drug product (µg/L)* (1.5 µg/day /0.00042 L/day) | 3500 µg/L |
| **Final AET for (HS-)GC/MS (3500 µg/L/ UF (2))*** | **1700 µg/L** |
| **Final AET for UPLC/MS (3500 µg/L/ UF (5))*** | **710 µg/L** |

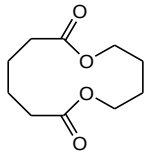
*As the infusion set is completely filled during the extraction procedure, as well as during real administration, the amount of extraction solvent and drug product in the system versus infusion set material can be considered identical at any point in time during the extraction procedure/administration. The applied flow rate during the extraction of 4 µL/h (see §7), only results in a daily extract volume of 96 µL, which implies that the extraction solvent contact time is higher than of the drug product in case of administering a daily volume of 420 µL (which is the maximum daily dose volume). As this would result in a longer accumulation time for extractables, the (final) AET calculation as well as the extraction conditions are considered to be appropriate and worst-case.

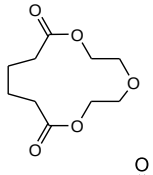
# Case study 1

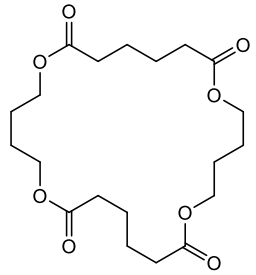
Results:

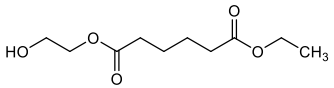
- 1,6-Dioxacyclododecane-7,12-dione
- 1,4,7-Trioxacyclotridecane-8,13-dione
- 1,6,13,18-Tetraoxacyclotetracosane-7,12,19,24-tetraone
- Ethyl (2-hydroxyethyl)adipate

From PU










Elements:

- Boron, Calcium, Silicon, Zinc

From rubber, PC, PE, MABS, PTFE

# Case study 1

## Leachables study: Yes or No?

USP 1664
(leachables associated with pharmaceutical packaging ***AND DELIVERY SYSTEMS***)

⇒ Simulation study can only replace leachable study if analytically not feasible

PQRI for **PARENTERAL DRUG PRODUCTS =>** "use of simulation study to replace leachable study should be justified"

FDA (Dan Mellon) (pharma packaging ***AND DELIVERY SYSTEMS***) => all leachables above threshold should be identified

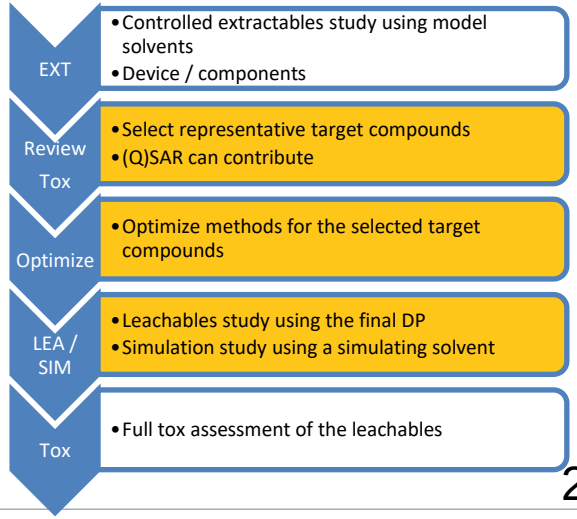
⟶ Perform leachable study

# Case study 1

- Optimized methods: choice for **Method Suitability Test (MST)**: spike in drug solution

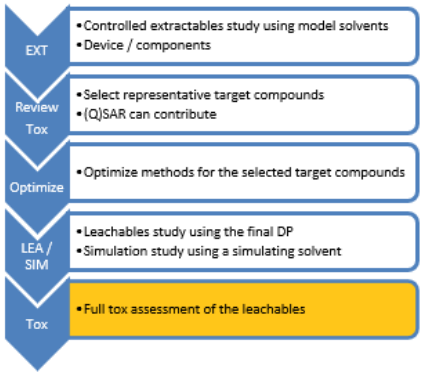
| Target compound | MST / Marker compound | Techniques |
|---|---|---|
| 1,6-Dioxacyclododecane-7,12-dione | 1,4-Dioxacyclododecane-7,12-dione **(marker)** | GC/MS & HRAM-UPLC/MS |
| 1,4,7-Trioxacyclotridecane-8,13-dione | 1,4,7-Trioxacyclotridecane-8,13-dione | GC/MS & HRAM-UPLC/MS |
| 1,6,13,18-Tetraoxacyclotetracosane-7,12,19,24-tetraone | 1,6,13,18-Tetraoxacyclotetracosane-7,12,19,24-tetraone | GC/MS & HRAM-UPLC/MS |
| Ethyl (2-hydroxyethyl) adipate | Bis (2-ethylhexyl) adipate **(marker)** | GC/MS & HRAM-UPLC/MS |

- Analytical program (on MST + contact sample)
  - Headspace-GC/MS (only screening)
  - GC/MS (screening + MST)
  - HRAM-UPLC/MS (only APCI – screening + MST)



# Case study 1

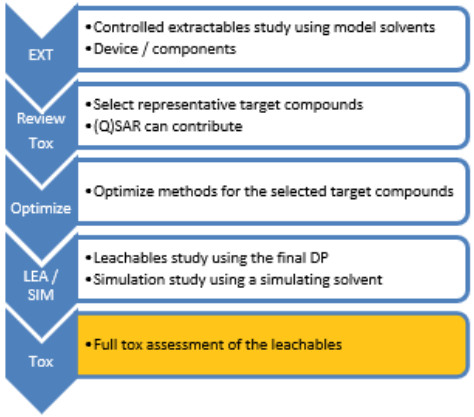
Results GC/MS




| | MST sample (spiked at 1.5 µg/day) | | Contact sample | |
|---|---|---|---|---|
| | Spiked | Measured | Measured | |
| 1,4,7-Trioxacyclotridecane-8,13-dione | 3440 | 1000 | | ND |
| 1,4-Dioxacyclotetradecane-5,14-dione (marker for 1,6-Dioxacyclododecane-7,12-dione) | 3410 | 1300 | << | 14000 |
| Bis(2-ethylhexyl)-adipate *(marker for Ethyl (2-hydroxyethyl)adipate)* | 3430 | 670 | | ND |
| 1,6,13,18-Tetraoxacyclotetracosane-7,12,19,24-tetraone | 3450 | 450 | | ND |

Further evaluation needed

# Case study 1




Results HRAM-UPLC/MS

| | MST sample (spiked at 1.5 µg/day) | | Contact sample | |
|---|---|---|---|---|
| | Spiked | Measured | | Measured |
| 1,4,7-Trioxacyclotridecane-8,13-dione | 3440 | 710 | | ND |
| 1,4-Dioxacyclotetradecane-5,14-dione (marker for 1,6-Dioxacyclododecane-7,12-dione) | 3410 | 3700 | << | 4800 |
| Bis(2-ethylhexyl)-adipate *(marker for Ethyl (2-hydroxyethyl)adipate)* | 3430 | 2100 | | ND |
| 1,6,13,18-Tetraoxacyclotetracosane-7,12,19,24-tetraone | 3450 | 930 | << | 1600 |

Further evaluation needed

# Case study 2

Purpose:

- FDA-CDRH
- Study design for implanted combination device
- Challenging analytical requirements

# Case study 2



- Drug products (minitablets) inside tubing (which also contains metal wire), placed in the bladder

tubing with tablets 

- Nature of contact
  - Implant (=> contact with tissue/tissue fluid (urine))
- Duration of contact
  - 3 months (long-term contact)

# Case study 2

## Extractables study

**ISO 10993-18**

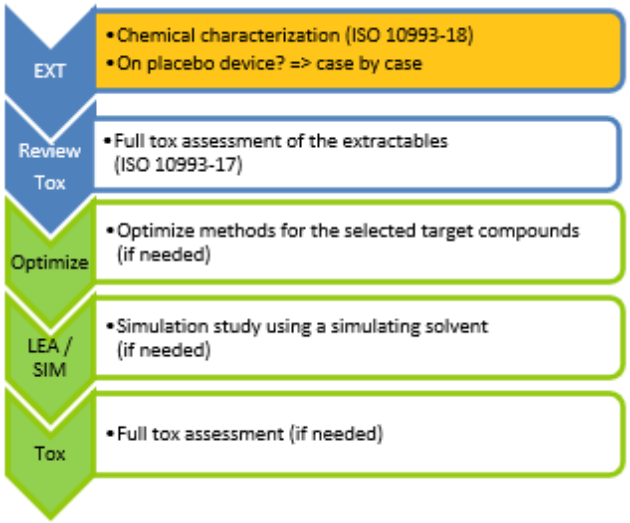
| Contact category | Recommended extraction conditions | Credible alternatives |
|---|---|---|
| Limited contact devices | Simulated use conditions[a] | Exaggerated conditions |
| Prolonged contact devices | Exhaustive conditions | Exaggerated conditions[b,c] |
| Long-term contact devices | Exhaustive conditions | Exaggerated conditions[b,c,d] |

at least polar and non-polar solvent

**FDA draft guidance**

**Table 1. Recommended extraction conditions.**

| | Duration of Contact | | |
|---|---|---|---|
| | Limited (< 24 h) | Prolonged (1-30 days) | Long-Term (> 30 days) |
| **Extraction duration/ number of cycles** | Exaggerated[a] extractions or clinically relevant worst-case conditions | Exhaustive or exaggerated[a,c] extractions | Exhaustive or exaggerated[a,c] extractions |
| **Types of solvents** | Polar and non-polar[b] | Polar and non-polar[b] | Polar, semi-polar, and non-polar |
| **Non-volatile residue (NVR) analysis recommended to demonstrate exhaustion** | N/A | Yes | Yes |



# Case study 2

## Extractables study

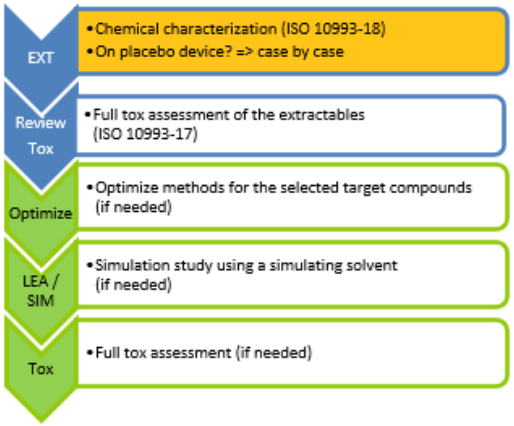
- Exhaustive determination on empty device (72h/50°C cycles; UPW, 60% EtOH, hexane)

  FDA is normally reluctant towards binary solvents however for this particular study, they have made an exception

- Exhaustive extraction on emptied devices

- FDA additionally requests (due to metal wire) an extraction with acidic UPW solvent

  ⟷ ISO 10993-18



# Case study 2

## Analytical requirements

- Spike & recovery to assess impact of sample preparation steps (for e.g. liquid/liquid extraction and of concentraction steps) also for extractables studies
- Quantification procedures should be well justified (RRF approach and/or use of surrogates)
- In some case fully validated methods are requested

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# Conclusions

**Path to market**

FDA

Competent authority

EMA

Notified body

# Conclusions

## General extractable (conditions)/leachable program (cf. case studies)

| (Externally) delivery devices | Implanted combination devices |
|---|---|
| CDER | CDRH |
| Simulation study (USP1663) | Exhaustive extractions (ISO10993-18) |
| Leachables ⟷ | “Pure” medical devices |

# Conclusions

**Analytical set-up**

Focus on quantitive aspects for implanted combination devices (CDRH)

- Extractable studies are often endpoint for medical devices

=> Important to verify study set-up details with FDA in advance (pre-sub/Qsub)

# Conclusions



***Container closure systems***

Recommendations & guidelines

Authority expectations

***Process materials***

Recommendations & guidelines ⟷ Authority expectations

***Medical devices & Combination devices***

Recommendations & guidelines ⟷ Authority expectations

# Questions??




PDA Parenteral Drug Association
PDA TRAINING