SERVICE DE PHARMACIE

Analyse des Additifs de Plastique en Milieu Hospitalier

16.09.2022

Journées Scientifiques

CCCTA

CHUV

Context

Pourquoi analyser des additifs de plastique dans un secteur de Pharmacie Hospitalière ??

Plastic medical devices

Context

Medication form Pharma Industries and Hospital Pharmacies are produced in highly regulated environments.

- Pharma - GMP environment

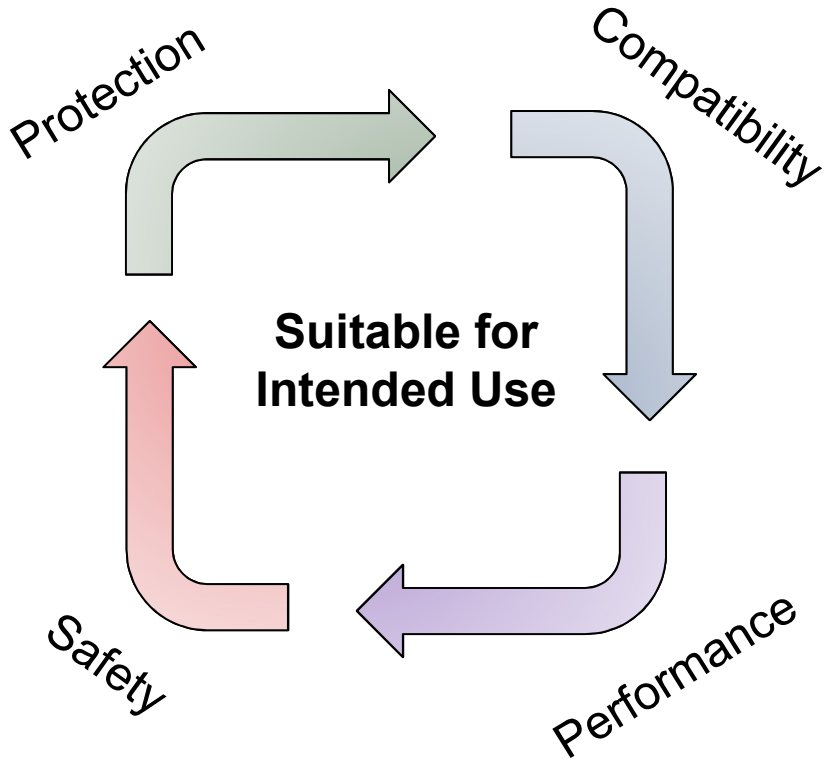
Medical devices are no exceptions

- High quality – certified by regulatory entities

Quality of Packaging Systems

Packaging systems are **qualified** for human use when:

- Protective
- Functional
- Compatible
- Safe

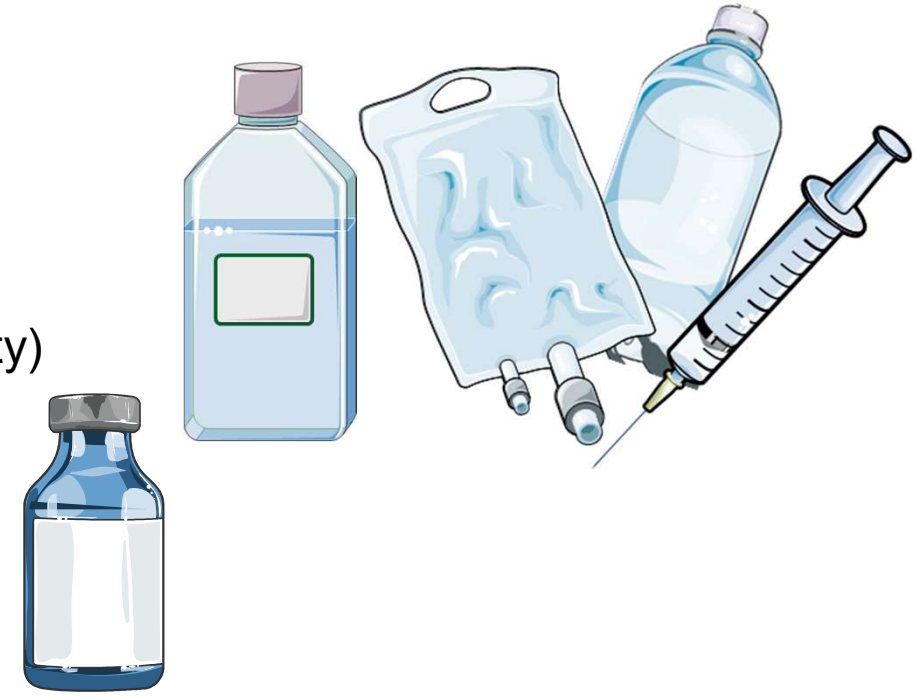


(a) Drug product **containers** and closures shall not be **reactive, additive, or absorptive…**

Medical plastics

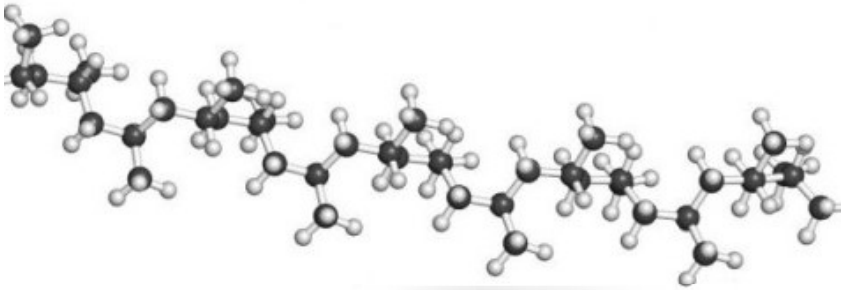
Different types used in Hospital Pharmacies:

- Polypropylene
- Co-extruded Polypropylene
- Polyethylene (low and high density)
- Cyclic olefin polymer (COP)
- Cyclic olefin co-polymer (COC)



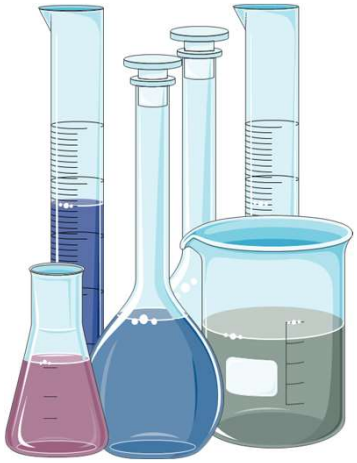
Medical plastics

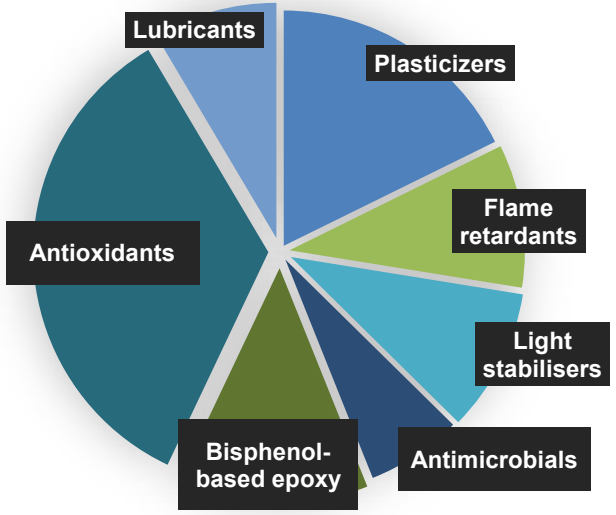
Plastic materials are made of:



➡ **Polymer strains**

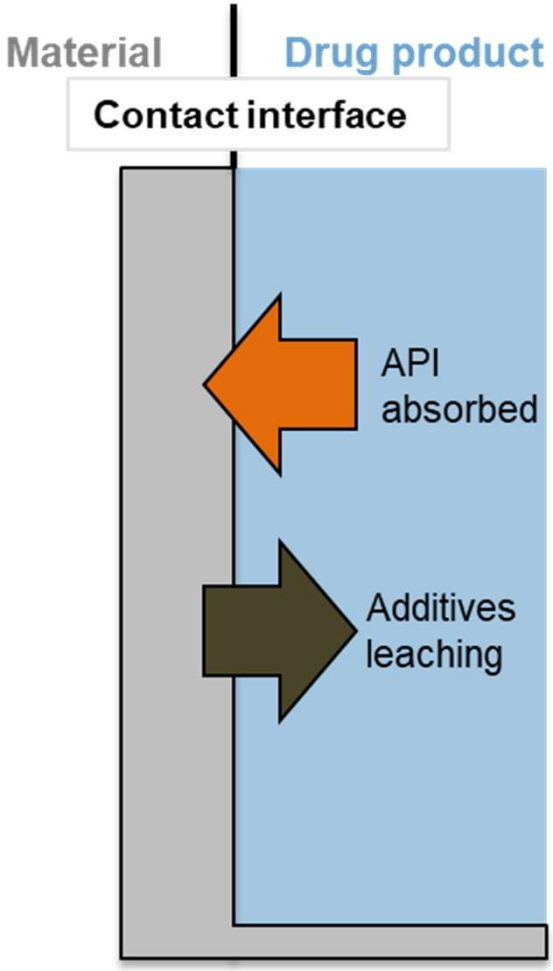
➡ **Additives**





✔ Enabling physical, chemical and biological resistance

Suitability for Use



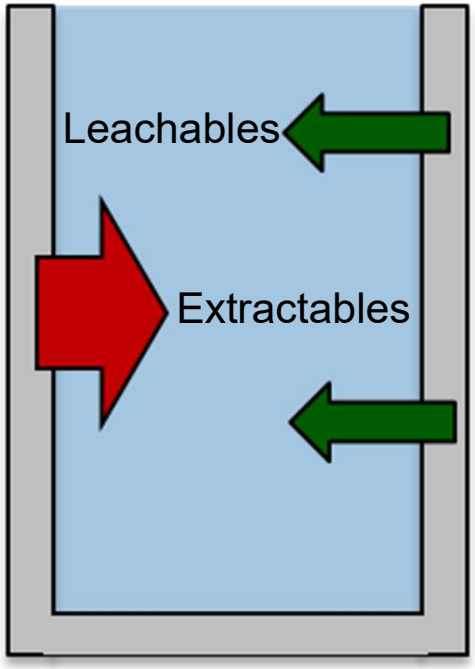
Problem…

- Interaction between the drug product and plastic medical devices
- The interaction may affect the composition of the drug product or the material
- The change of the composition of the drug product or the material may adversely impact them or may cause toxic adverse effects to the user or the patient.

Extractable vs. Leachable Study

Extractable study

- Harsher conditions
- Extraction solvents
- Specified conditions
- Few hours
- Performed by the MD manufacturer



Leachable study

- Softer conditions
- Solvent = drug product
- Real conditions
- Few months / years
- Performed by the drug product manufacturer

Worst case scenario

Real life scenario

Extractable vs. Leachable Study

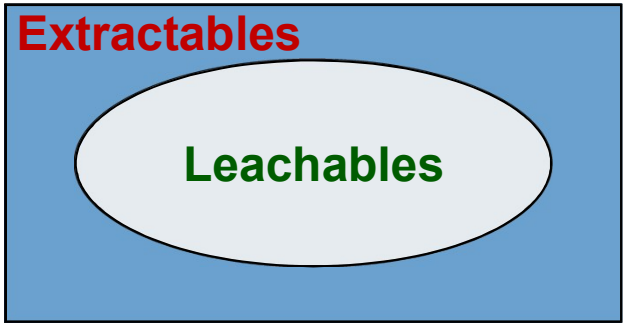
Extractables

Chemical compounds that can be extracted out of the packaging component.

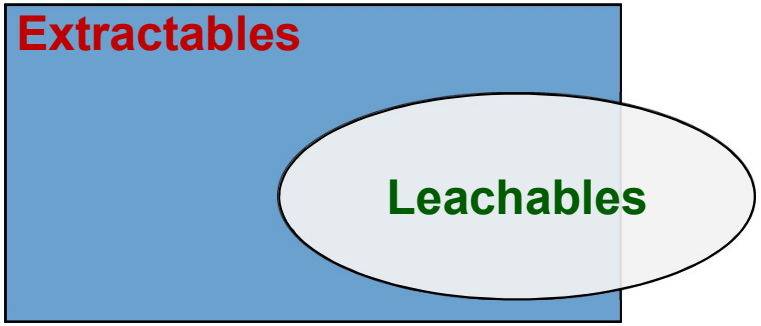
Leachables

Chemical compounds from the packaging component that leach into the drug product.

Ideal



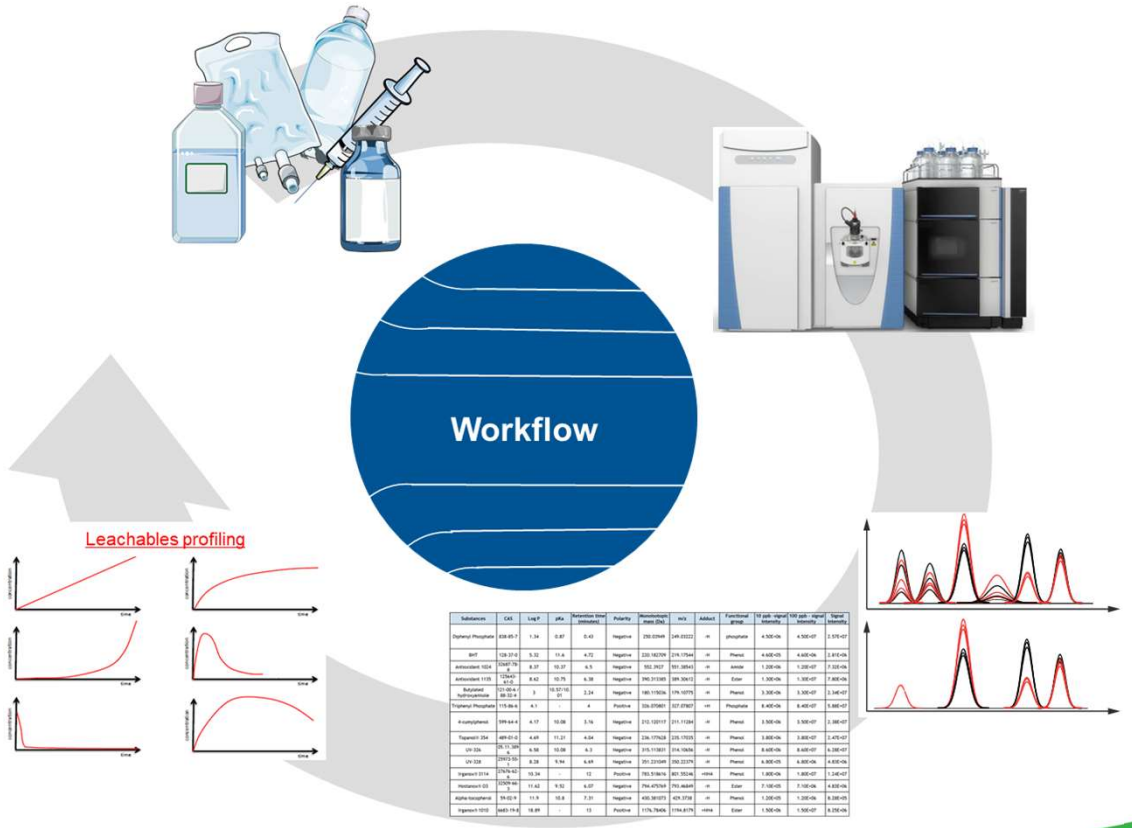
Real-world



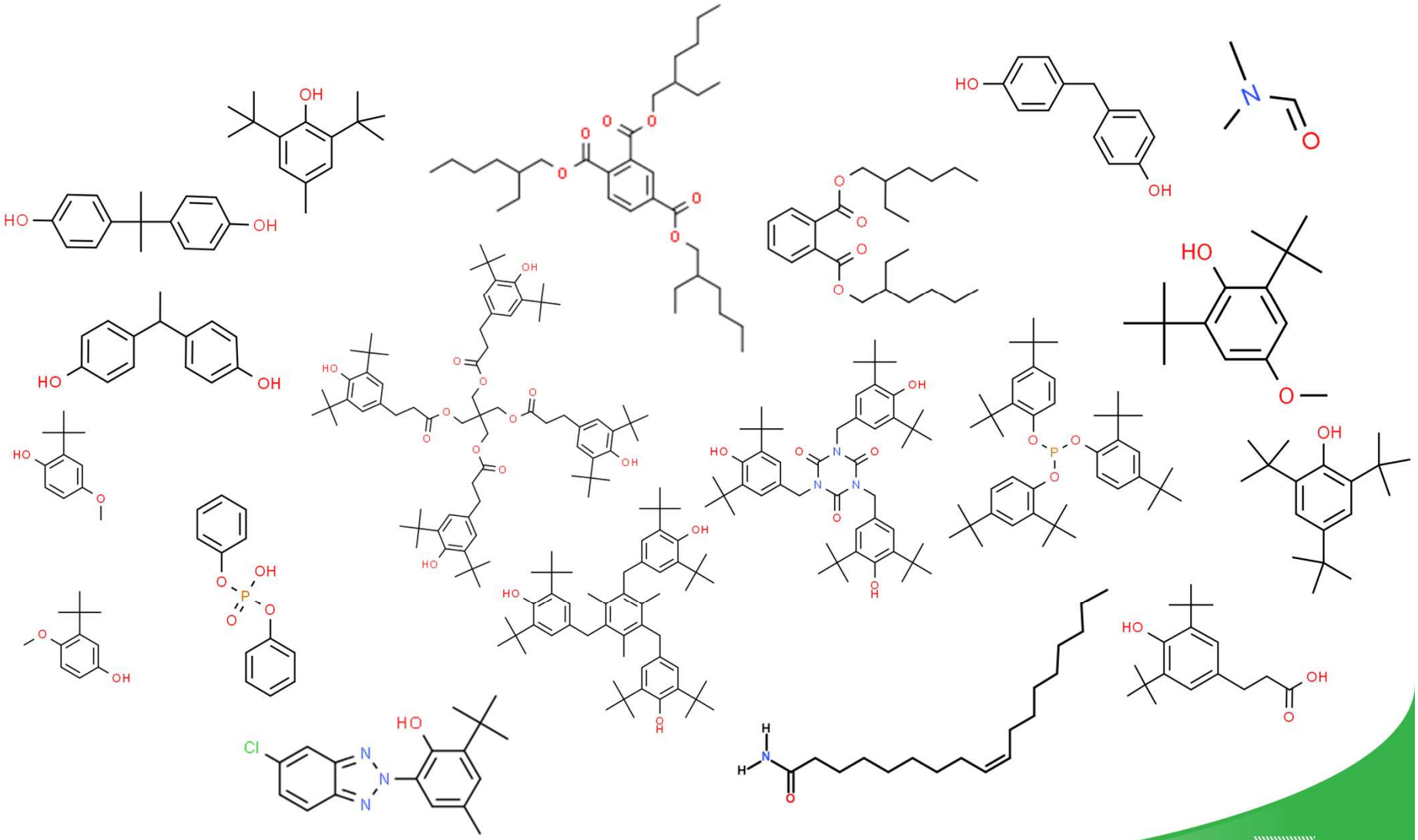
Our interest is on leachables compounds.

General aim of the lab

- Develop and implement a screening workflow for the monitoring of leachables.



Compounds of interest



LC-MS Development

Column :

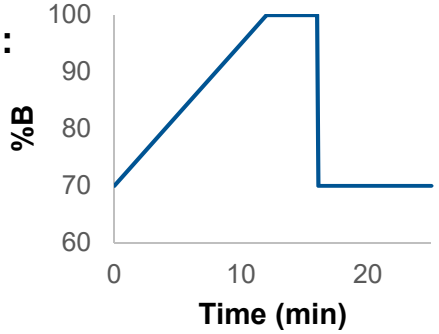
BEH Phenyl 1.7µm, 2.1 x 100mm

T: 60° C

Flow rate: 0.2 mL/min

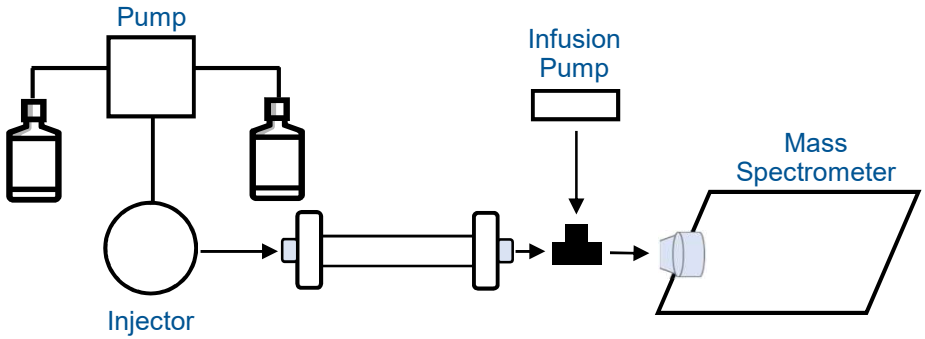
Mobile Phase:

A : H_2O
B : MeOH



30 reference compounds
(representative of different additives classes)

LC-MS Development



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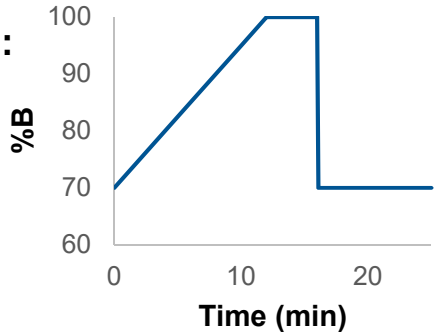


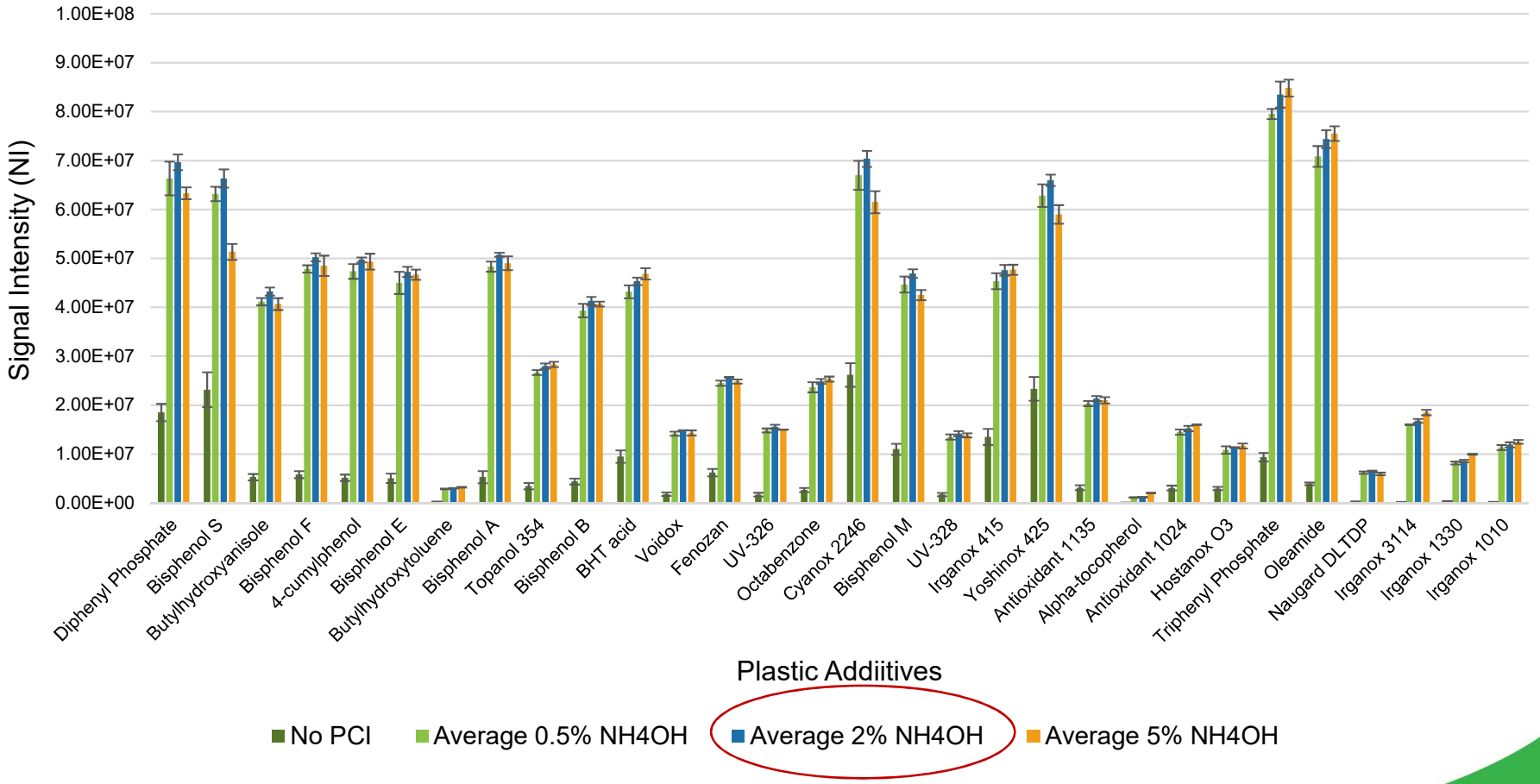
Post Column Infusion (PCI) :

- Different concentration:
  NH_4OH 0.5%, 2% & 5%
- Different flow rate:
  0.5; 1.0; 2.0; 4; & 6 µL/min
- 30 reference compounds

Tan D. et al., 2018. Talanta, 182, 590-594

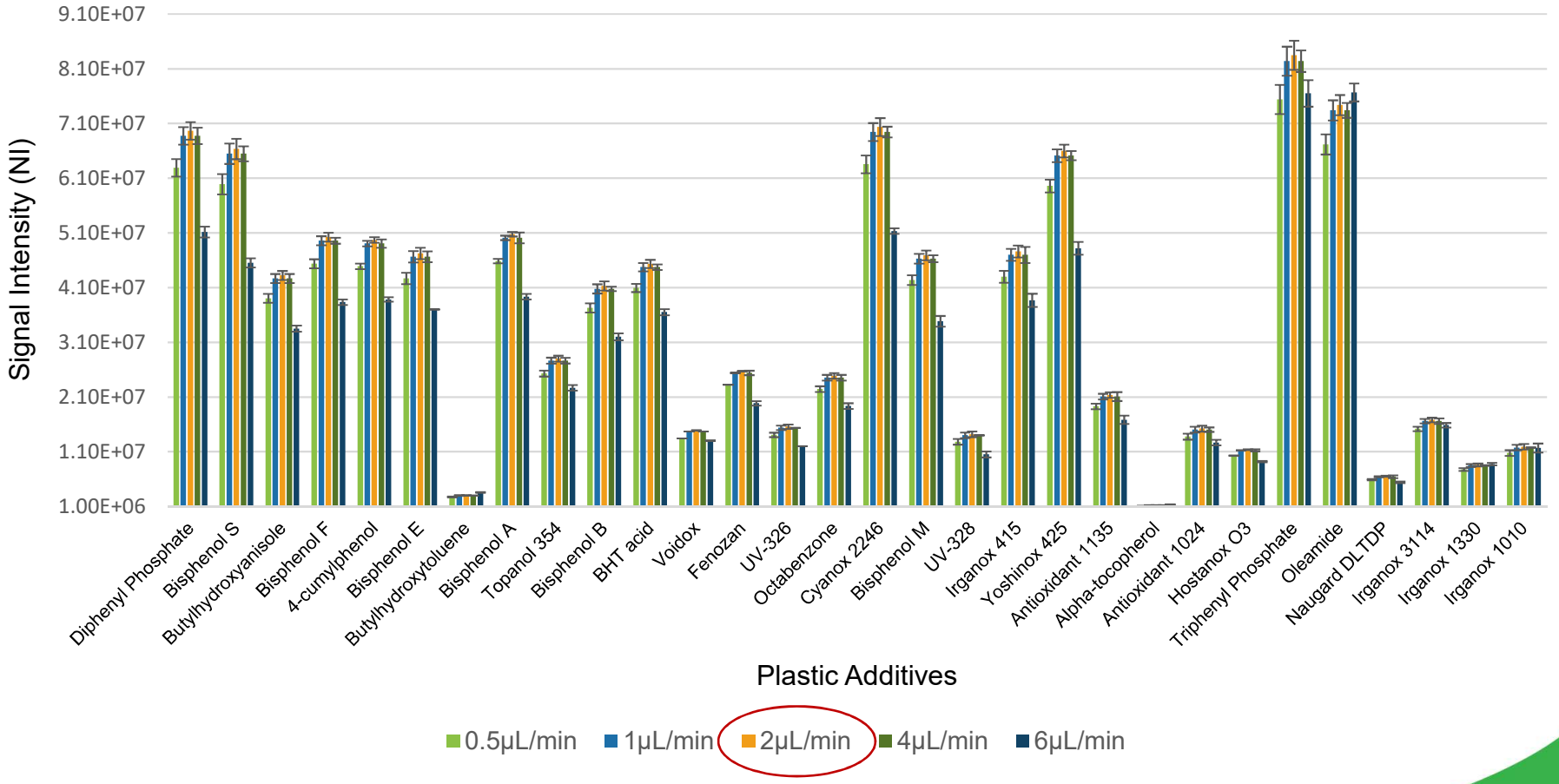
PCI Development

NH4OH Concentration :



PCI Development

PCI flow rate :



PCI Development

- Detects and amplifies different functional groups in both polarities
  - Esters, phosphates, ethers, siloxanes, amide, amines, ketones, aldehydes (positive mode)
  - Hydroxyls, phenols, carboxylic acids (negative mode)
- Low sensitivity : LOD at 0.03 ng/mL, except for Vitamin E, which go as low as around 8 ng/mL

Database

ChemSpider
Search and share chemistry

Endocrine Disruptor Lists

PubChem

ECHA
EUROPEAN CHEMICALS AGENCY

B|BRAUN
SHARING EXPERTISE

TEDX
THE ENDOCRINE DISRUPTION EXCHANGE
Partners in Science

DEDuCT
Database of Endocrine Disrupting Chemicals and their Toxicity Profiles

Baxter

efsa
European Food Safety Authority

UN environment programme
50
1972-2022

BD

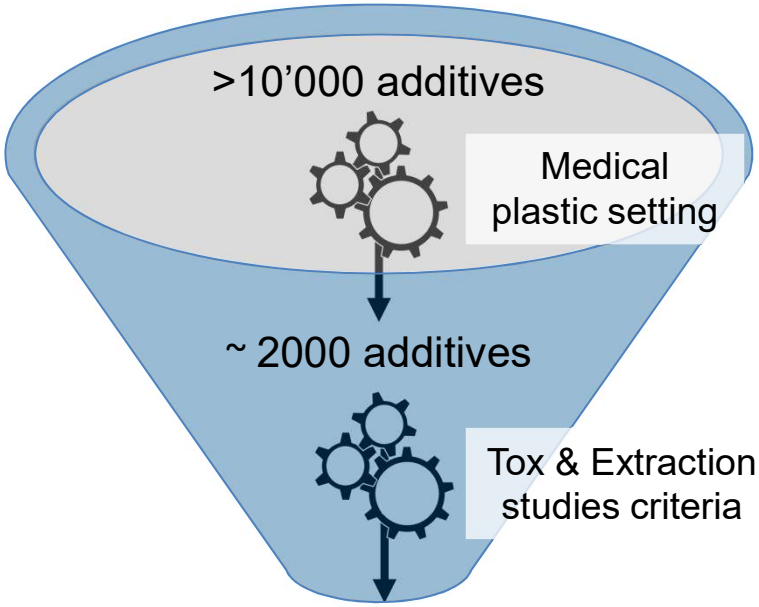
EPA
United States Environmental Protection Agency

SpecialChem
The material selection platform

CompTox Chemicals Dashboard

PubMed.gov

FDA U.S. FOOD & DRUG ADMINISTRATION
Endocrine Disruptor Knowledge Base

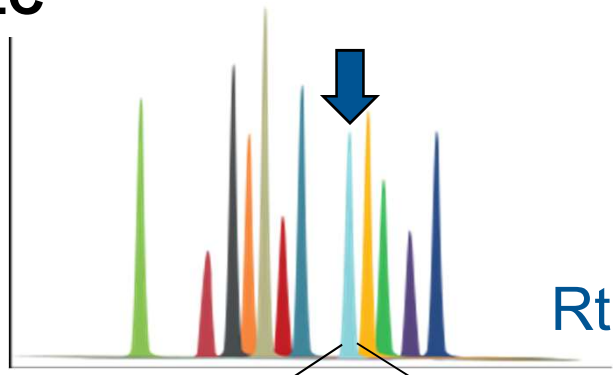


300 additives

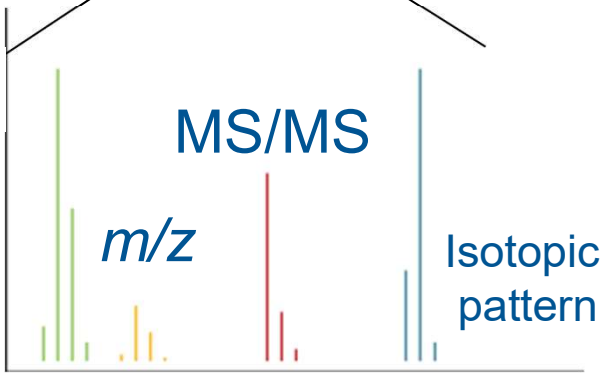
Leachables identification

In-house database

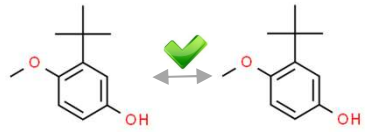
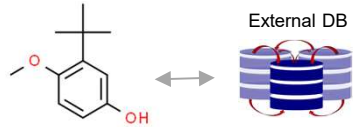
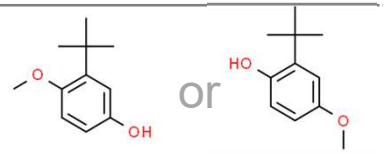
1) LC



2) MS



Identification confidence levels

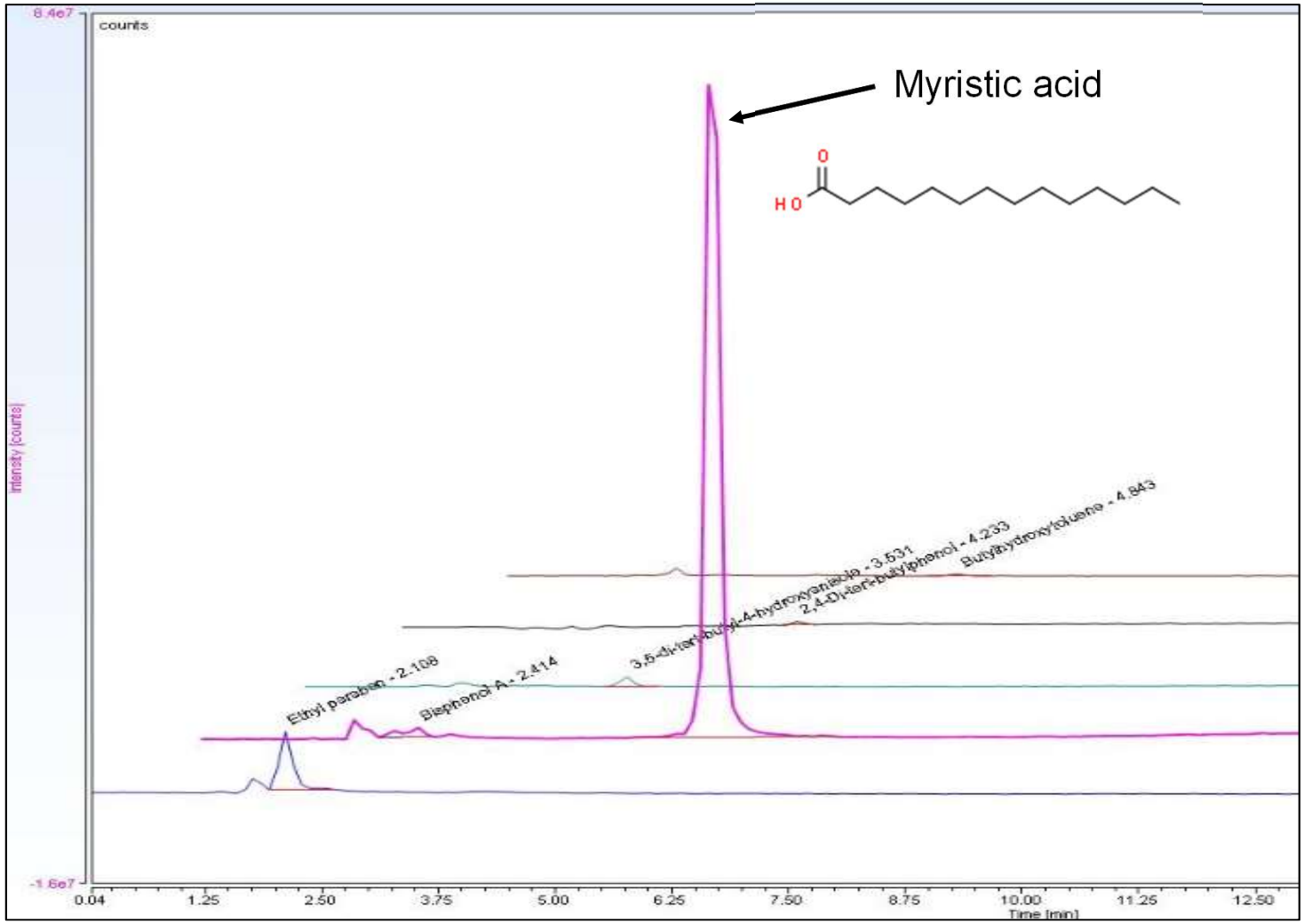
1	**Confirmed structure** vs. reference standard, in-lab	
2	**Probable structure** a) By library spectrum match b) By diagnostic evidence	
3	**Tentative candidate(s)** Structure, substituents, class	
4	**Unequivocal molecular fromula** Exact mass of interest	207.0895 Da $C_{11}H_{13}NO_3$

Celma A. et al., 2020. Environ. Sci. Technol., 54, 23, 15120-15131

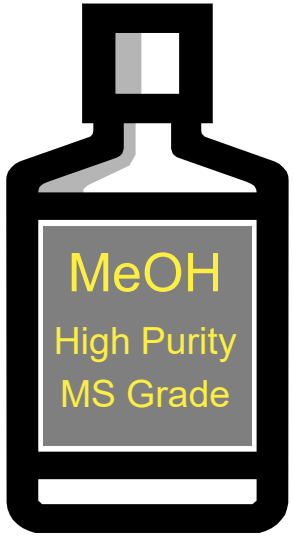
Contaminants of the system

Plastic components of the LC system

Contaminants of the system

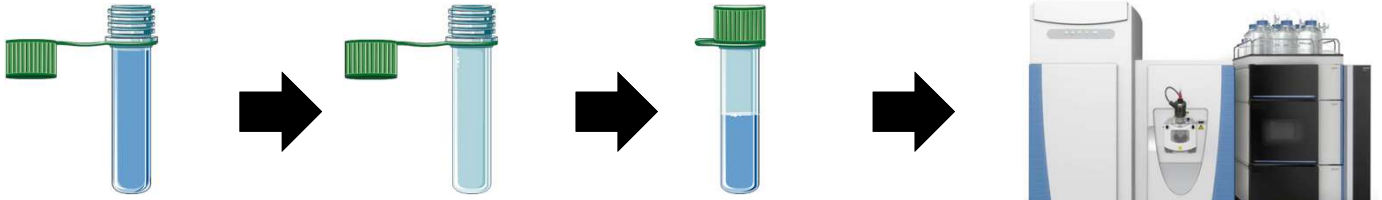


Solvent Profiling



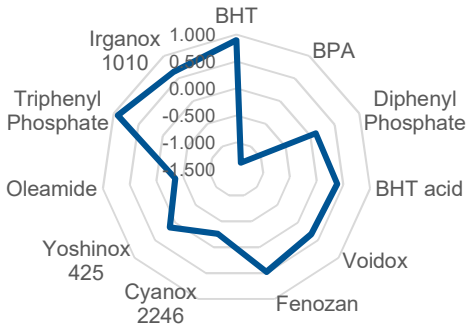
Are they so pure ???

From a plastic additives point of view...

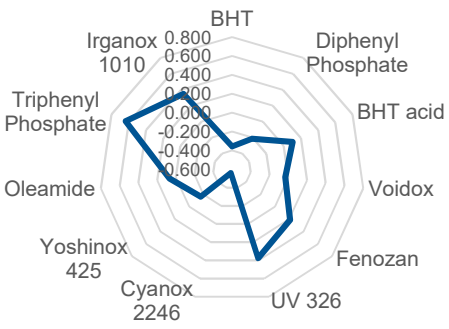


Solvent Profiling

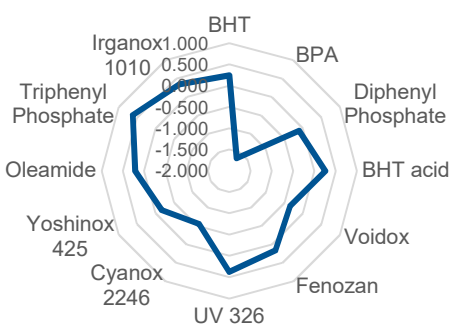
H_2O



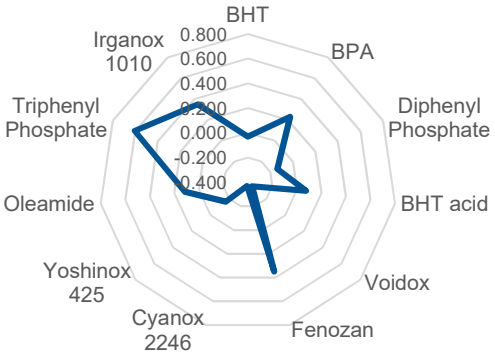
MeOH



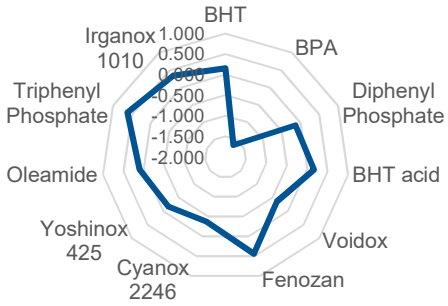
ACN



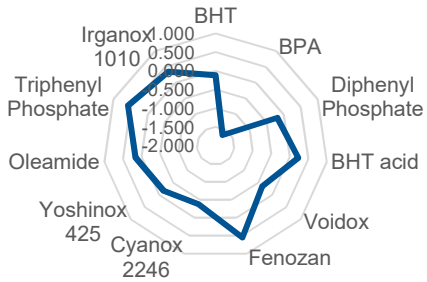
IPA



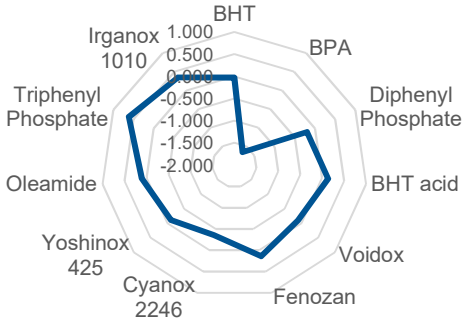
Acetone



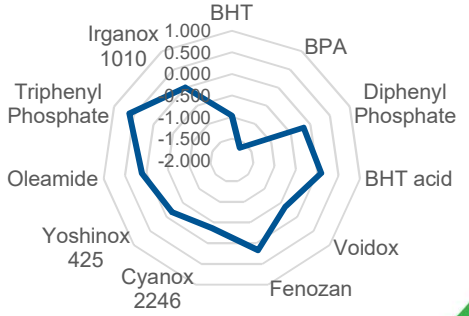
Ethyl Acetate



DCM



Hexane

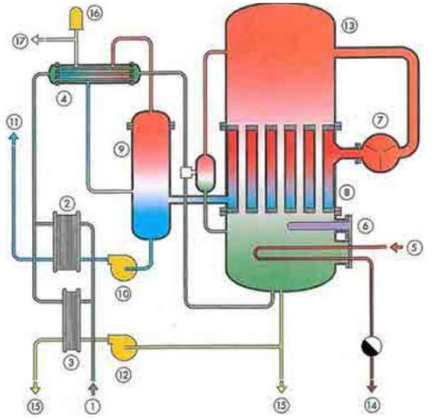


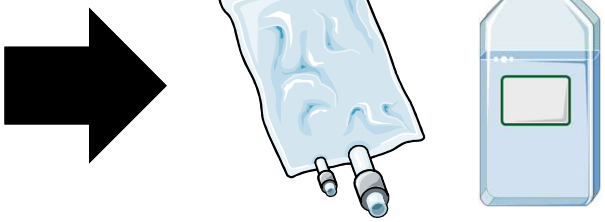
Medical Water

Source of WFI Water in Hospitals :

From industrial suppliers

Internally: water loop with distillation system





Packaging

Medical Water

Source of WFI Water in Hospitals :

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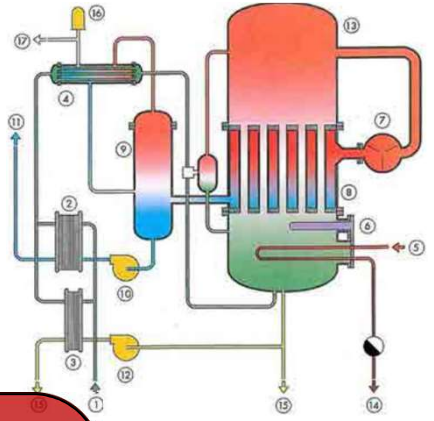
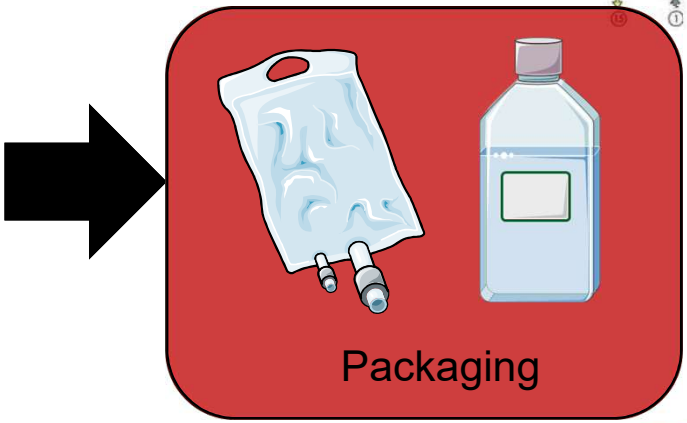
Internally: water loop with distillation system



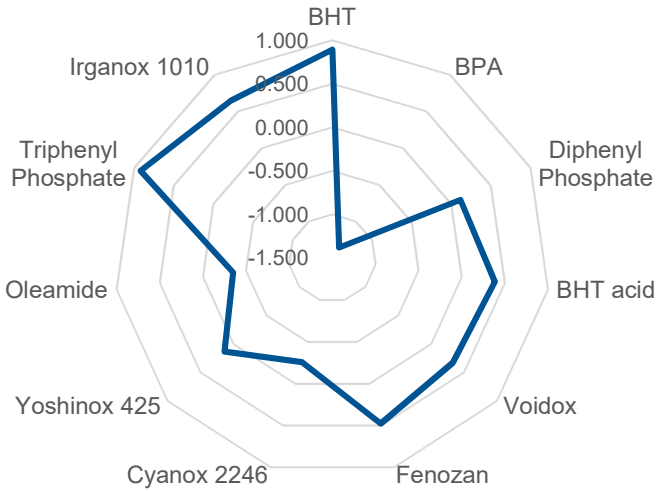


Autoclave

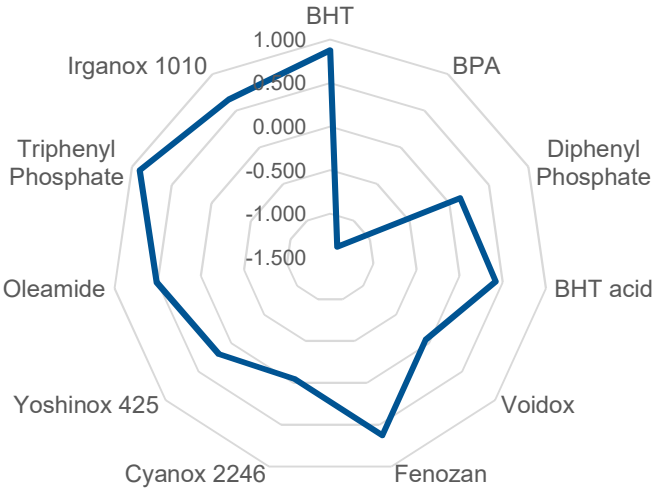
Moist heat: 121 C, 30 min

Medical Water

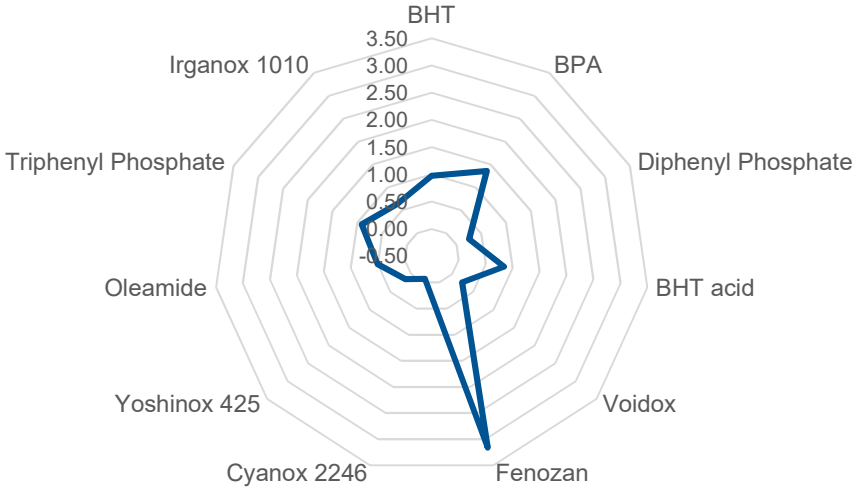
MS Quality H_2O



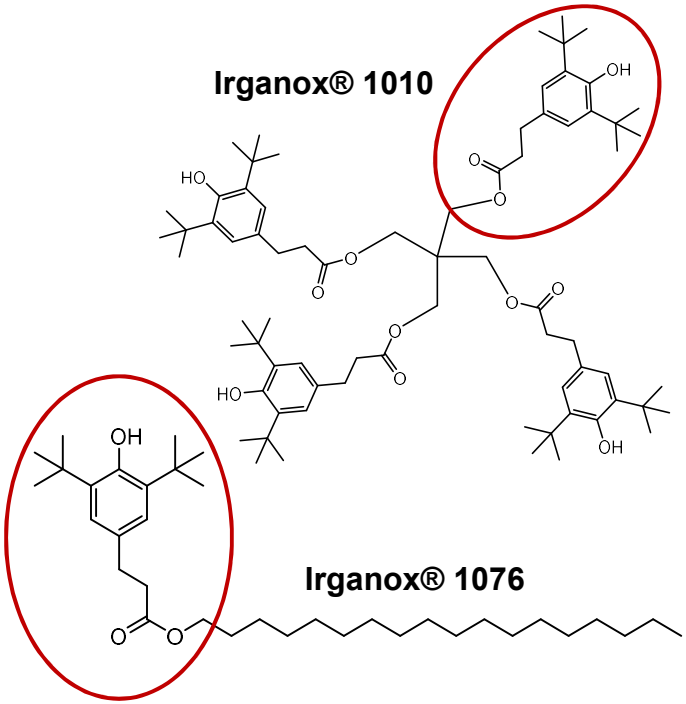
Medical grade H_2O pre-autoclaved



Medical grade H_2O post-autoclaved

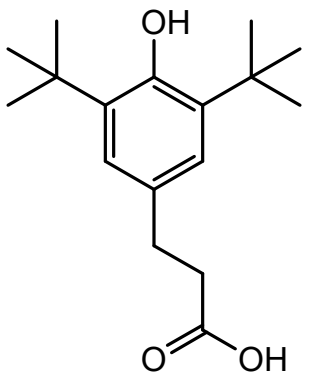


Fenozan



Antioxidants

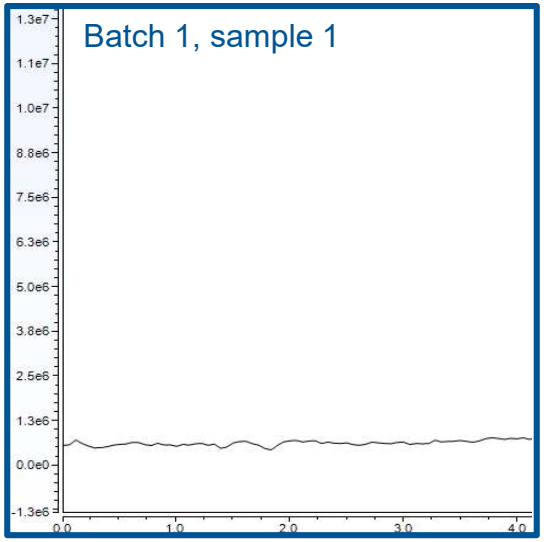
Heat sterilisation

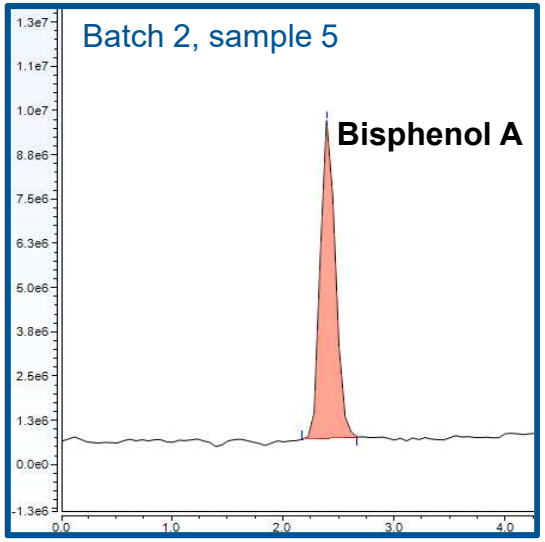


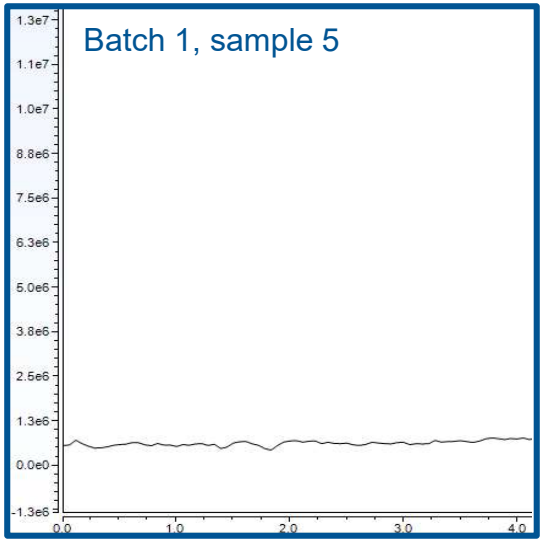
Fenozan-acid

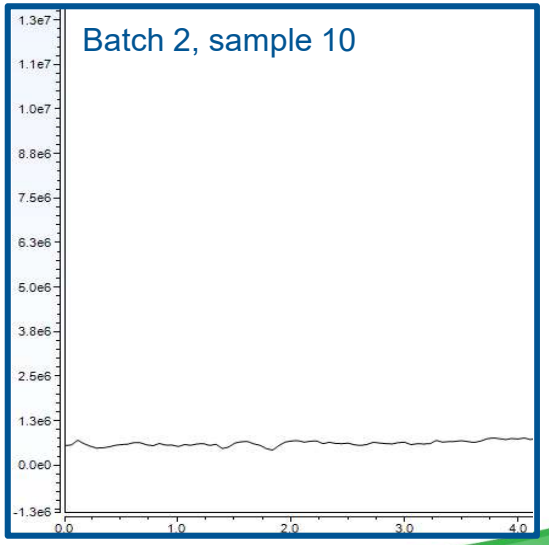
pH modification may affect the physico-chemical stability of the drug solution: solubility issues, chemical stability of the API.

NIAS


Batch 1, sample 1
1.3e7
1.1e7
1.0e7
8.8e6
7.5e6
6.3e6
5.0e6
3.8e6
2.5e6
1.3e6
0.0e0
-1.3e6
0.0
1.0
2.0
3.0
4.0


Batch 2, sample 5
Bisphenol A
1.3e7
1.1e7
1.0e7
8.8e6
7.5e6
6.3e6
5.0e6
3.8e6
2.5e6
1.3e6
0.0e0
-1.3e6
0.0
1.0
2.0
3.0
4.0

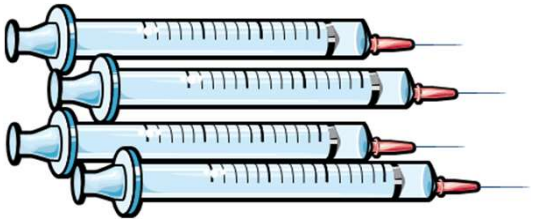

Batch 1, sample 5
1.3e7
1.1e7
1.0e7
8.8e6
7.5e6
6.3e6
5.0e6
3.8e6
2.5e6
1.3e6
0.0e0
-1.3e6
0.0
1.0
2.0
3.0
4.0


Batch 2, sample 10
1.3e7
1.1e7
1.0e7
8.8e6
7.5e6
6.3e6
5.0e6
3.8e6
2.5e6
1.3e6
0.0e0
-1.3e6
0.0
1.0
2.0
3.0
4.0

Dose banding

Concept of standardisation of the doses of a drug

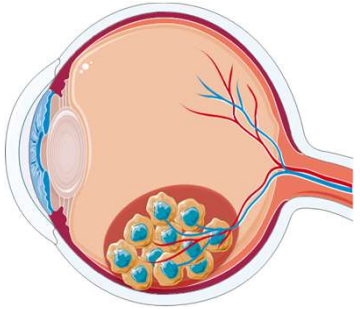
Ready to use syringes



Melphalan

200 µg/mL

Retinoplastoma treatment



- Patients safety
- Caregivers safety

Dose banding

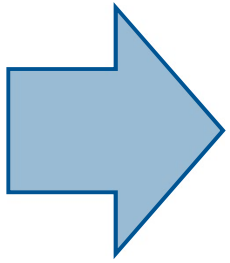
AVIS DE SÉCURITÉ

Lorsque des seringues et des aiguilles étaient utilisées pour des injections intra-oculaires, il y avait un risque de « corps flottants » dans les yeux des patients, qui serait dû à la **silicone**...

… Le danger potentiel est le dépôt de **gouttelettes** d'huile de silicone **dans le vitreux**.

… **affectent** le champ de vision du patient.

… Les corps flottants peuvent nécessiter une vitrectomie permettant leur suppression.



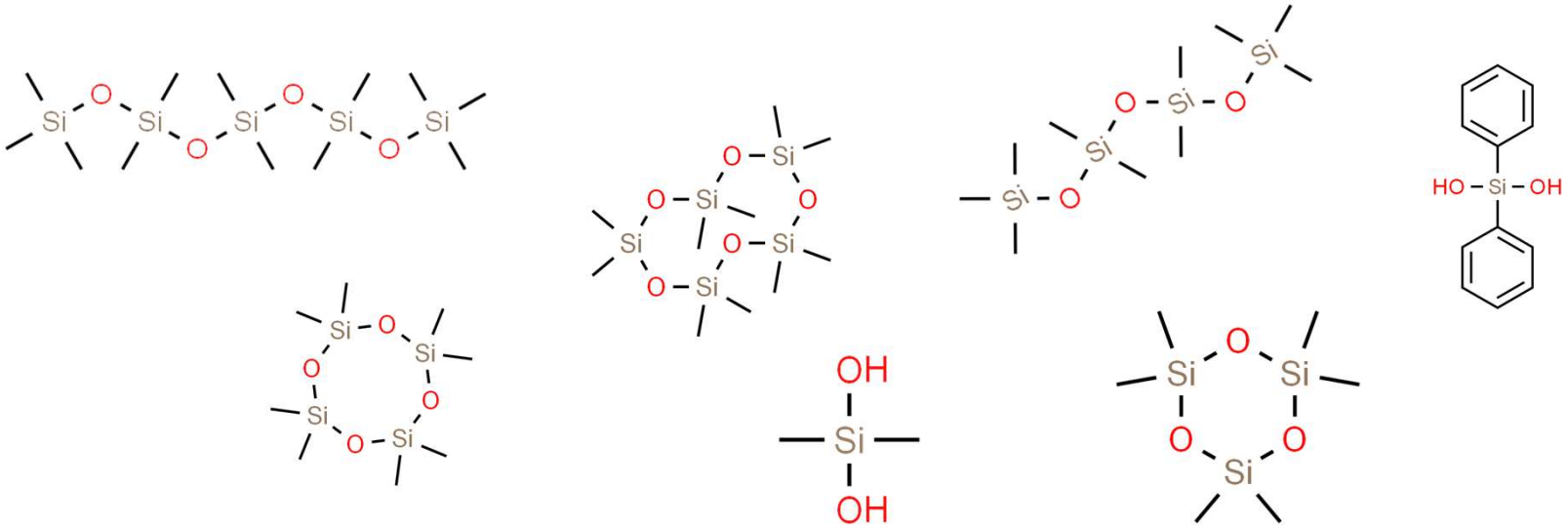
Nos seringues ne sont pas validées pour usage intraoculaire.

Dose banding

AVIS DE SÉCURITÉ

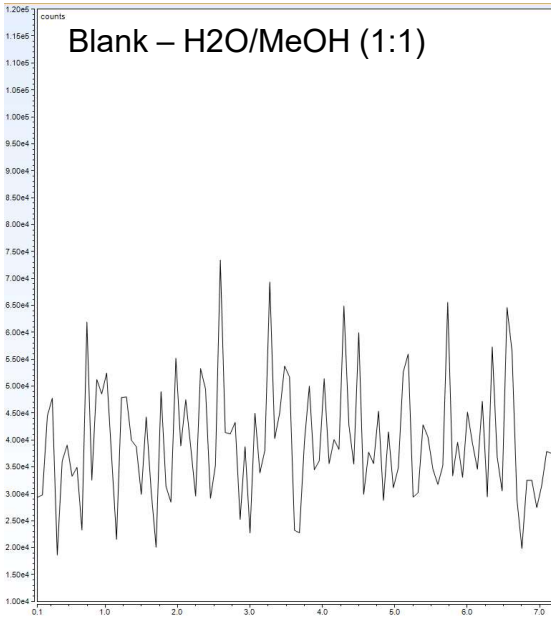
Dose banding

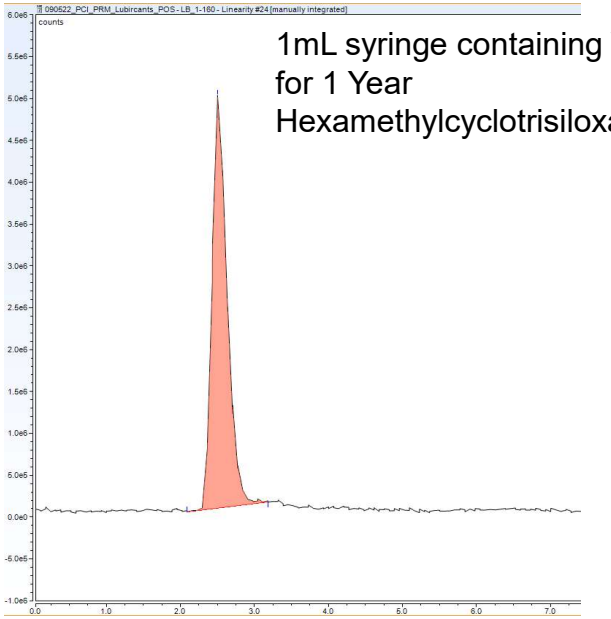
Silicone derivatives are problematic to analyze by LC-MS

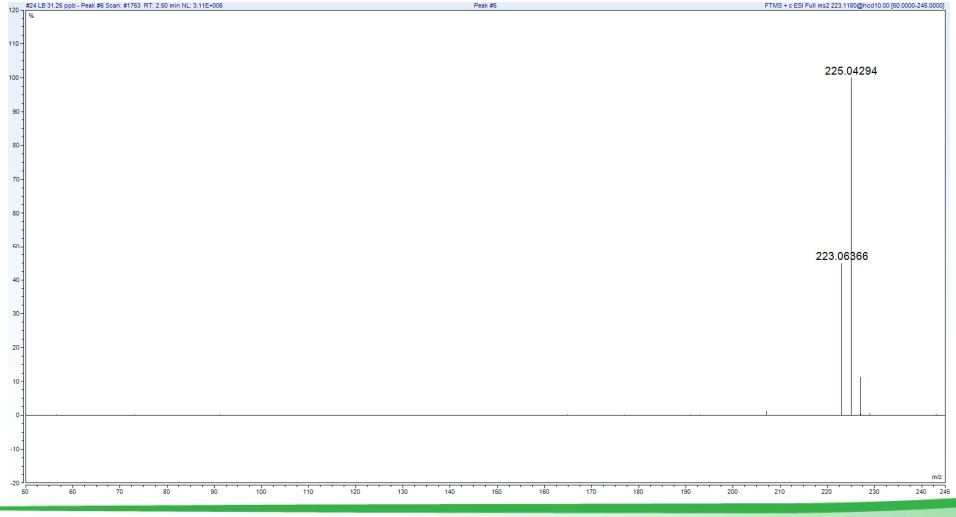


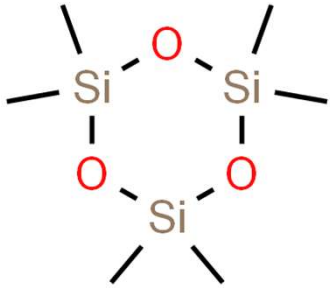
- Volatile compounds
- Difficult to ionize in ESI

Dose banding

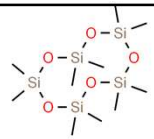
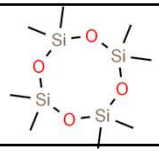
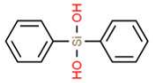




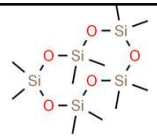
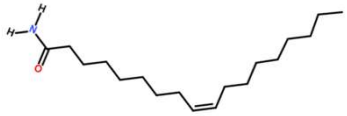
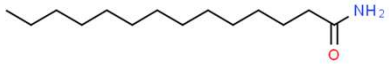




Dose banding

N°	Molecular Structure	Name of Substances	CAS N°	Rt (min)	*m/z*	MS/MS
1		Dodecamethylpentasiloxane	141-63-9	V	V	V
2		Decamethyltetrasiloxane	141-62-8	V	V	V
3		Decamethylcyclopentasiloxane	541-02-6	V	V	V
4		Octamethylcyclotetrasiloxane	556-67-2	V	V	V
5		Diphenylsilanediol	947-42-2	V	V	V
6		Hexamethylcyclotrisiloxane	541-05-9	V	V	V

Dose banding

N°	Molecular Structure	Name of Substances	CAS N°	Rt (min)	*m/z*	MS/MS
1		Decamethylcyclopentasiloxane	541-02-6	V	V	N/A
2		Oleamide	301-02-0	V	V	V
3		Tetradecanamide	638-58-4	V	V	V

What are the risks ?

To use plastic packagings in Hospitals

Frequency
Patients
Preparation of the medication
Risks of the medication

What are the risks ?

To use plastic packagings in Hospitals

At-risk population

Chronic administration

Time of contact

Added value of treatments

Frequency
Patients
Preparation of the medication
Risks of the medication

Aknowledgements

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Thank you for your attention!