PDA Training Course Extractables & Leachables

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E&L on combination devices

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CONNECTING PEOPLE SCIENCE AND REGULATION®

Outline

- Regulatory framework
- Case studies

Regulatory framework - definition

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, Insulin pen/pump, Metered dose inhaler, Transdermal patch, Nasal spray, Antimicrobial would 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-labelled	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

Primary mode of action	Regulatory pathways	FDA devision
Device	Pre-market approval (PMA), de novo classification request or 510(k) submission	CDRH
Drug	New drug application (NDA) or abbreviated new drug application (ANDA)	CDER
Biologic	Biologic License Application (BLA)	CBER

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

Regulatory framework – USA

- ISO 10993-18: chemical characterization for medical devices
  - US FDA has its own view and interpretation of the standard
- USP<1663> and USP<1664> on Extractables & leachables (containers)
- USP<665> and USP<1665> on Extractables & leachables (single-use systems)

➔ Choose the appropriate guidance based on the Primary mode of action

Regulatory framework – USA

	CDER	CDRH
Extractables	•Controlled extractables study using model solvents •Device / components	• Chemical characterization (ISO10993-18) • On placebo device? => case by case
Review Tox	•Select representative target compounds •(Q)SAR can contribute	• Full tox assessment of the extractables (ISO10993-17)
Method optimization	•Optimize methods for the selected target compounds	• Optimize methods for the selected target compounds (if needed)
Leachables/ simulation	•Leachables study using the final DP •Simulation study using a simulating solvent	• Simulation study using a simulating solvent (if needed)
Tox	•Full tox assessment of the leachables	• Full tox assessment of the leachables (if needed)

Regulatory framework

- **Step 1**: Medical Device Regulation EU-MDR

ISO10993-18	• Chemical characterization according to ISO10993-18
ISO10993-17	• Toxicological Risk Assessment according to ISO10993-17
Notified body	• Submit the file to the notified body • => Approval

Regulatory framework

- **Step 2**: Compatibility with the drug product

(USP<1663>)	• Evaluate ISO10993-18 extraction conditions and results • If needed, perform additional extractables testing
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 simuating solvent
Tox	• Full tox assessment of the leachables

Practical approaches and considerations

- Extraction conditions => see previous sessions
- How low do you need to go?

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
SCT (µg/day for drugs/biologics	1.5 (5 might be acceptable)				1.5
SCT (µg/day) for inhalation products	0.15				

Practical approaches and considerations

- Extraction conditions => see previous sessions
- How low do you need to go?
- The use of Uncertainty Factors
  - USP<1663>: UF of 2 is typically acceptable
  - ISO10993-18: UF to be justified based on
    - In-house database: $UF = \frac{|1}{1-RSD}$ (@Nelson: GC: 2; LC: 5)
    - Literature: frequent values are GC:4 and LC: 10

Case study 1

- Drug product
  - Aqueous and contains API, TRIS buffer, NaCl, m-Cresol – pH 6.5
  - Delivery device:
    - Cassette: bromobutyl rubber, PC, SS, PE, PU and MABS
    - Infusion device: MABS, PTFE, PE and PU
  - Flow rates: 1 – 100 µL/h
- Nature of contact
  - Externally communicating device
  - Subcutaneous injection (= blood path, indirect)
- Duration of contact
  - Max 72 h (= prolonged contact)

Case study 1

The design of the extraction study should take into account the nature of contact (of the device) with the potentially affected user; the influence of (or interaction with) other substances such as drugs in an administration device may also need to be considered.

Table 2 — Recommended extraction conditions

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]

provides an added margin for uncertainty in the toxicological risk assessment, and can be appropriate in many circumstances. However, care must be taken to limit the extent of overestimation, as overly aggressive extractions conditions can lead to an altered extractables' profile.

The recommended extraction conditions in Table 2 will, in many circumstances, provide such an appropriate overestimation. However, in certain circumstances, the overestimation provided by the recommended exhaustive extraction conditions will be excessive and thus the recommended extraction circumstances are not appropriate. For all device classifications, alternative credible extraction conditions can be considered and used if deemed appropriate. The use of alternative extraction conditions shall be documented and justified. Extractions done for specific purposes other than

This paragraph points to simulation study

Case study 1

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

Considering replication of extractions, a single extraction replicate for each vehicle shall be sufficient in those circumstances where it can be established that the variation in the test article's composition and/or the variation in the extraction process is low, establishing that the single extraction is properly representative of the test article and the extraction process. In cases where other information (e.g. engineering testing) indicates higher variability either within or across test article units or lots or inherent to the extraction process, multiple (e.g. duplicate or triplicate) extractions can be necessary. Multiple extractions should also be performed in those circumstances where the test article and/or extraction variability is unknown. Regardless of the number of replicate extractions performed, the number of extracts generated should be justified.

The analytical process should be replicated by testing multiple aliquots of the extract, to account for analytical variation. Although triplicates are recommended, a smaller number of replicates can be more practical, if justified.

"Based on our experience one of the items the FDA did not completely agree with was the aspect of replicates. They are adamant for replicates, with 3 being a minimum"

Practical issues:

- Not enough extract coming from 1 device
- "Combined" extract from 24 devices should give a good "average"

Case study 1

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

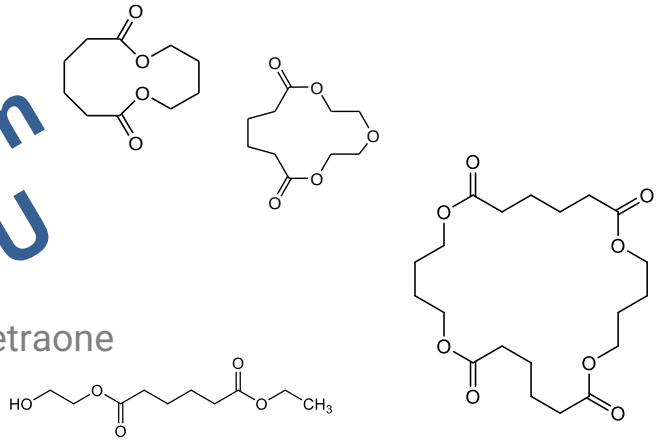
Safety concern threshold (PQRI))	1.5 µg/day
Maximum daily dose volume (information provided by the sponsor)	0.00042 L
Analytical Evaluation Threshold (AET) in drug product (µg/L)* (1.5 µg/day /0.00042 L/day)	3500 µg/L
Final AET for (HS-)GC/MS (3500 µg/L/ UF (2))*	**1700 µg/L**
Final AET for UPLC/MS (3500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

The information from this study will be used to determine the risk associated with the estimated chemical release. If a toxicological risk assessment determines that a chemical or chemicals could be a risk to the potentially affected individual using the extractables data, a more clinically relevant extraction can be done to more precisely estimate the amount of the chemical or chemicals released from the medical device in clinical use (see 5.8). When a more clinically relevant extraction cannot be justified, other risk mitigation strategies can include targeted analysis, biological testing, reduction of the chemical in the device, and in some cases, labelling as described in ISO 14971, ISO 10993-1 and ISO 10993-17.

No leachables study if tox assessment can rule out concern

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 (pharma packaging and delivery systems) => all leachables above threshold should be identified

→ Perform leachable study based on strictest interpretation of guidelines/recommendations + no tox assessment was performed on extractables

Case study 1

Technique detected in EXT study	Target compound	CAS no.	Technique in LEA study	MST compound/marker
GC/MS HRAM-UPLC/MS (ESI) HRAM-UPLC/MS (APCI)	1,6-dioxacyclododecane-7,12-dione	777-95-7	GC/MS and HRAM-UPLC/MS (APCI)	*1,4-Dioxacyclotetradecane-5,14-dione*
HRAM-UPLC/MS (ESI) HRAM-UPLC/MS (APCI)	1,6,13,18-Tetraoxacyclotetracosane-7,12,19,24-tetraone	ToxID 459		1,6,13,18-Tetraoxacyclotetracosane-7,12,19,24-tetraone
HRAM-UPLC/MS (ESI)	1,4,7-Trioxacyclotridecane-8,13-dione	6607-34-7		1,4,7-Trioxacyclotridecane-8,13-dione
	Ethyl (2-hydroxyethyl)adipate	ToxID 6581		*Bis(2-ethylhexyl)-adipate*

Case study 1

- Optimized methods: choice for Method Suitability Test
- Analytical program
  - 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

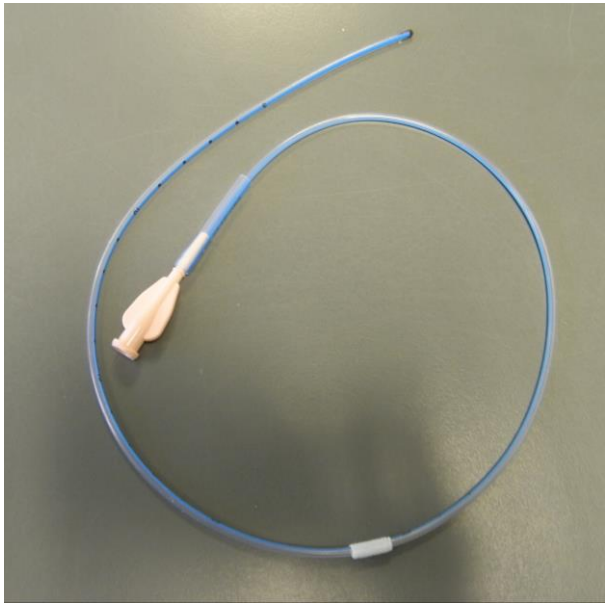
Results HRAM-UPLC/MS

	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

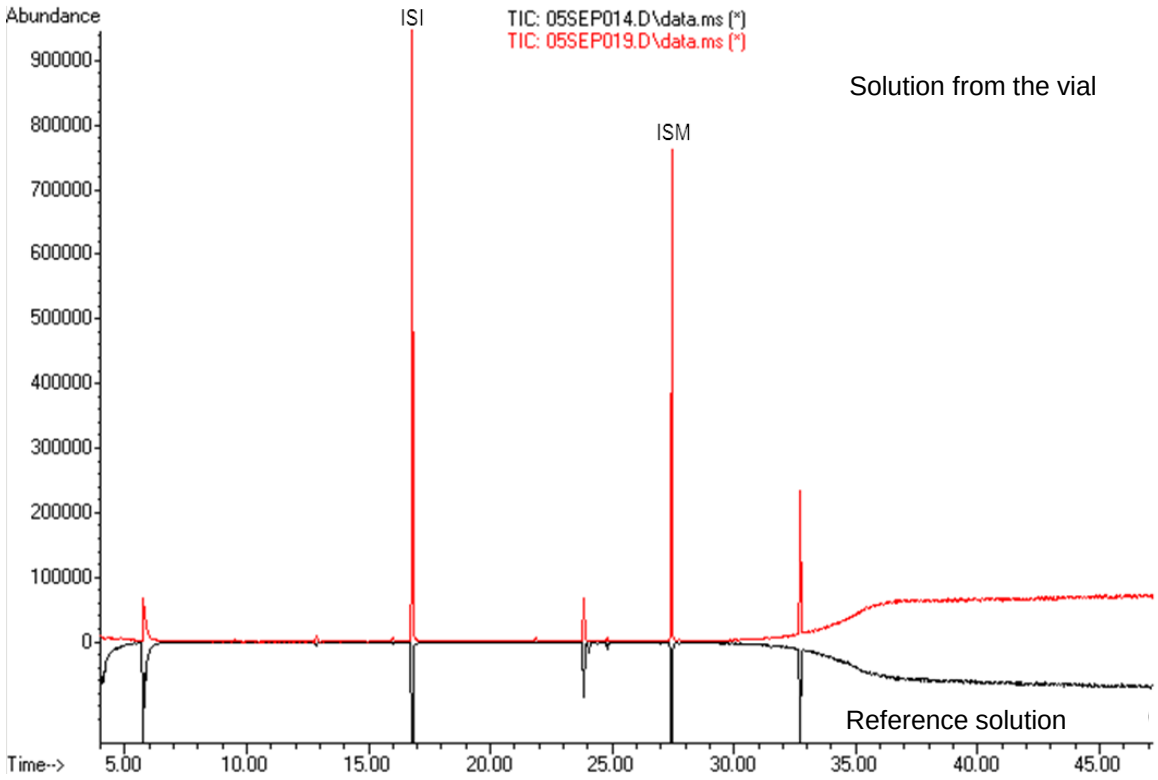
Further evaluation needed

Case study 2

- Infusion of a DP by means of a pump with cassette, extension tubing and catheter
- Catheter (silicon): 50+ extractables
- The sponsor decided to test the pump, cassette, extension tubing and catheter for leachables
  - Fill the cassette with DP and diluent and plug into the pump
  - The solution was pumped through the extension tubing
  - A catheter was attached to the extension tubing
    - The catheter was insterted in a custom made glass tube



Case study 2


Abundance
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Solution from the vial
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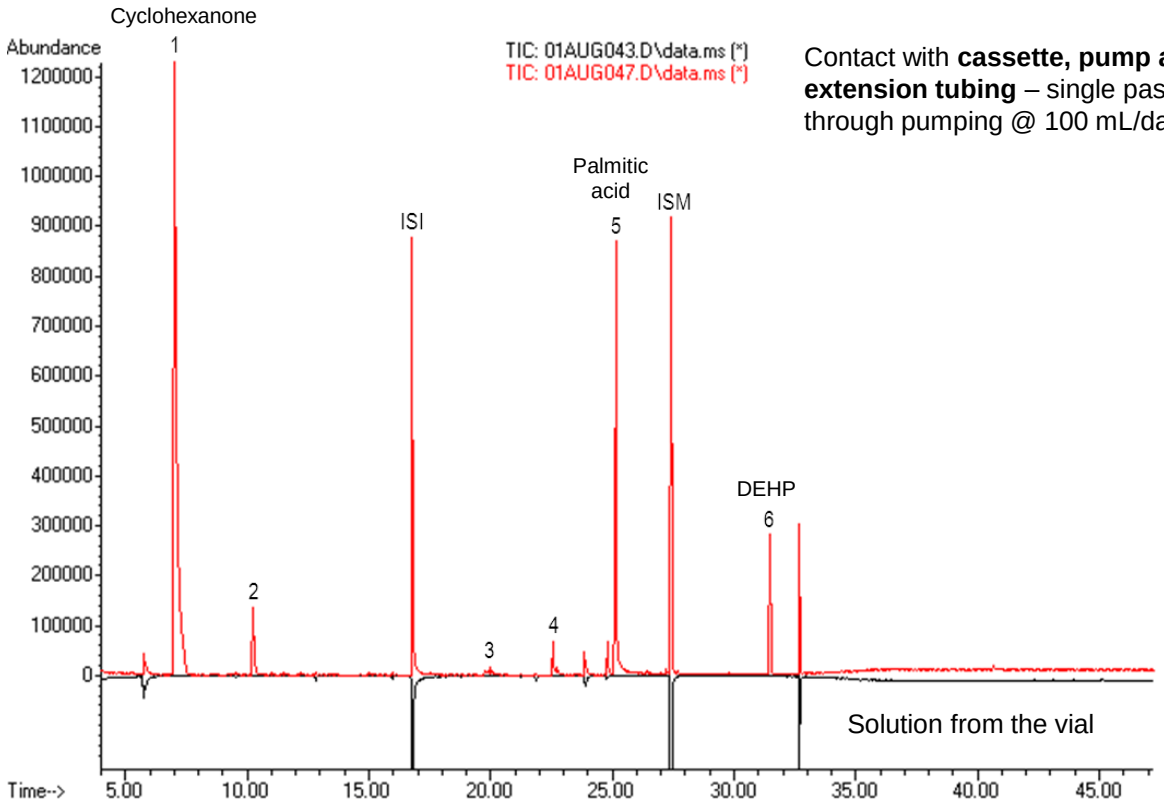
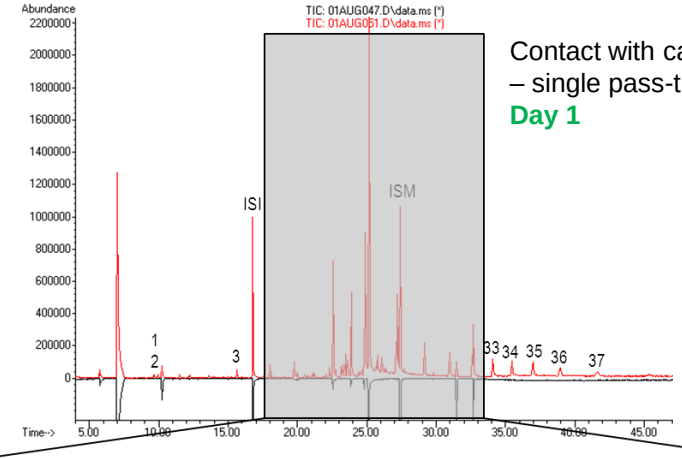
Case study 2



Contact with **cassette, pump and extension tubing** – single pass-through pumping @ 100 mL/day

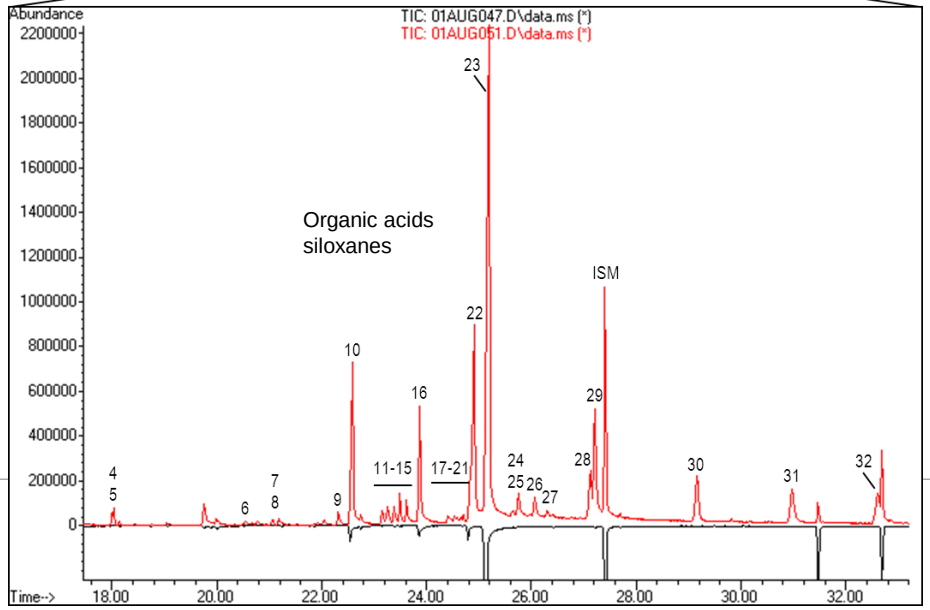
Case study 2



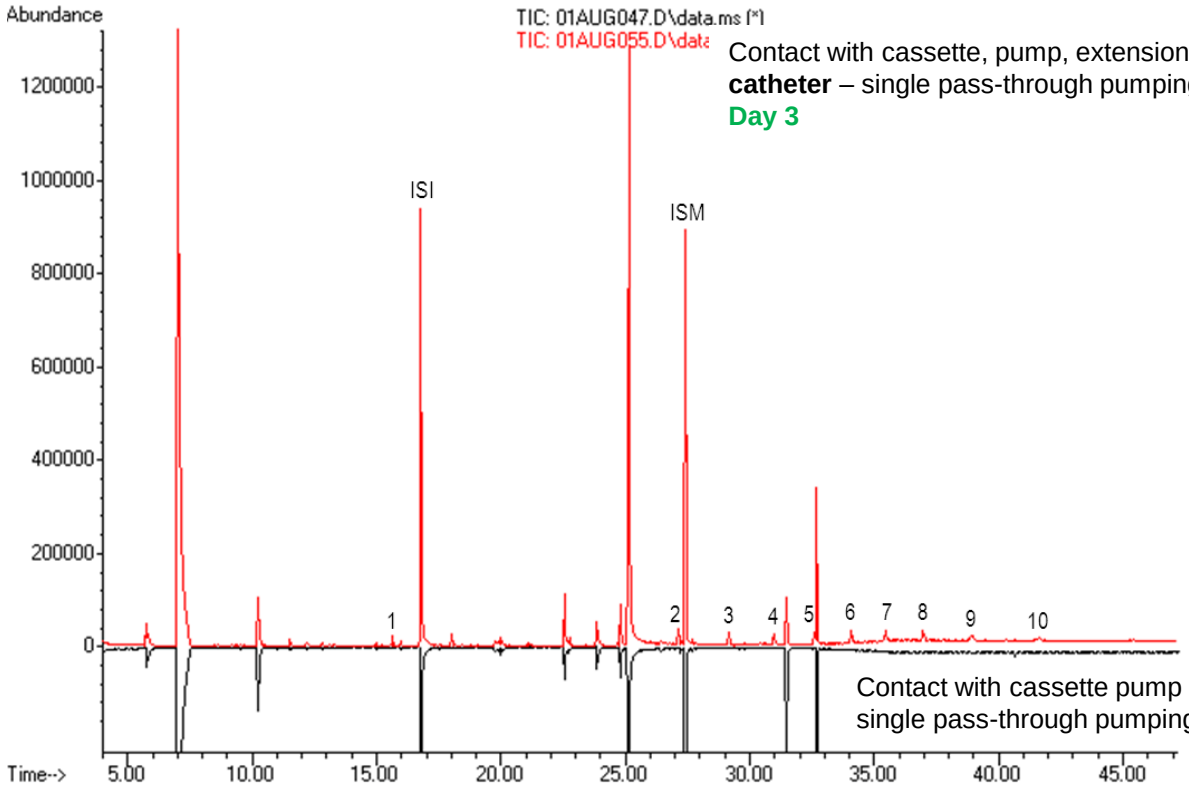
Contact with cassette, pump, extension tubing and **catheter** – single pass-through pumping @ 100 mL/day

Day 1

Contact with cassette pump and extension tubing – single pass-through pumping @ 100 mL/day



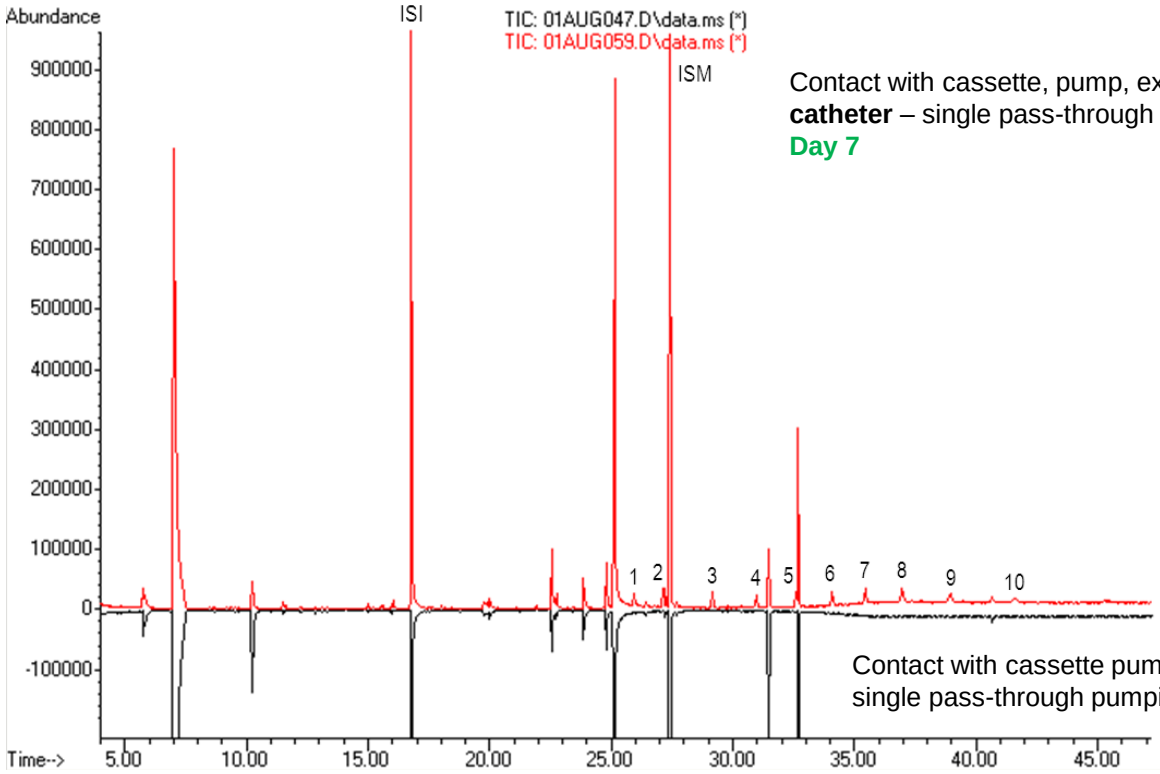
Case study 2



Contact with cassette, pump, extension tubing and **catheter** – single pass-through pumping @ 100 mL/day
Day 3

Contact with cassette pump and extension tubing – single pass-through pumping @ 100 mL/day

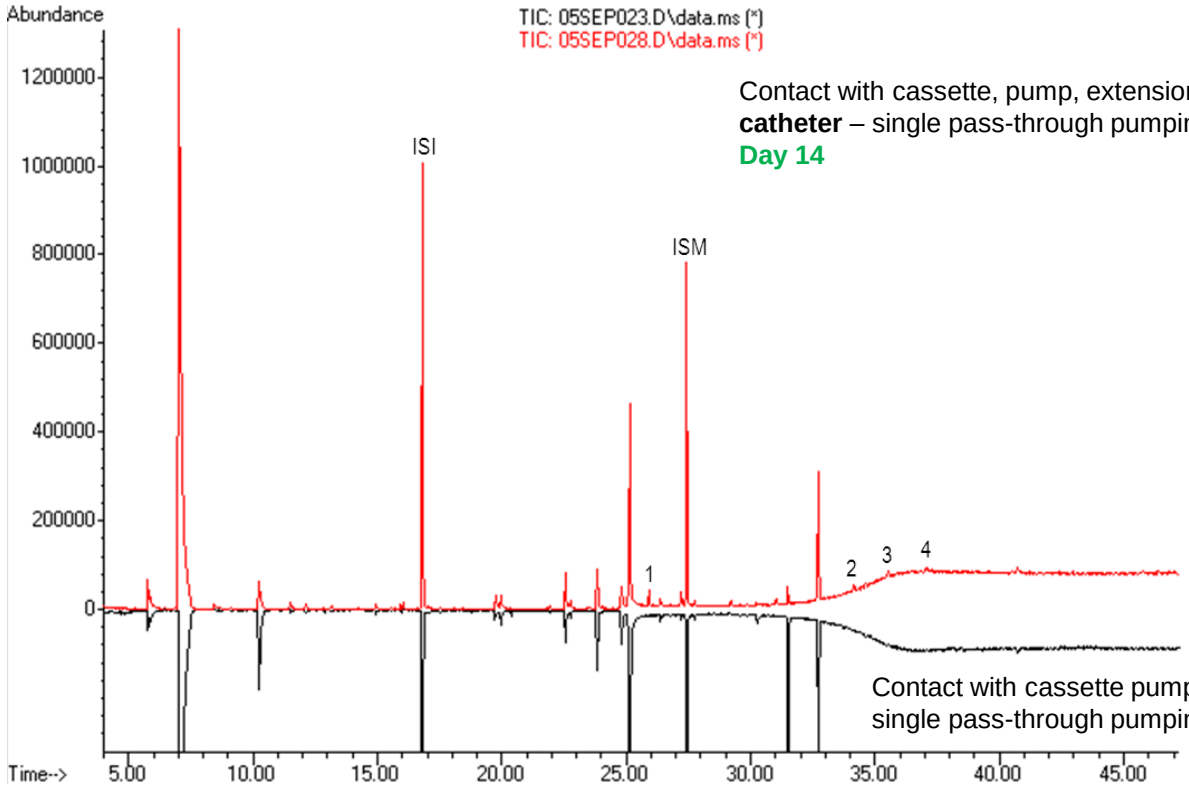
Case study 2



Contact with cassette, pump, extension tubing and **catheter** – single pass-through pumping @ 100 mL/day
Day 7

Contact with cassette pump and extension tubing – single pass-through pumping @ 100 mL/day

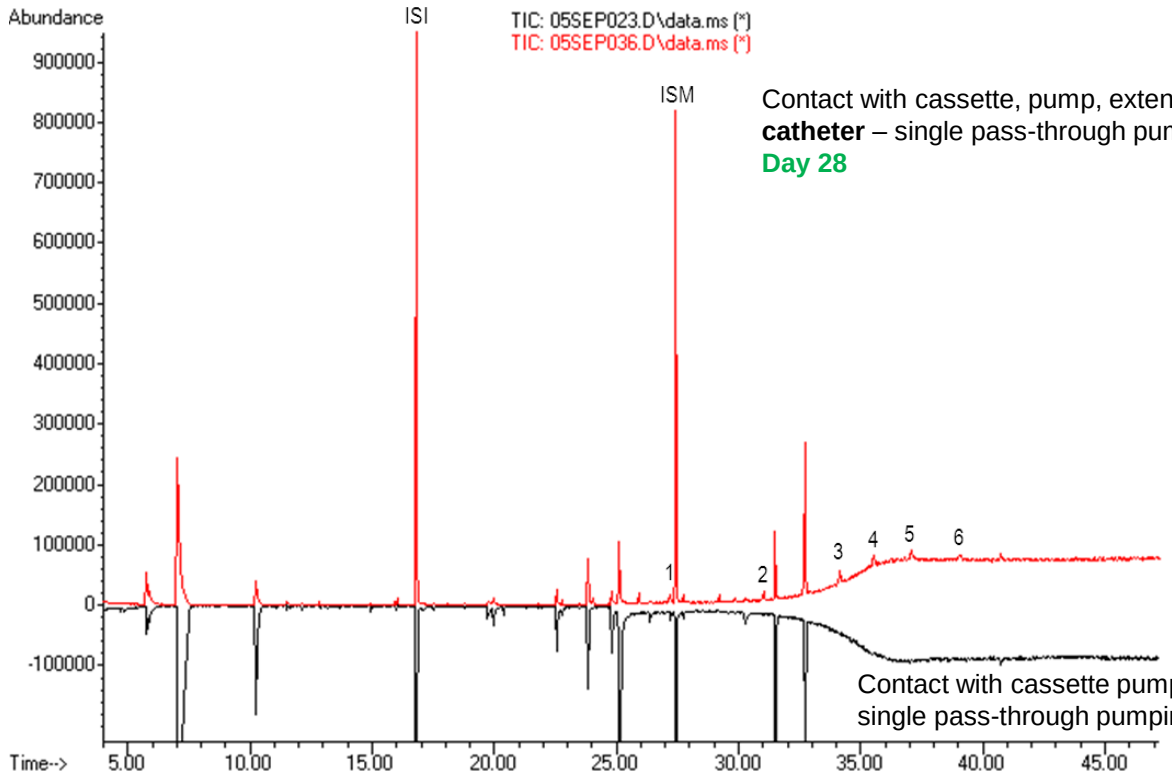
Case study 2



Contact with cassette, pump, extension tubing and **catheter** – single pass-through pumping @ 100 mL/day
Day 14

Contact with cassette pump and extension tubing – single pass-through pumping @ 100 mL/day

Case study 2



Contact with cassette, pump, extension tubing and **catheter** – single pass-through pumping @ 100 mL/day
Day 28

Contact with cassette pump and extension tubing – single pass-through pumping @ 100 mL/day

Conclusions

Path to market

- USA: what is the main mode of action?
- EU: first MDR then local authorities

Leachables/simulation studies

- Don’t underestimate the leaching during the first hours in the use of the administration device
- Leaching may continue long

Questions??