Applying the New ISO 10993

(Risk-based Approach to Biocompatibility)

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Standards for **Presentation**

ISO 10993 Suite

Standards that cover all testing under "Biological evaluation of medical devices"

US FDA guidance document

"Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process'" issued June 16, 2016.

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CHANGE

The Years of Change in Biocompatibility

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Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"

International Organization for Standardization

Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process

EU Medical Device Regulation

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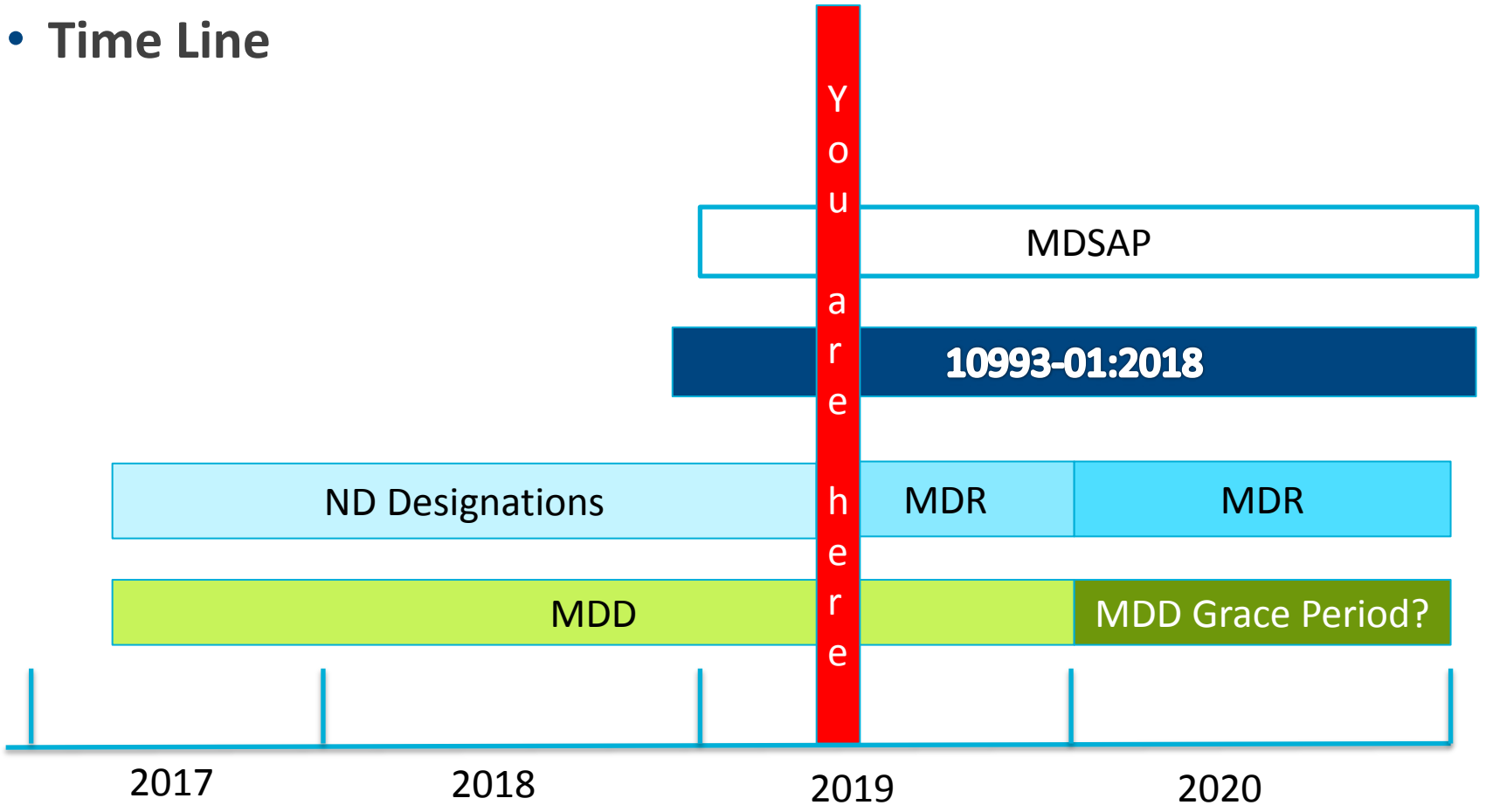
The MDR Countdown!

- **Time Line**



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Then Everything Changed….

More Governance

More Clinical Data

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Now the Clock is Ticking

- Are we going to be ready?

MedTech Europe

Our industry is prepared to submit product files to comply with the new Medical Device Regulation (MDR). However, we cannot do so. The new regulatory system is not ready to function. The deadline for the system to be fully operational is not 26 May 2020, the date of MDR application as the Commission continues to suggest. The deadline for the system to be ready for our industry to comply is now.

Re: Open letter on the implementation and readiness status of the new Medical Device Regulation 745/2017 (MDR)

Dear Vice-President Katainen,

I am writing to you regarding an issue of absolute urgency for patient care across Europe and for the internal market at large. The medical device industry in Europe confirms that without immediate action by the European Commission, the new regulatory system will not be ready on time to ensure continued access of patients and healthcare systems to life-saving and life-transforming devices.

Our industry is prepared to submit product files to comply with the new Medical Device Regulation (MDR). However, we cannot do so. The new regulatory system is not ready to function. The deadline for the system to be fully operational is not 26 May 2020, the date of MDR application as the Commission continues to suggest. The deadline for the system to be ready for our industry to comply is now.

One of the critical concerns is the designation and capacity of Notified Bodies, which the European Commission and Member States are still assessing to the new rules. It is only after being designated that

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The Links

http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf

http://data.consilium.europa.eu/doc/document/ST-10728-2016-INIT/en/pdf

https://standards.aami.org/higherlogic/ws/public/download/11414/Public%20Review%20Draft%20CDV_2%2010993_1.pdf

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Is Your Backpack Too Full?

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Is biocompatibility really necessary?

"My device has been on the market for years…"

"We only use biocompatible materials…"

"Our materials are made according to ASTM standards…"

"We did some testing during the device R&D…"

"Our device is only used for 5 minutes…"

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Past Approach

"I don't have to understand the material's impact on the body."

"I don't have to understand the testing" (black box approach)

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Past Approach

Vs.

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Past Approach

Device contact

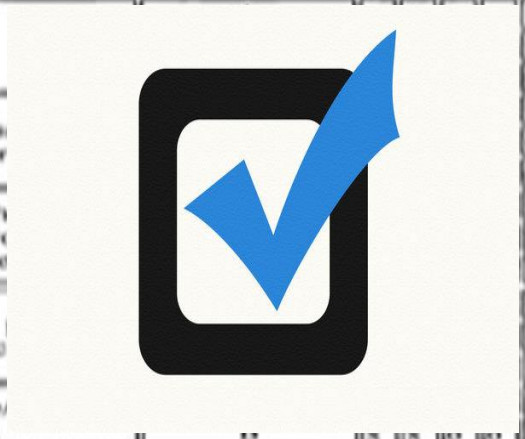
Contact time

Perform tests

510(k) Memorandum - #G95-1 Table 1

Initial Evaluation Tests for Consideration

Device Categories			Biological Effect
Body Contact (see 4.1)		Contact duration (see 4.2) A-limited (24h) B-prolonged (24h to 30 days) C-permanent (>30days)	Cytotoxicity; Sensitization; Irritation or intracutaneous reactivity; Acute systemic toxicity; Subacute or subchronic toxicity; Genotoxicity; Implantation; Hemocompatibility
Surface devices	Skin	A	
		B	
		C	
	Mucosal membrane	A	
		B	
		C	
	Breached or compromised surface	A	
		B	
		C	
External communicating devices	Blood (indirect)	A	
		B	
		C	
	Tissue/dentin communicating*	A	
		B	
		C	
	Circulating blood	A	
		B	
		C	
Implant devices	Tissue/bone	A	
		B	
		C	
	Blood	A	
		B	
		C	



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Past Approach

- Didn't understand
  - Materials
  - Testing

510(k) Memorandum - #G95-1 Table 1

Initial Evaluation Tests for Consideration

Device Categories			Biological Effect															
Body Contact (see 4.1)		Contact duration (see 4.2) A-limited (24h) B-prolonged (24h to 30 days) C-permanent (>30days)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Acute Systemic Toxicity (oral)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Hemocompatibility							
Surface devices	Skin	A																
		B																
		C																
	Mucosal membrane	A																
		B																
		C																
	Breached or compromised surface	A																
		B																
		C																
External communicating devices	Blood (indirect)	A																
		B																
		C																
	Tissue/bone/dentin communicating*	A																
		B	X	X	O	O	O	X	X									
		C	X	X	O	O	O	X	X									
	Circulating blood	A	X	X	X	X		O[A]		X								
		B	X	X	X	X	O	X	O	X								
		C	X	X	X	X	X	X	O	X								
Implant devices	Tissue/bone	A	X	X	X	O												
		B	X	X	O	O	O	X	X									
		C	X	X	O	O	O	X	X									
	Blood	A	X	X	X	X				X	X							
		B	X	X	X	X	O	X		X	X							
		C	X	X	X	X	X	X	X		X							

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Table A.1: Biocompatibility Evaluation Endpoints

Medical device categorization by			Biological effect												
Nature of Body Contact		Contact Duration	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Acute Systemic Toxicity	Material-Mediated Pyrogenicity	Subacute/Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental Toxicity#	Degradation@
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – permanent (> 30 d)													
Surface device	Intact skin	A	X	X	X										
		B	X	X	X										
		C	X	X	X										
	Mucosal membrane	A	X	X	X										
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O			
	Breached or compromised surface	A	X	X	X	O	O								
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O	O		
External communicating device	Blood path, indirect	A	X	X	X	X	O				X				
		B	X	X	X	X	O	O			X				
		C	X	X	O	X	O	X	X	O	X	O	O		

Material Evaluation

[63] Device categorization information can be obtained informally via email, or as a part of ODE's Pre-Submission process. Refer to FDA's guidance document "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff - Guidance for Industry and FDA Staff" (February 18, 2014).

Nature of Body Contact		Contact Duration A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Acute Systemic Toxicity	Material-Mediated Pyrogenicity	Subacute/Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental Toxicity#	Degradation@
Category	Contact														
	Tissue+/bone/ dentin	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Circulating blood	A	X	X	X	X	O		O		X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		
Implant device	Tissue+/bone	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Blood	A	X	X	X	X	O		O	X	X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		

X = ISO 10993-1:2009 recommended endpoints for consideration*

O = Additional FDA recommended endpoints for consideration*

Note * All X's and O's should be addressed in the biological safety evaluation, either through the use of existing data, additional endpoint-specific testing, or a rationale for why the endpoint does not require additional assessment.

Note + Tissue includes tissue fluids and subcutaneous spaces

Note ^ For all devices used in extracorporeal circuits

Note # Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, devices with relevant target populations (e.g., pregnant women), and/or devices where there is the probability for local presence of device materials in the reproductive organs.

Note @ Degradation information should be provided for any devices, device components, or materials remaining in contact with tissue that are intended to degrade.

Table A.1 — Endpoints to be addressed in a biological risk assessmen

Medical device categorization by			Endpoints of biological e							
Nature of body contact		Contact duration								
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – Long term (>30 d)	Physical and/or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material mediated pyrogenicity[a]	Acute systemic toxicity[b]	Subacute toxicity[b]	Subchronic toxicity[b]
Surface medical device	Intact skin	A	X[g]	E[h]	E	E				
		B	X	E	E	E				
		C	X	E	E	E				
	Mucosal membrane	A	X	E	E	E				
		B	X	E	E	E		E	E	
		C	X	E	E	E		E	E	E
	Breached or compromised surface	A	X	E	E	E	E	E		
		B	X	E	E	E	E	E	E	
		C	X	E	E	E	E	E	E	E
Externally communicating medical device	Blood path, indirect	A	X	E	E	E	E	E		
		B	X	E	E	E	E	E	E	
		C	X	E	E	E	E	E	E	E
	Tissue/ bone/ dentin[i]	A	X	E	E	E	E	E		
		B	X	E	E	E	E	E	E	
		C	X	E	E	E	E	E	E	E
	Circulating blood	A	X	E	E	E	E	E		
		B	X	E	E	E	E	E	E	
		C	X	E	E	E	E	E	E	E

ISO 10993 and RISK

ISO 10993 is intended as a guidance to determine the potential biological risks arising from the use of medical devices.

Meaning, what is the risk of my materials and processes to the patient?

ISO 10993-1: Biological evaluation of medical devices – Part 1: Evaluation and testing within a **risk** management process

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Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"

Section III. Risk Management for Biocompatibility Evaluations

"Such a process should generally begin with assessment of the device, including the **material components**, the **manufacturing processes**, the **clinical use of the device**…" Considering this information, the **potential risks from a biocompatibility perspective** should be identified. Considering the potential biological impact, a plan should be developed … **either by biocompatibility testing or other evaluations that appropriately address the risks.**

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Incorporating Risk

What is **Risk**?

ISO 14971 Definition: Combination of the **probability of occurrence** of harm and the **severity of that harm.**

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Biological Safety Evaluation

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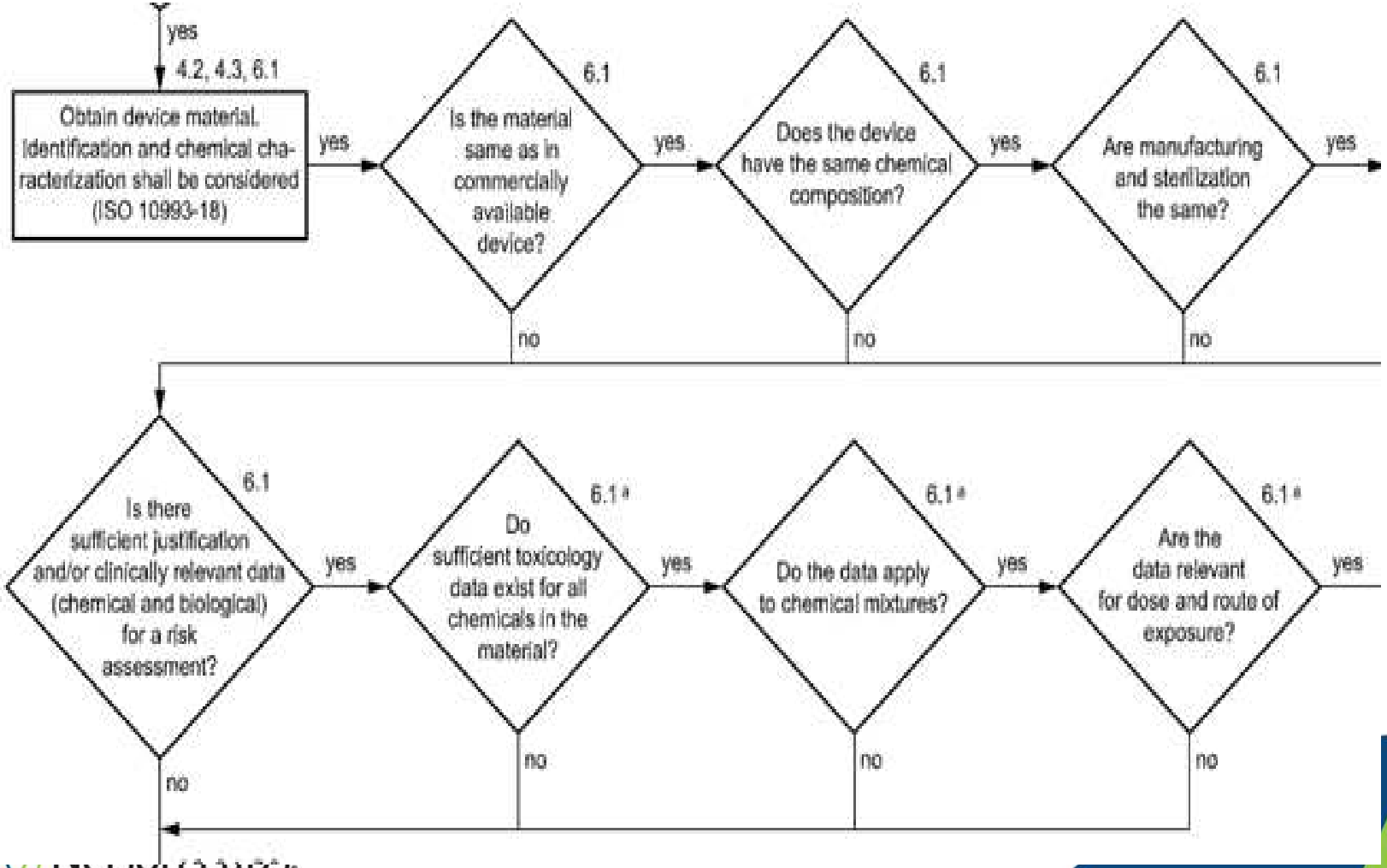
Biological Evaluation Plan (BEP)

Identify Risks by identifying what we already know



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Material Characterization

"In the selection of materials to be used in device manufacture, the **first consideration shall be fitness for purpose with regard to characteristics and properties of the material**, which include chemical, toxicological, physical, electrical, morphological and mechanical properties." ISO 10993-1

Biological Evaluation Plan (BEP)

Material Characterization

"The extent of chemical characterization required should reflect the **nature** and **duration** of the clinical exposure and shall be determined by the toxicological risk assessor based on the data necessary to evaluate the biological safety of the device…This procedure should consider **each of the materials** used in a medical device in addition to the requirement for chemical characterization of the finished device." ISO 10993-18

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Biological Evaluation Plan (BEP)

Material Characterization

Possibly…

- New materials
- Leveraged materials
- Material interactions?
- Combination products
- Supplier testing information
- Chemical characterization testing

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Biological Evaluation Plan (BEP)

Material Characterization

Supplier information

- Claims ISO 10993 compliance – what does that mean?
- Claims USP Class VI

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Biological Evaluation Plan (BEP)

USP Class VI

- Testing spelled out in the USP Pharmacopeia <88>
- Used for raw material plastic classification “Class VI certification”
- Originally designed to test pharmaceutical containers

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Biological Evaluation Plan (BEP)

USP Class VI Regiment

- Irritation
- Systemic Injection
- Implantation (1 week)

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Biological Evaluation Plan (BEP)

Material Characterization

Manufacturers need to have **solid relationships with suppliers** and ensure full disclosure of materials through:

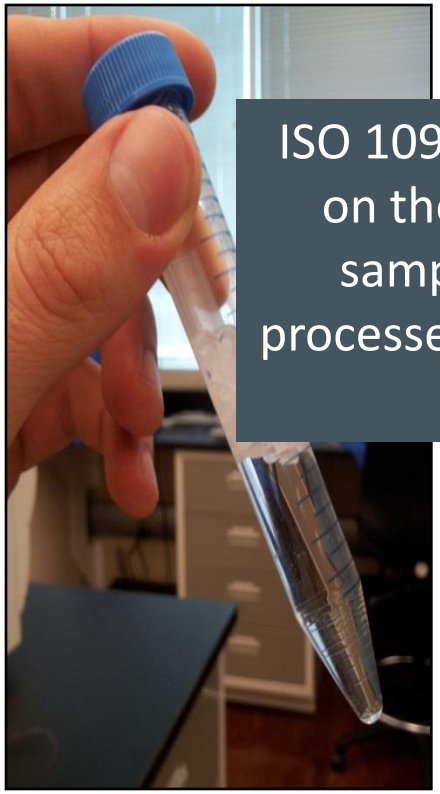
Manufacturing agreements	Composition disclosures	Processing aide and residual chemical disclosure	Material Safety Data Sheets (MSDS)	Device Master File Information availability to the regulatory authorities

Biological Evaluation Plan (BEP)

HANDS ON

Test Sample Selection

ISO 10993-1, 6.2.1 a) “Testing shall be performed on the sterile final product, or representative samples from the final product or materials processed in the same manner as the final product (including sterilization).”



Raw Material

Finished Device

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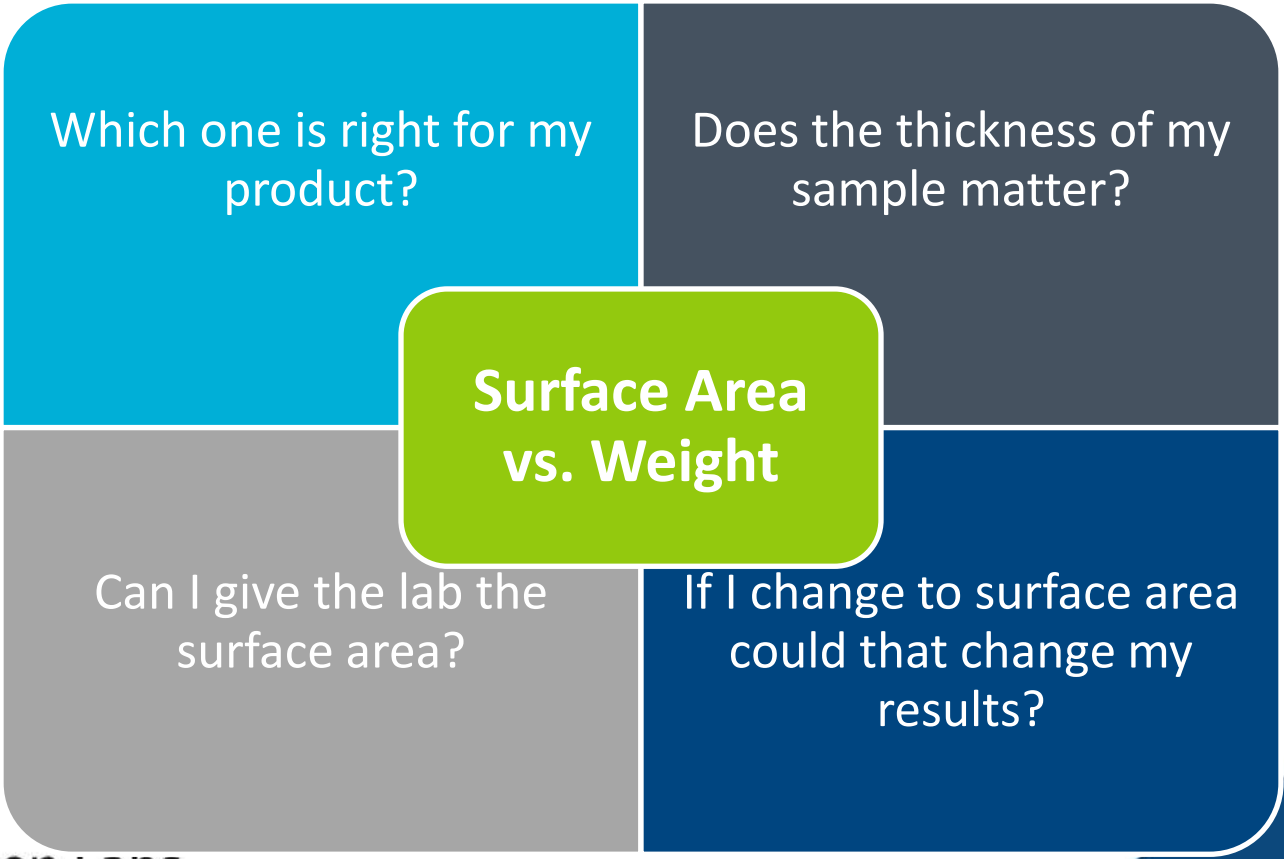
Biological Evaluation Plan (BEP)

Test Sample Preparation



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Biological Evaluation Plan (BEP)

Test Sample Preparation

Weight (93.9 g)/(0.2g/mL)=468.5 mL

Surface Area (115.8 cm^2)/(3cm^2/mL)=38.6 mL

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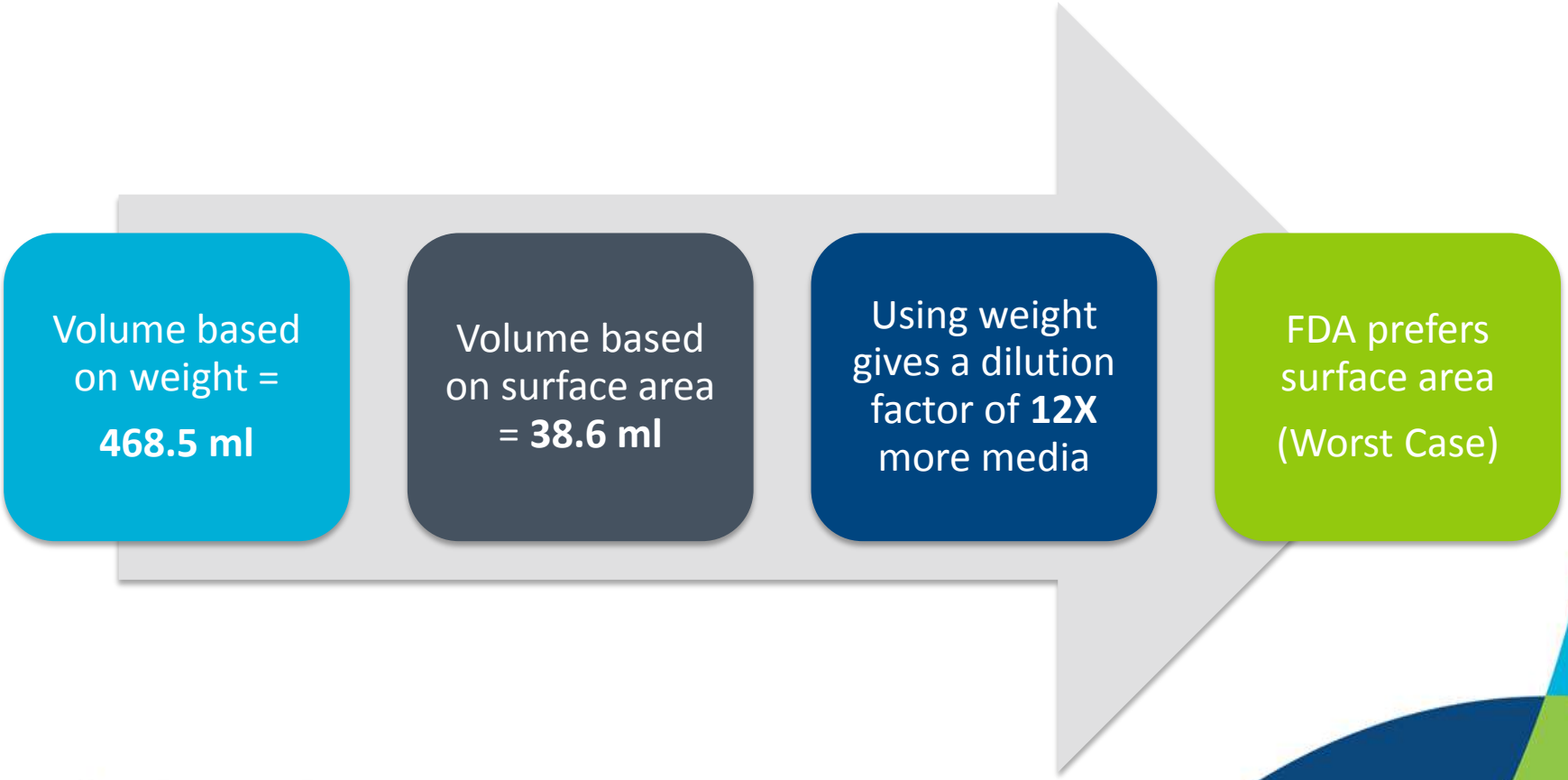
Biological Evaluation Plan (BEP)

Test Sample Preparation



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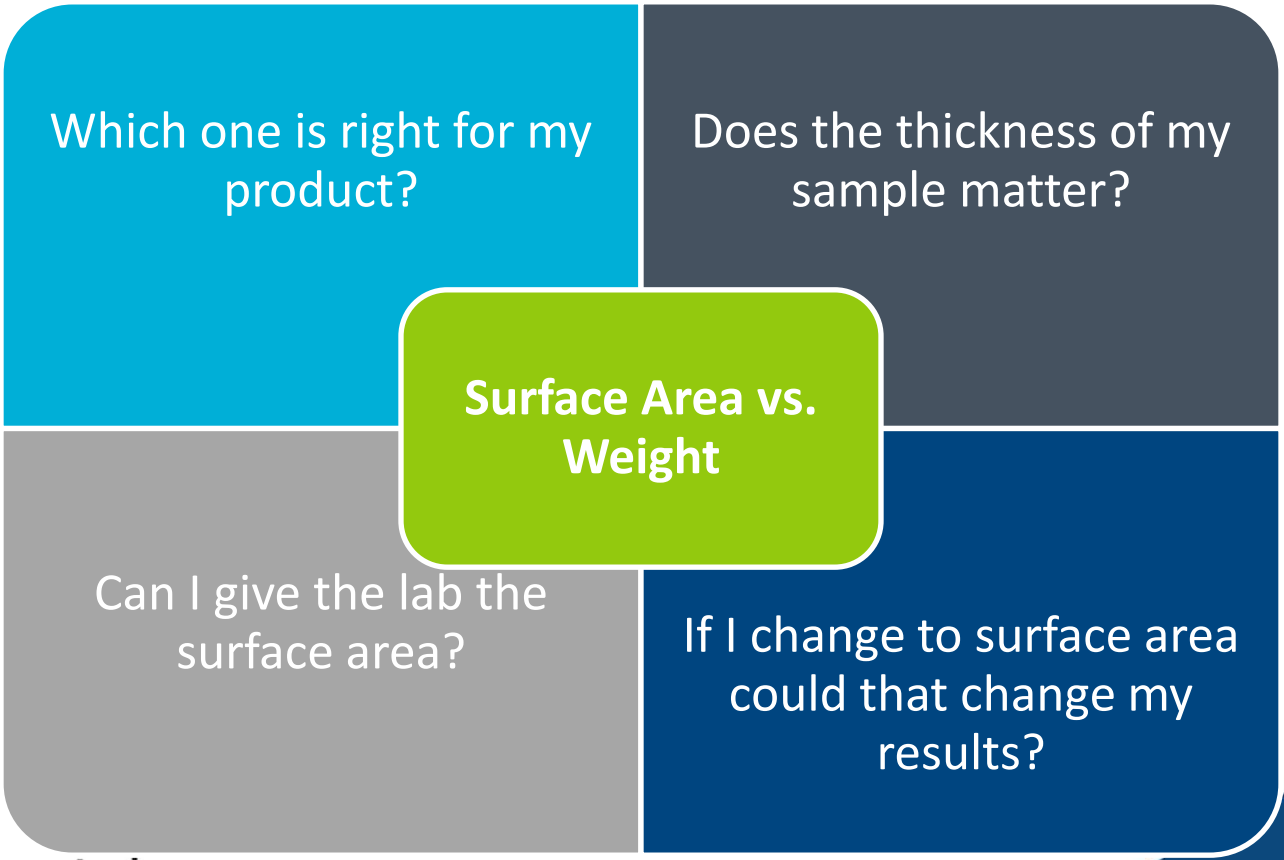
Biological Evaluation Plan (BEP)

Test Sample Preparation



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Biological Evaluation Plan (BEP)

Test Sample Preparation

Extraction Time and Temperature
per ISO 10993-12

- 37°C for 24 hours
- 37°C for 72 hours
- 50°C for 72 hours
- 70°C for 24 hours
- 121°C for 1 hours

Cytotoxicity only

How do I choose?

Does it matter?

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Biological Evaluation Plan (BEP)

What should be included in a BEP?

- Material information
  - Suppliers
  - Patient contact
  - Specification sheets
  - Testing information on raw materials
- Device description and categorization
  - Include pictures
- Special Test Sample Preparations
  - Master product
  - Absorption capacity
  - Parts to include or exclude
  - Cut/don't cut
- Testing and risk assessments
  - Identify tests to perform based on risk to patient
  - Include conversation of areas where there is no risk (important if FDA asks for consideration in a particular area that does not apply to your specific device.)
  - Toxicological Risk Assessments

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Questions about Step 1: BEP?

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Phase 2: Testing and Risk Assessments

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Introduction to Chemical Characterization (E&L)

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Outline

1. **Some definitions**

2. **Why performing a chemical characterization**

3. **Set-up of chemical characterization:**
   - **3.1 Sample preparation**
   - **3.2 Analysis of the extracts**
   - **3.3 Identification of the extracted compounds**

4. **Case studies**

Outline

1. **Some definitions**

2. Why performing a chemical characterization

3. Set-up of chemical characterization:
   - 3.1 Sample preparation
   - 3.2 Analysis of the extracts
   - 3.3 Identification of the extracted compounds

4. Case studies

What's in a name?

Extractable:

- Chemical entity: organic or inorganic
- Extracted from device under **controlled and extreme (lab) conditions**
  - High temperature, long time, multiple sterilization cycles
  - Extreme solvents

Leachable:

- Chemical entity: organic or inorganic
- Extracted from device under **real use conditions**
  - Temperature of use, time of use, sterilization cycles of use
  - Mild solvents

What's in a name?

Extractable:

- Chemical entity: organic or inorganic
- Extracted from device under controlled and extreme (lab) conditions
  - High temperature, long time, multiple sterilization cycles
  - Extreme solvents

= chemical characterization

What's in a name?

Material characterization: Physical and chemical characteristics

- Physical : for implants and circulating blood
- Chemical: list of materials of construction, chemicals, processing aids(%)

Chemical characterization:

- in case not sufficient information, to assess degradation products (polymers), residuals, (primary and secondary) packaging

What is good material information?

- When talking about materials with the goal of avoiding chemistry testing, one must be totally unambiguous.

What is good material information?

- Not all materials with the same name are the same
- **Per FDA guidance document**: The best way to specify a material is with as much of the following as possible:
  - The name and CAS number
  - The chemical supplier with structural information and details of manufacturing process
  - The specific amounts of each chemical in a material formulation
  - Processes that the material is exposed to

Outline

1. Some definitions

2. **Why performing a chemical characterization**

3. Set-up of chemical characterization:
   - 3.1 Sample preparation
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   - 3.3 Identification of the extracted compounds

4. Case studies

Why Consider E&L

Biocompatibility Testing

Genotoxicity ~$19K
Sub-Chronic ~$26K
Chronic ~$150K
Carcinogenicity ~$1 M

Extensive ~$25K
Regular ~$19K

Chemistry E&L

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Why Consider E&L

Biocompatibility testing takes time

Sub-Chronic	~13 Weeks
Chronic	~26 Weeks
Carcinogenicity	~18 Months+

Chemistry E&L

Extensive	~8-14 Weeks

Why Consider E&L

Biocompatibility results are pass/fail

Chemistry E&L results provide detailed results

- What does the device release?
- How much?

Why Consider E&L

1. Predict relevant biological endpoints through analytical chemistry tests and deduction (sparing cost, time, and animal life)

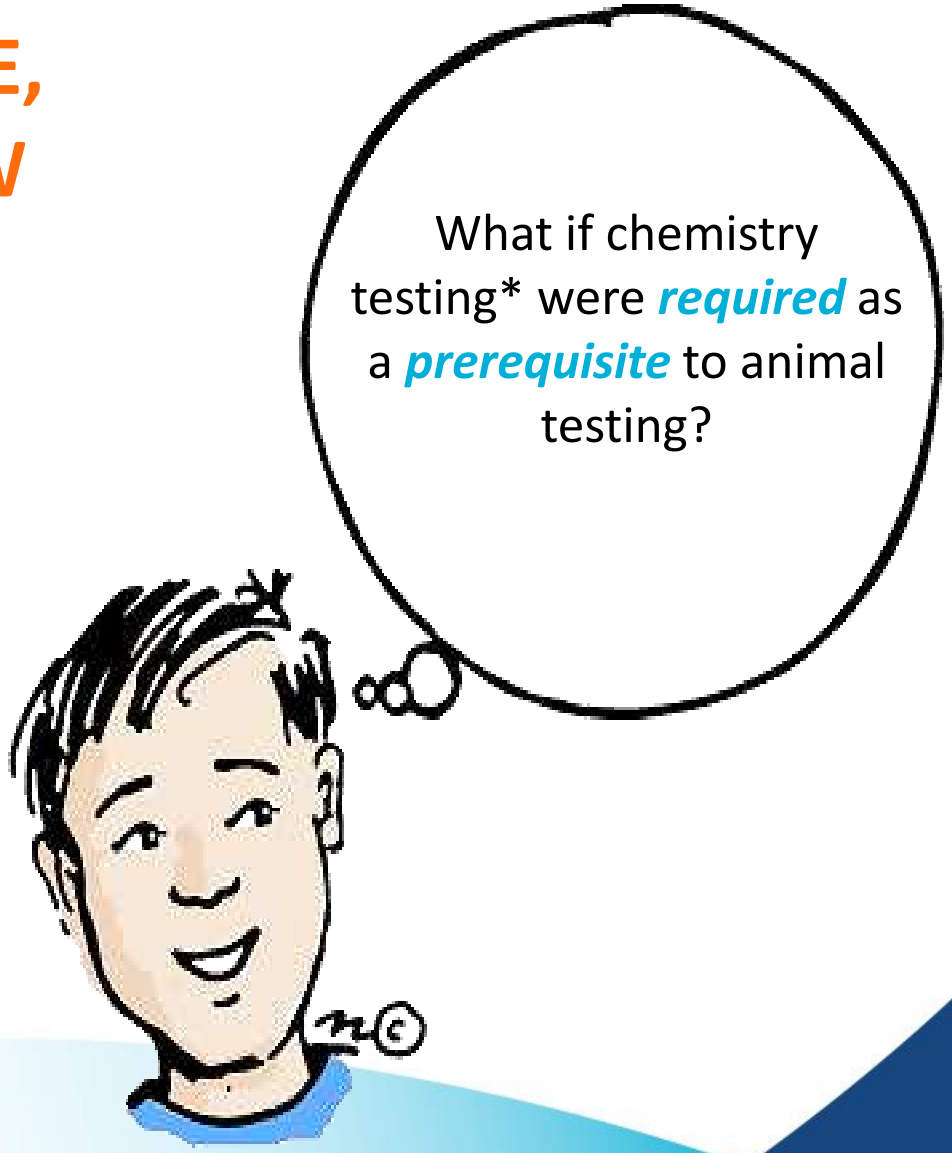
2. Gain understanding of device materials and processing towards prevention and correction of problems

Why Consider E&L

FDA

Regulatory bodies are requesting E&L more frequently

Chemistry is the **FUTURE, and the FUTURE IS NOW**



*Good information on materials and processing may be substituted for testing

Why Consider E&L

Outline

1. Some definitions

2. Why performing a chemical characterization

3. **Set-up of chemical characterization:**
   - **3.1 Sample preparation**
   - **3.2 Analysis of the extracts**
   - **3.3 Identification of the extracted compounds**

4. Case studies

Standards for E&L testing

- Provides guidance for the biological evaluation of medical devices within a risk management process

ISO 10993 -1

- Provides guidance for the extraction conditions and solvents to select

ISO 10993 -12

- Provides guidance for establishing limits for compounds related to materials

ISO 10993-17

- Outlines the test options for device materials

ISO 10993-18

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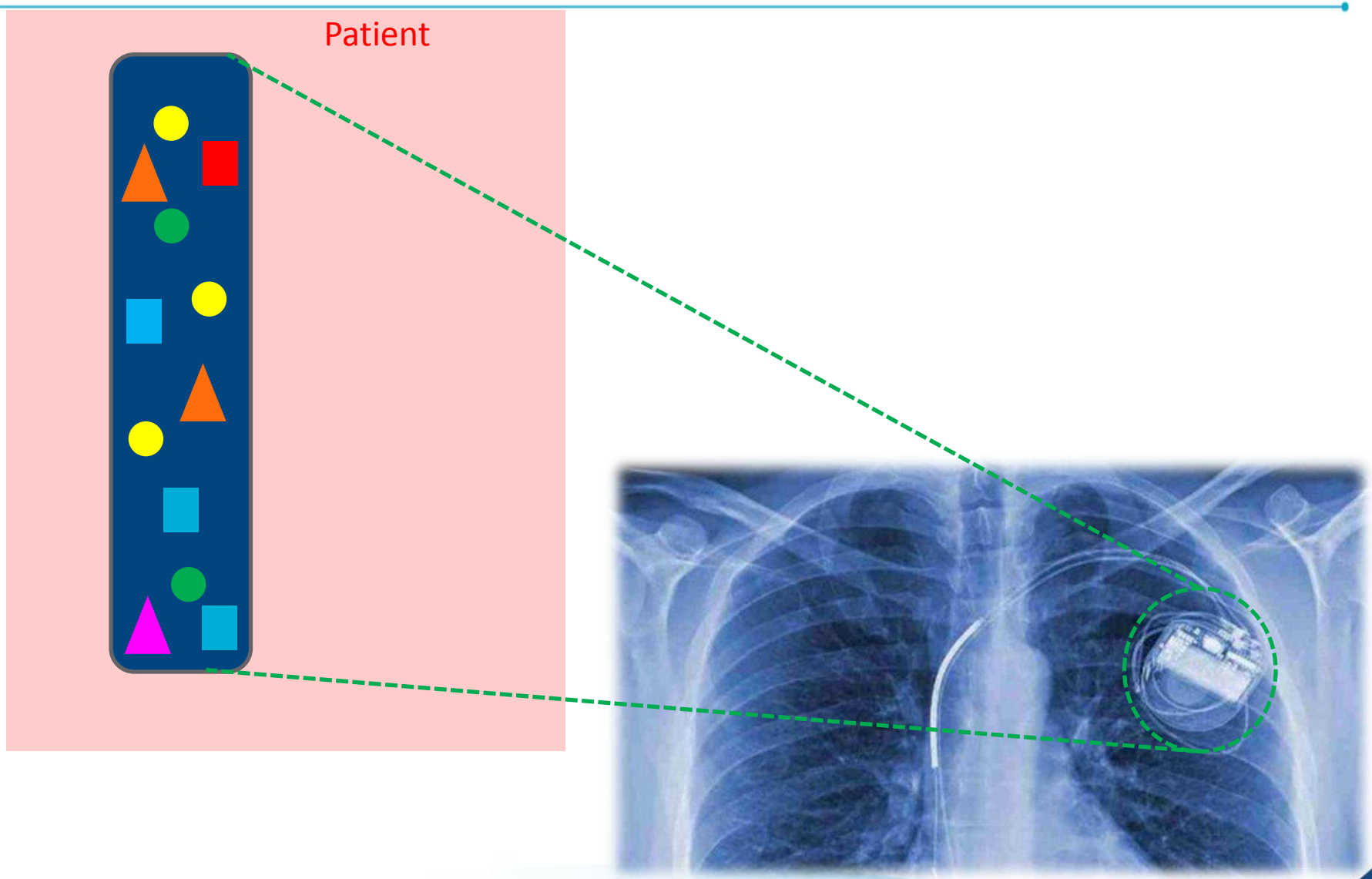
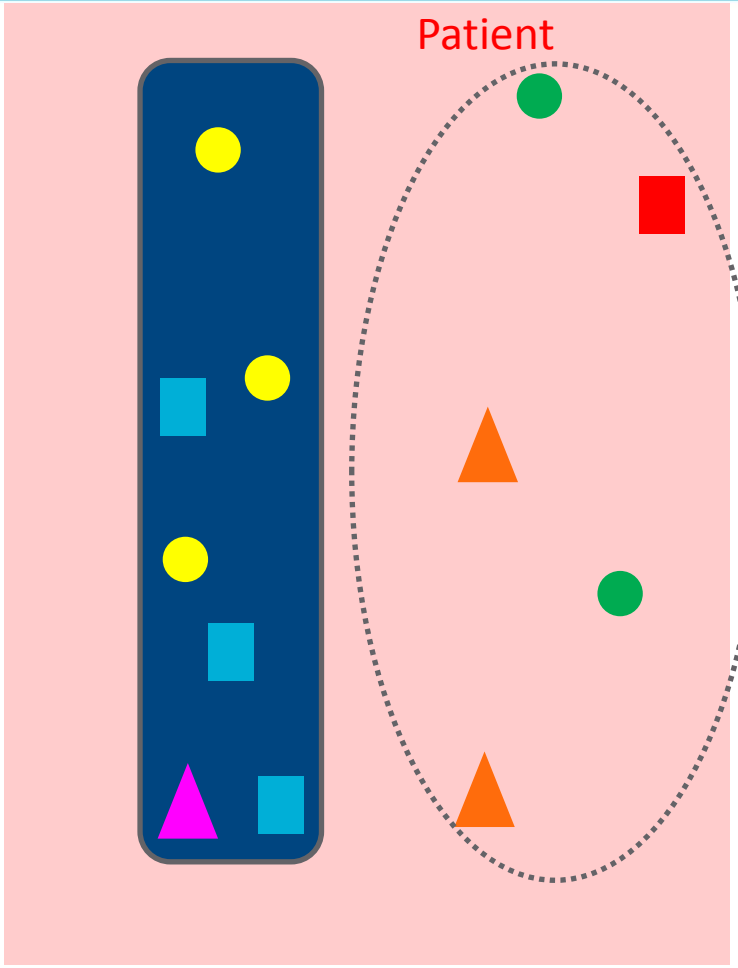
E&L testing: What are we looking for ?



E&L testing: What are we looking for ?



Which compounds are migrating?

Outline

1. Some definitions

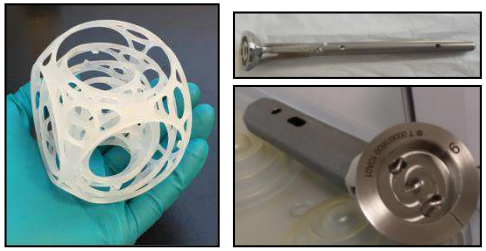
2. Why performing a chemical characterization

3. **Set-up of chemical characterization:**
   - **3.1 Sample preparation**
   - 3.2 Analysis of the extracts
   - 3.3 Identification of the extracted compounds

4. Case studies

E&L testing: How to design it ?

Solvents

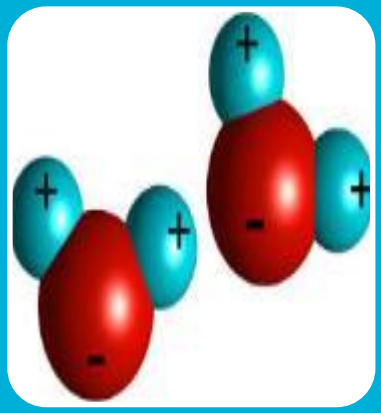


Extraction conditions

Extraction volume

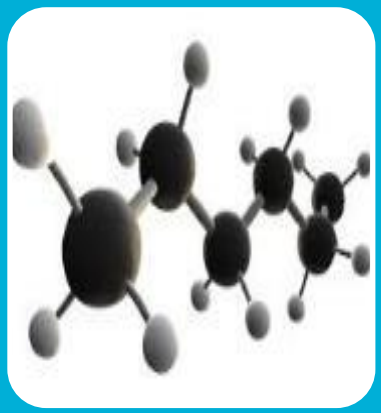
Exhaustive extraction? Implants

Extraction solvent



POLAR VEHICLE

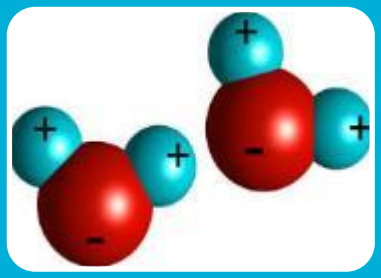
- Ultra Pure Water
- Physiological saline
- Culture media without serum → not compatible with high-end analytical equipment



NON-POLAR VEHICLE

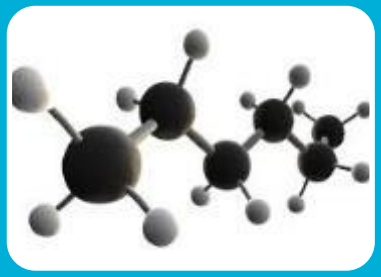
- Vegetable oil → not compatible with high-end analytical equipment
- HEXANE

Extraction solvent



POLAR VEHICLE

- Ultra Pure Water
- Physiological saline
- Culture media without serum → not compatible with high-end analytical equipment



NON-POLAR VEHICLE

- Vegetable oil → not compatible with high-end analytical equipment
- HEXANE

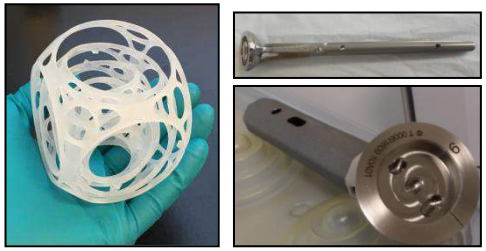
SEMI-POLAR VEHICLE

- X % Ethanol in water
  → mimicking blood contact
- Pure Isopropanol, pure Ethanol

E&L testing: How to design it ?

Solvents

Extraction conditions



Extraction volume

Exhaustive extraction? Implants

Extraction conditions

Incubation

- **agitation or circulation**
- Static → Justify!

Time and temperature

- ~~37°C for 72 h~~
- 50°C for 72 h
- 70 °C for 24 h
- 121 °C for 1 h

Extraction conditions

Incubation

- **agitation or circulation**
- Static → Justify!

Time and temperature

- ~~37°C for 72 h~~
- 50°C for 72 h
- 70 °C for 24 h
- 121 °C for 1 h

Extraction conditions

Remark: perform extraction on all parts that come in (in)direct contact with the patient (ex. Tubing, filters, ...)

However: all parts should have same MD category; e.g. External communicating part + permanent implant

Extraction conditions

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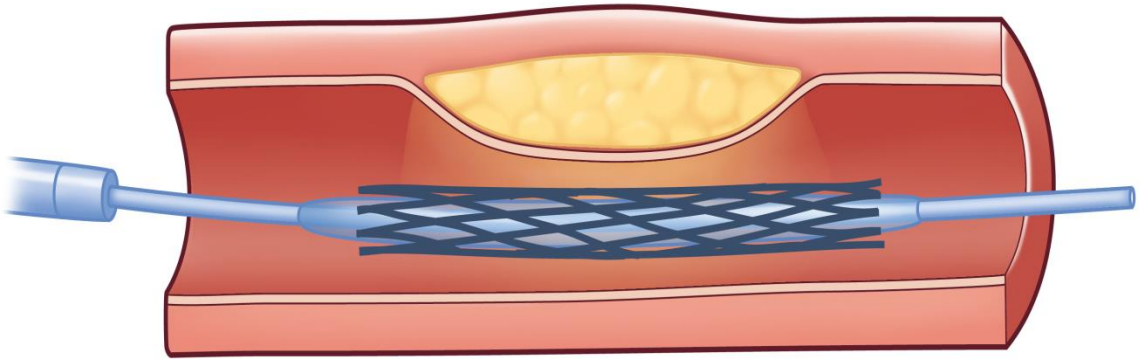
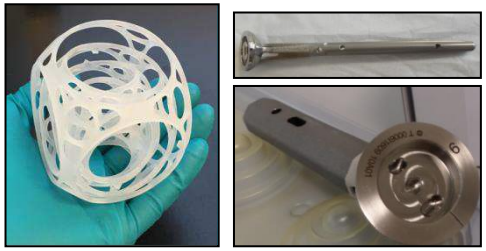
However: all parts should have same MD category; e.g. External communicating part + permanent implant



E&L testing: How to design it ?

Solvents



Extraction conditions

Extraction volume

Exhaustive extraction? Implants

Extraction ratio

- Europe ≠ USA

Extraction ratio

- Surface/volume
  - 3 cm²/mL
  - 6 cm²/mL
- Weight/volume
  - 0.2 g/mL

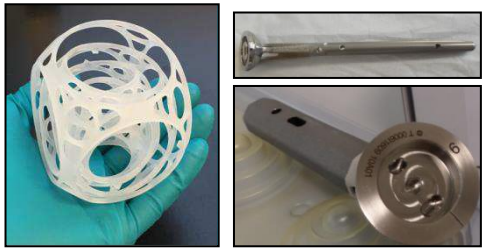
Shape & Thickness

Samples need to be submerged completely

- Shape extraction container
- Available amount of devices
- Shape device

E&L testing: How to design it ?

Solvents



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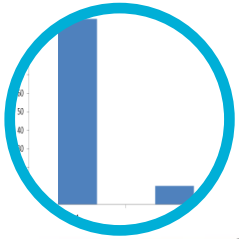
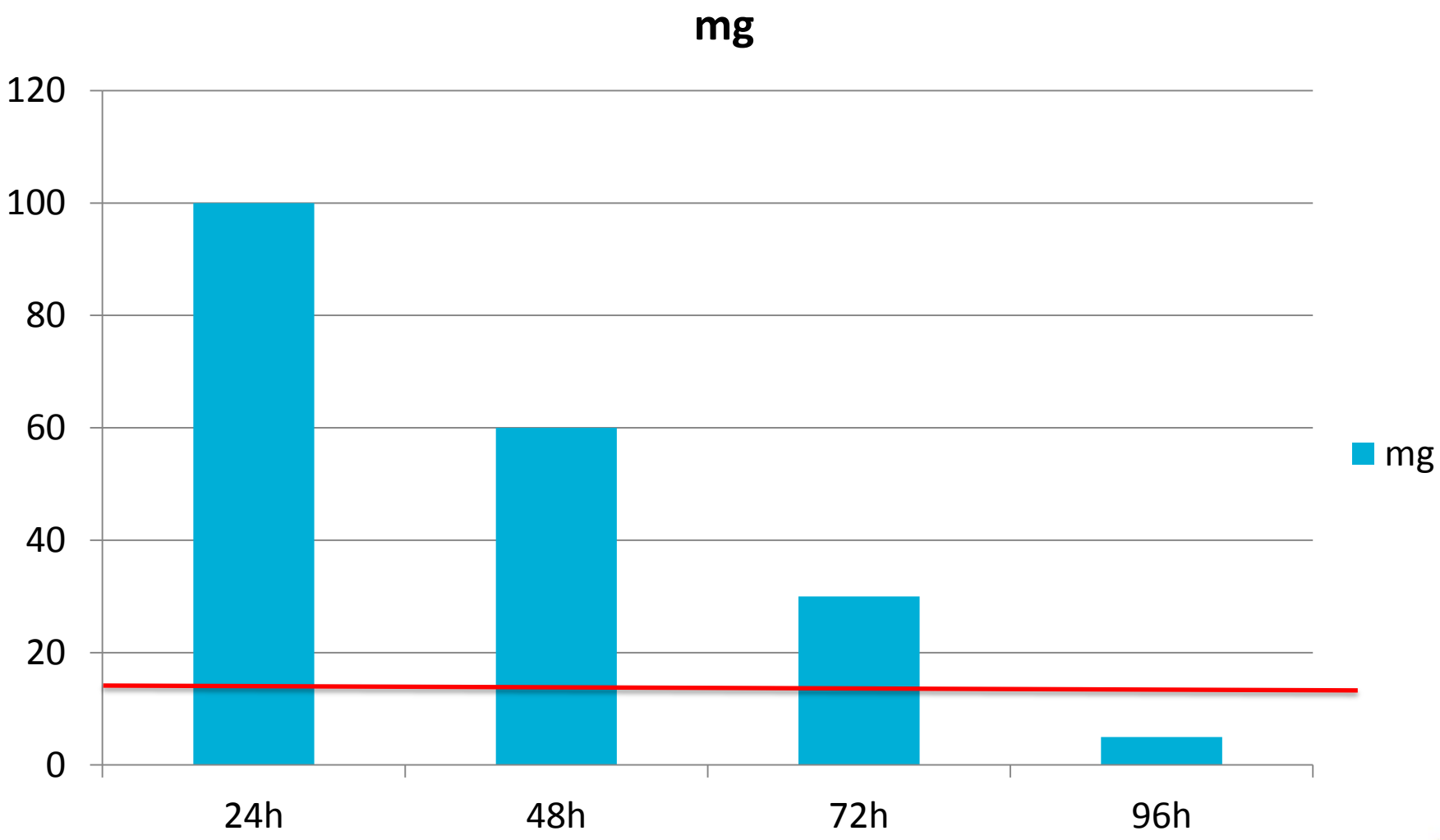
Extraction volume

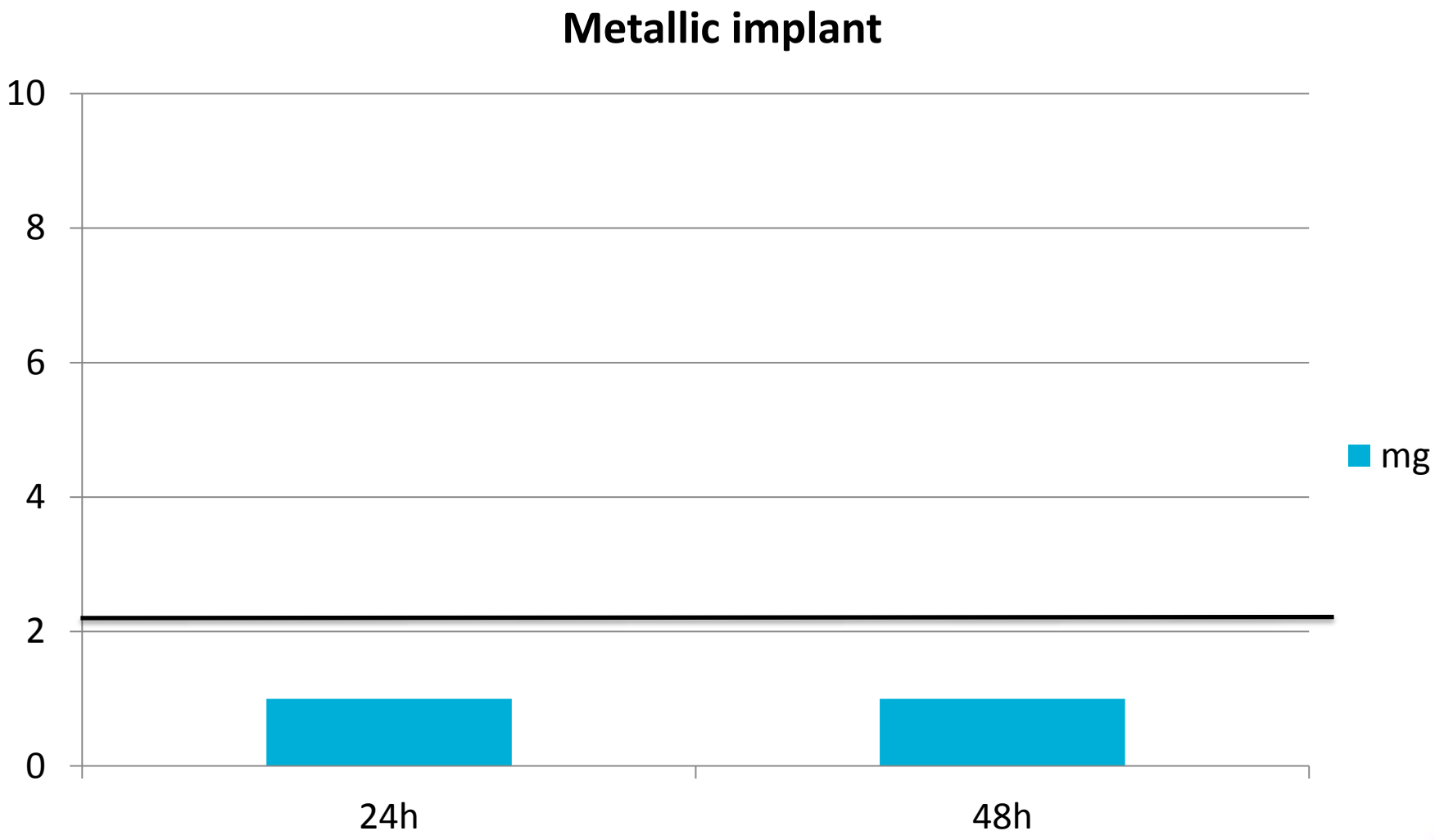


Exhaustive extraction? Implants

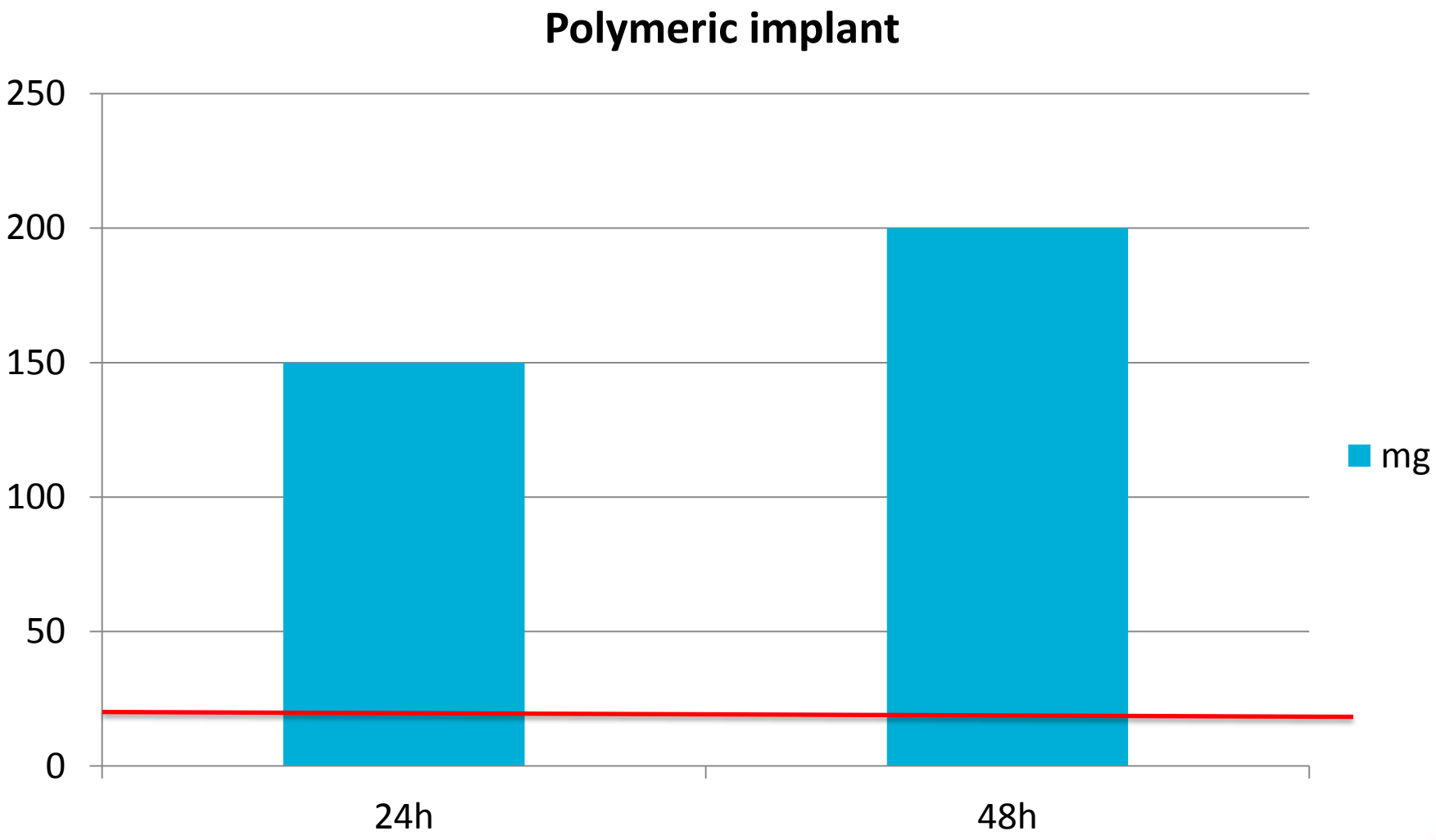
E&L testing: Exhaustive extraction (in theory)



E&L testing: Exhaustive extraction (in practice)



E&L testing: Exhaustive extraction (in practice)



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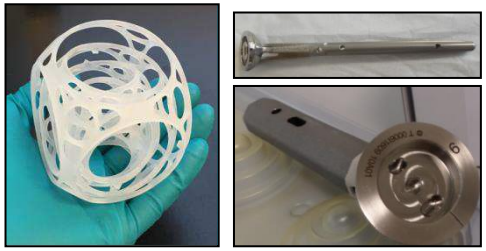
E&L testing: How to design it ?



Solvents

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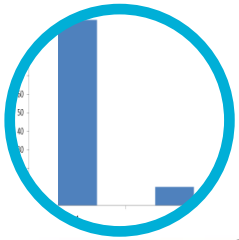
Extraction volume

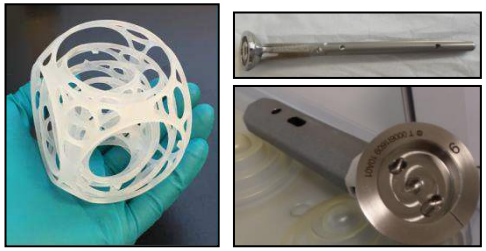


Exhaustive extraction? Implants

ANALYSES OF THE EXTRACTS

E&L testing: How to design it ?

CURRENT



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Extraction conditions

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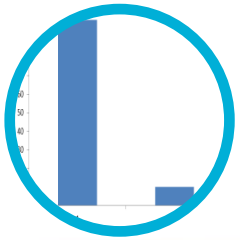

Exhaustive extraction?

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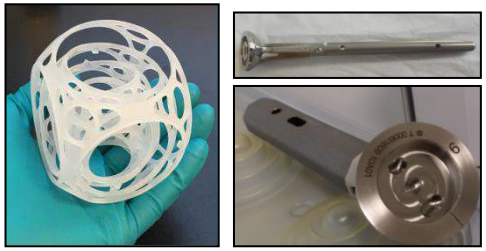
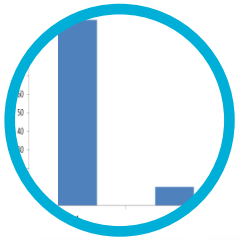


Solvents

Extraction conditions

Extraction volume



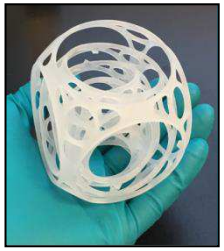
Exhaustive extraction?

ANALYSES OF THE EXTRACTS

ISO 10993-18

E&L testing: How to design it ?

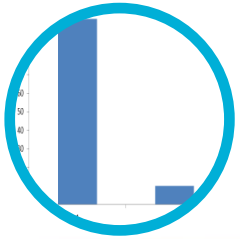
FUTURE



Solvents

Extraction conditions

Extraction volume



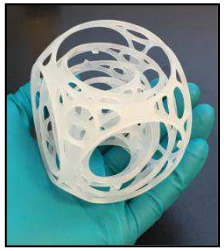
Exhaustive extraction?

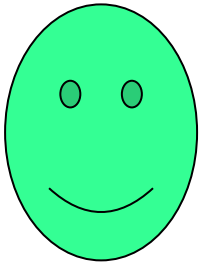
ANALYSES OF THE EXTRACTS

Nelson Labs
A Sotera Health company

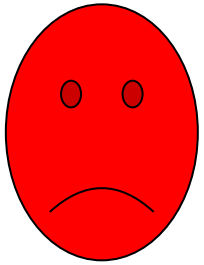
E&L testing: Analysis of the extracts

E&L testing: Analysis of the extracts



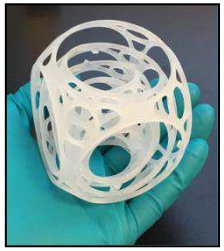


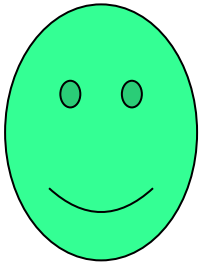
Safe



Not Safe

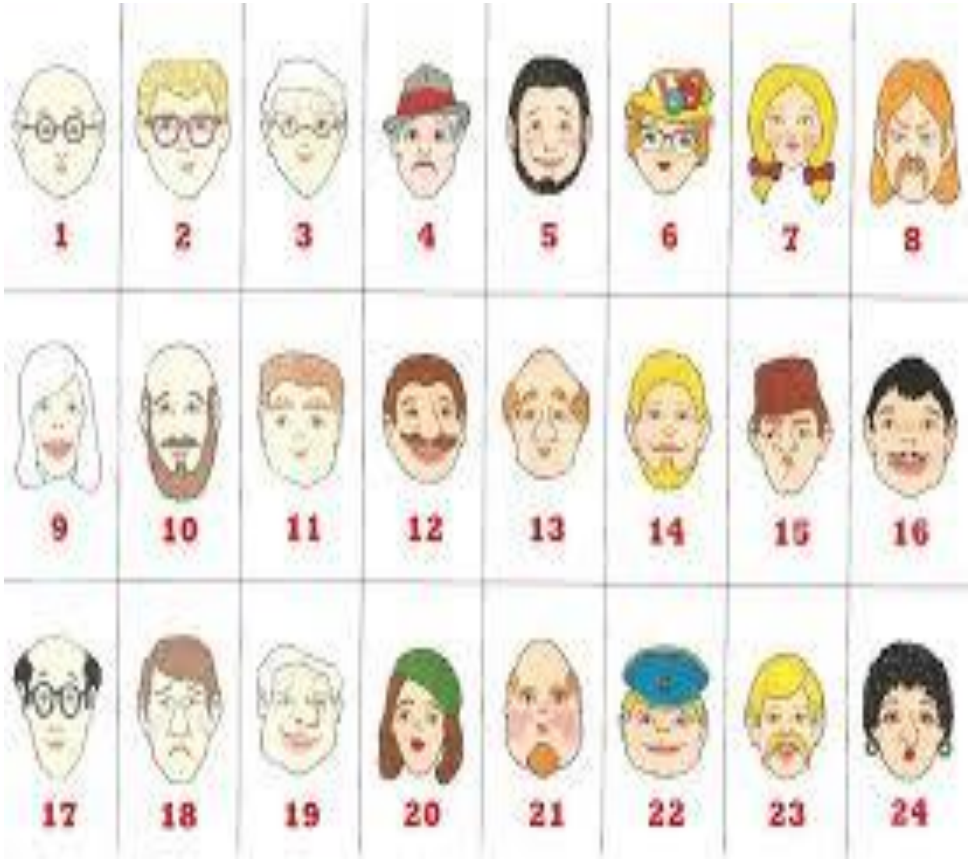
E&L testing: Analysis of the extracts





Safe

Not Safe



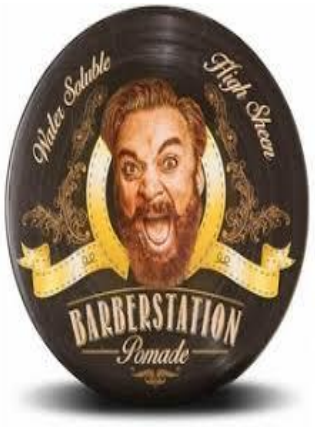
Extracted compounds

Nelson Labs
A Sotera Health company


20
7
24
9
6

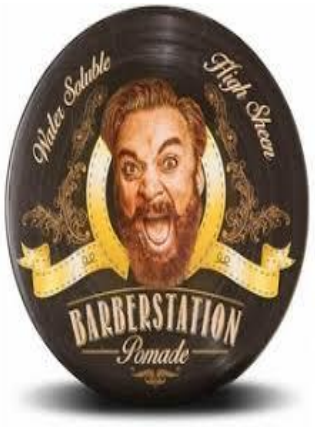
5/24


5
8
10
14
12
16
21
23


Water Soluble
High Sheen
BARBERSTATION
Pomade


5
8
10
14
12
16
21
23
20
7
24
9
6

13/24


Water Soluble
High Sheen
BARBERSTATION
Pomade


4
11
13
15
18
19
22


Wallpaper
Adhesive
Heavy Duty


4
11
13
15
18
19
22
5
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14
12
16
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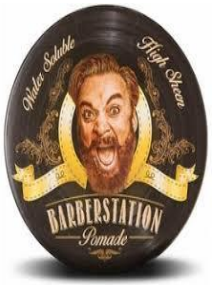
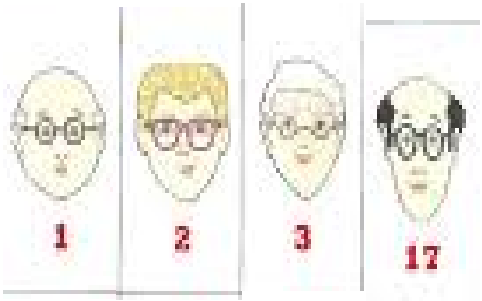
23
20
7
24
9
6

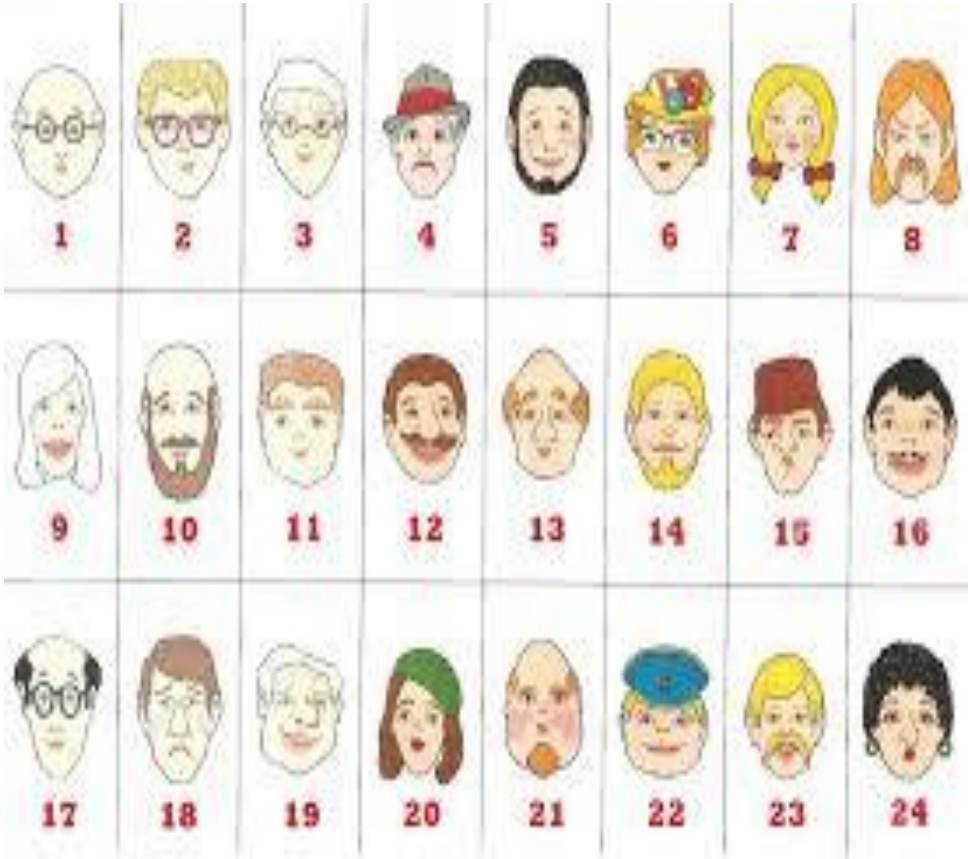
20/24


Wallpaper
Adhesive
Heavy Duty


Water Soluble
High Sheen
BARBERSTATION
Pomade


1
2
3
17

24/24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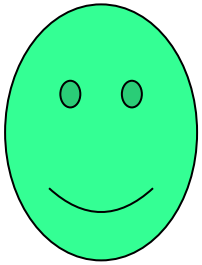
Perfax
Wallpaper
Adhesive
Heavy Duty


BARBERSTATION
Pomade

E&L testing: Analysis of the extracts



Safe

Detect and identify the whole set of potentially hazardous compounds: missing a compound could be a fatal error for patient safety

E&L testing: Analysis of the extracts

ANY Substance

(That Could Leave The Device)

Inorganic

(not carbon based)

Metals

Organic

(carbon based)

Very Small Molecu
Volatile Organic
(VOCs)

Small Molecules
Semi-Volatile Organ
(SVOCs)

Big Molecules – Non
Volatile Organics
(NVOCs)

Nelson Labs
A Sotera Health company

E&L testing: Analysis of the extracts

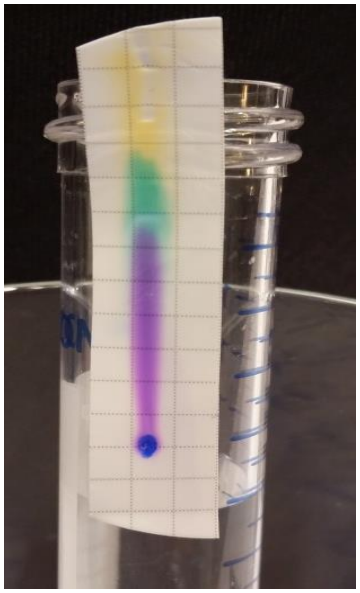
Organic
(carbon based)

- Before substances can be identified and measured, **they have to be separated** from each other.

E&L testing: Analysis of the extracts

Organic
(carbon based)

- Before substances can be identified and measured, **they have to be separated** from each other.
- Organic compounds can be separated using **chromatography**.



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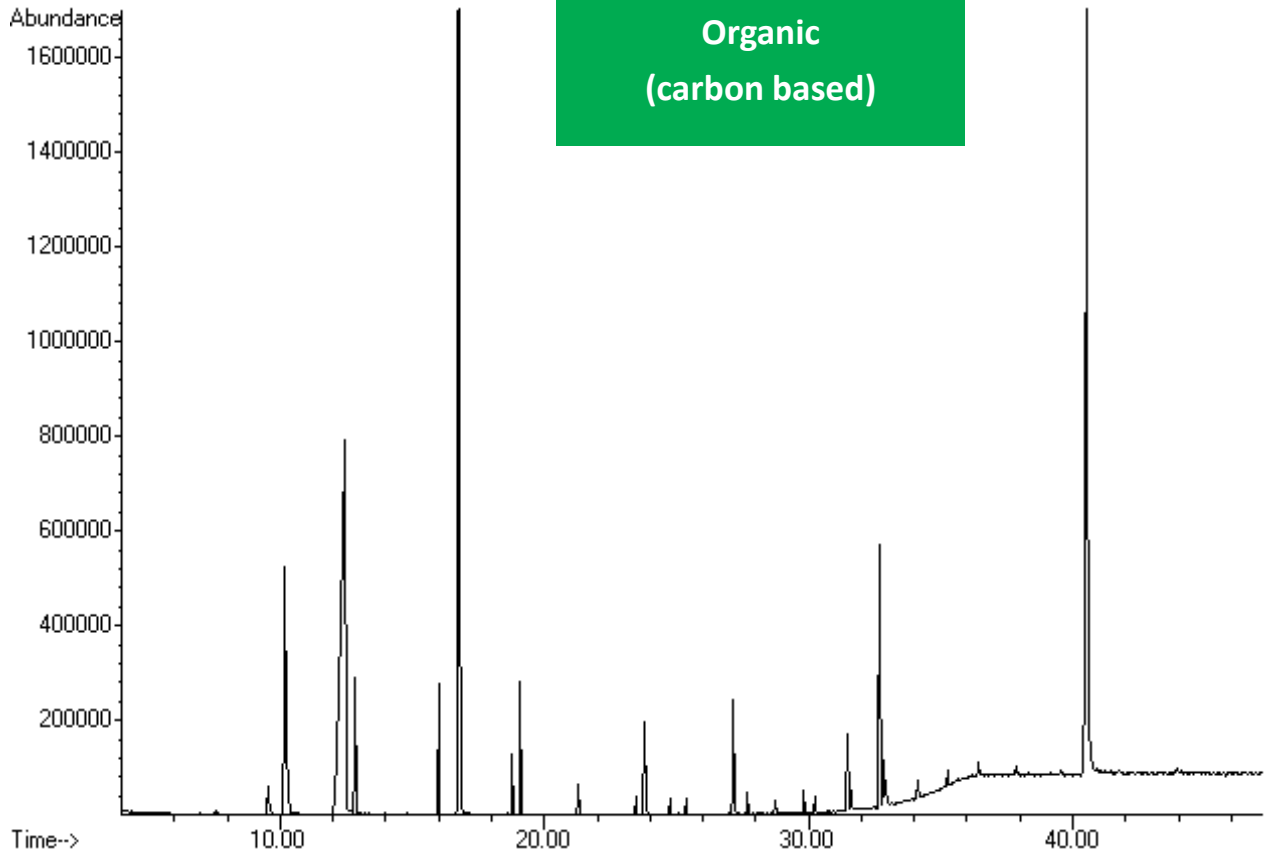
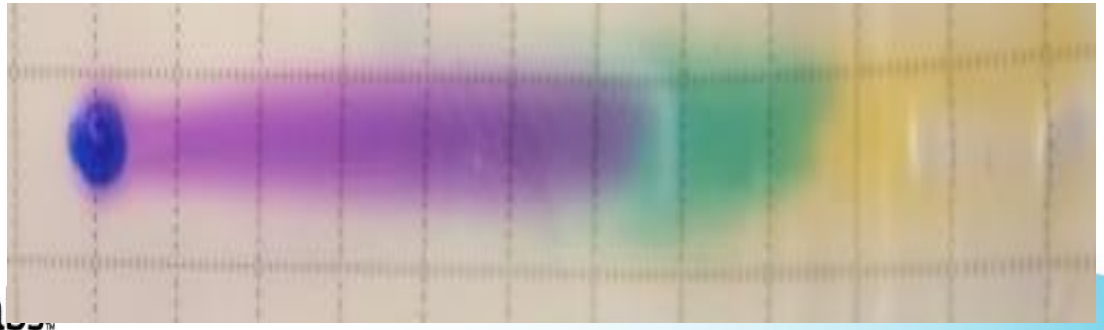


Organic
(carbon based)

Chromatogram
in stead of paper



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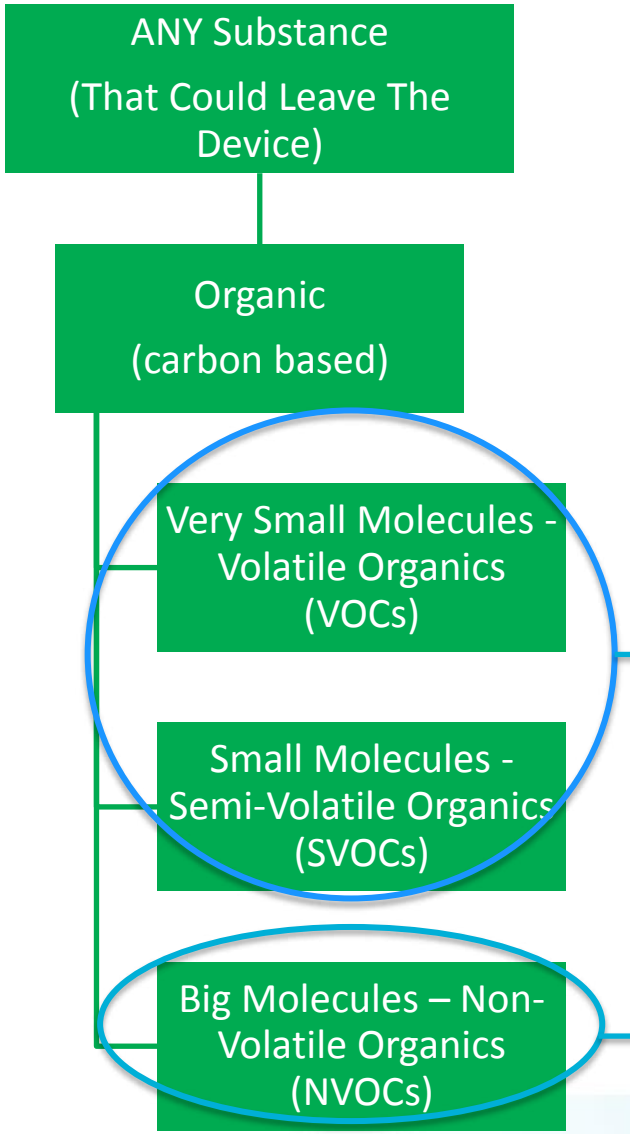


Small molecules evaporate easily, suitable for gas chromatography (**GC**)

Big molecules do not evaporate easily, suitable for liquid chromatography (**LC)**

How to design a E&L study ?

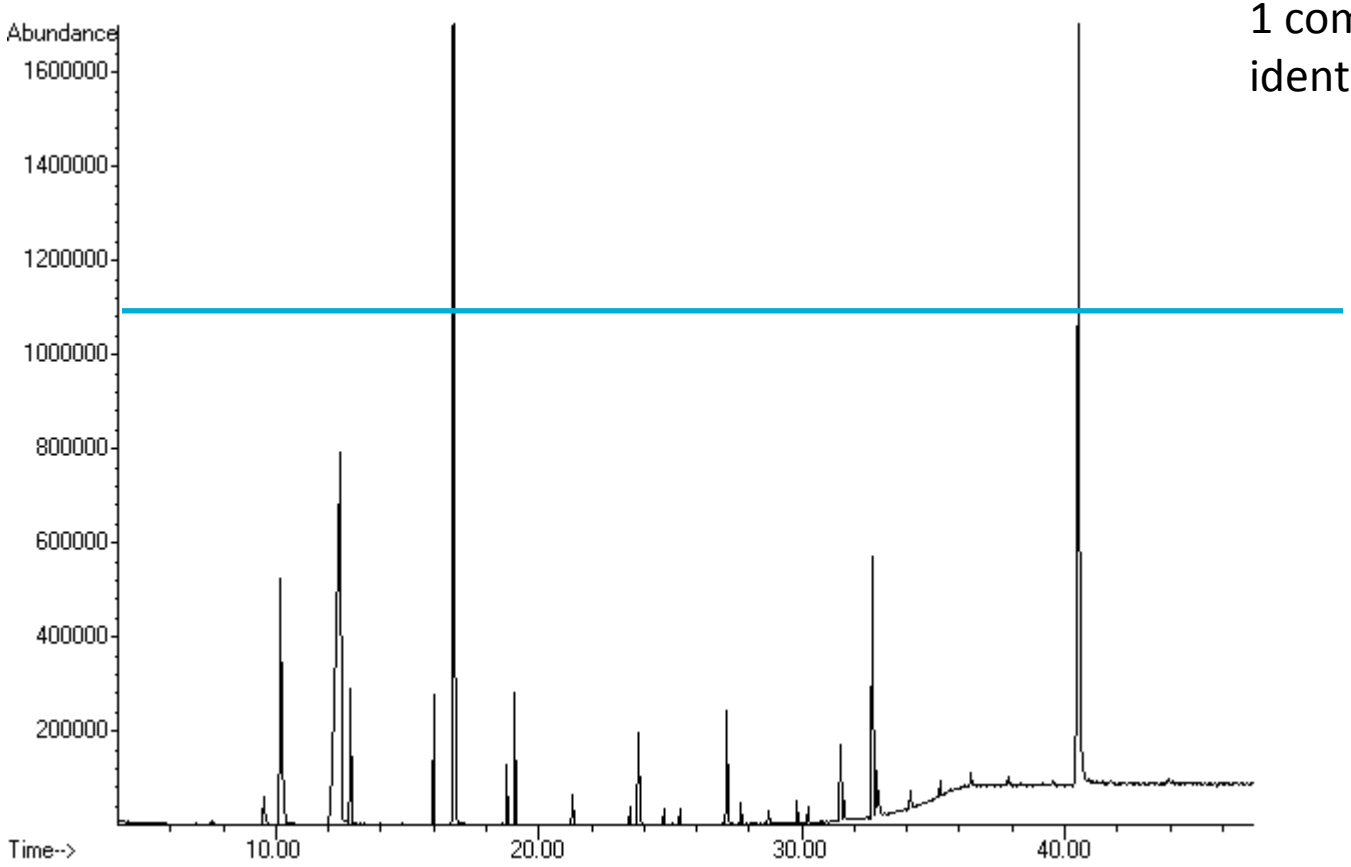
Performing the analyses at the right level

E&L testing: Analysis of the extracts

Organic
(carbon based)

Evaluation?

ISI



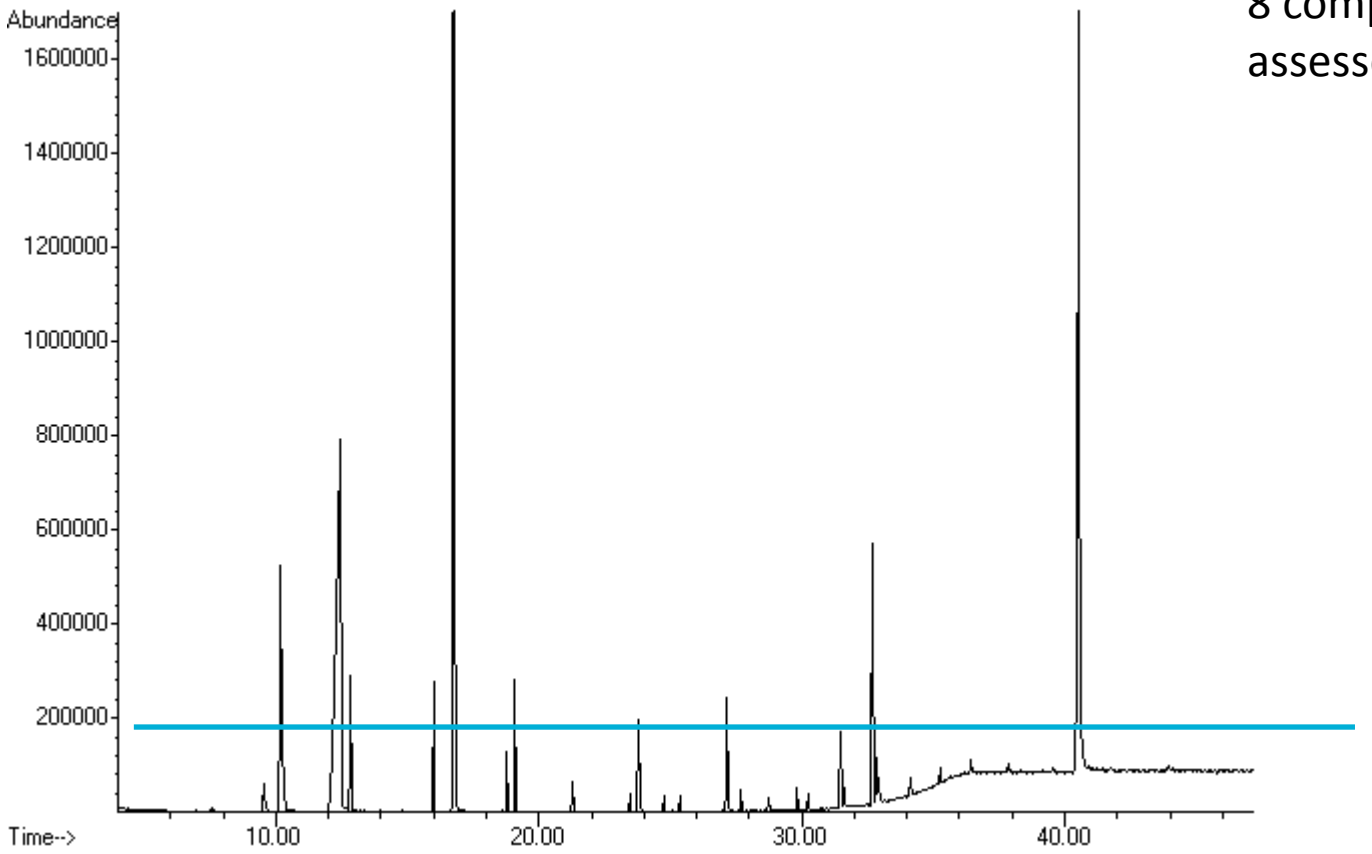
1 compound will be finally identified and assessed

E&L testing: Analysis of the extracts

Organic
(carbon based)

Evaluation?

ISI



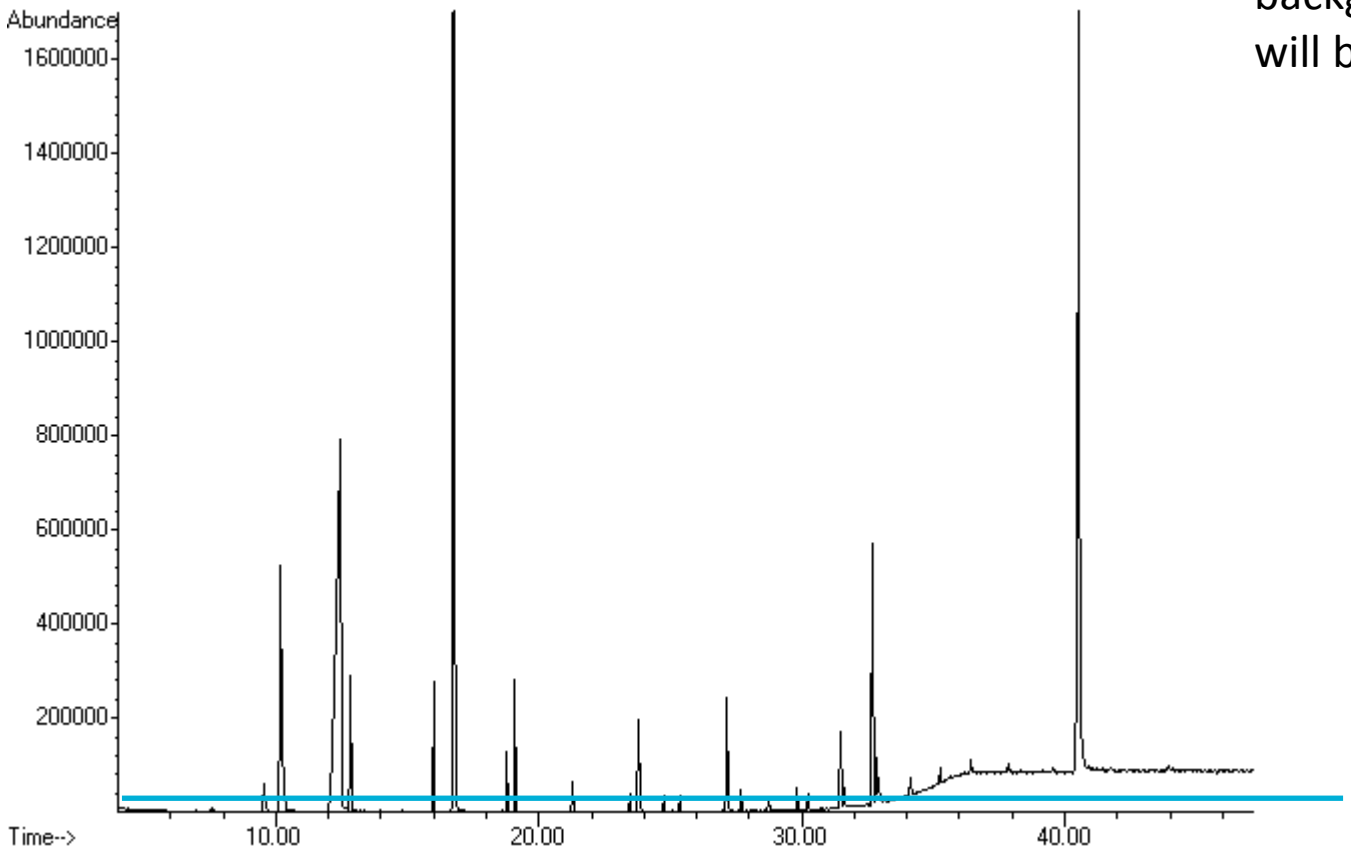
8 compounds will be finally assessed

E&L testing: Analysis of the extracts

Organic
(carbon based)

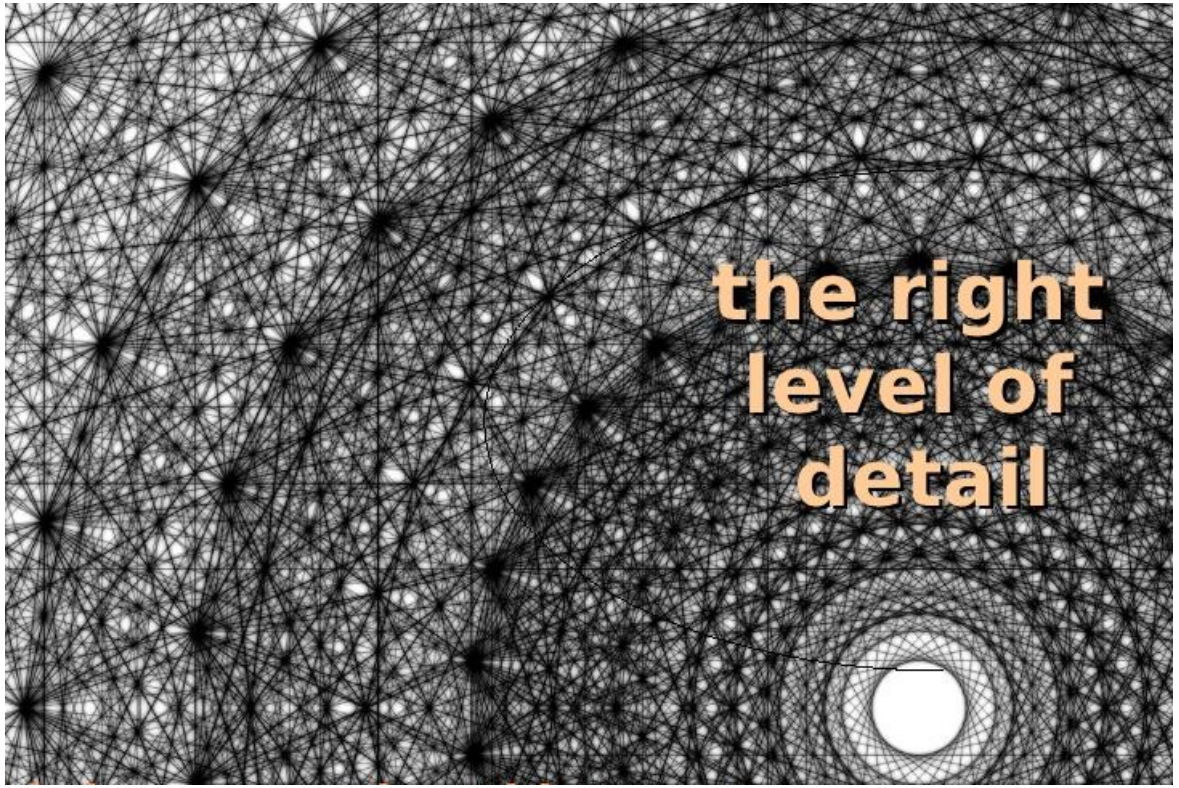
Evaluation?

ISI



background compounds will be finally assessed

E&L testing: Analysis of the extracts: Notion of AET



Analytical **E**valuation **T**hreshold

E&L testing: Analysis of the extracts: Notion of AET

The AET is defined as the threshold below which the analyst need not to identify or quantify leachables or extractables or report them for potential toxicological assessment

E&L testing: Analysis of the extracts: Notion of AET

- Reference guideline for drug products: ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (2014)

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

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Limited + prolonged exposure

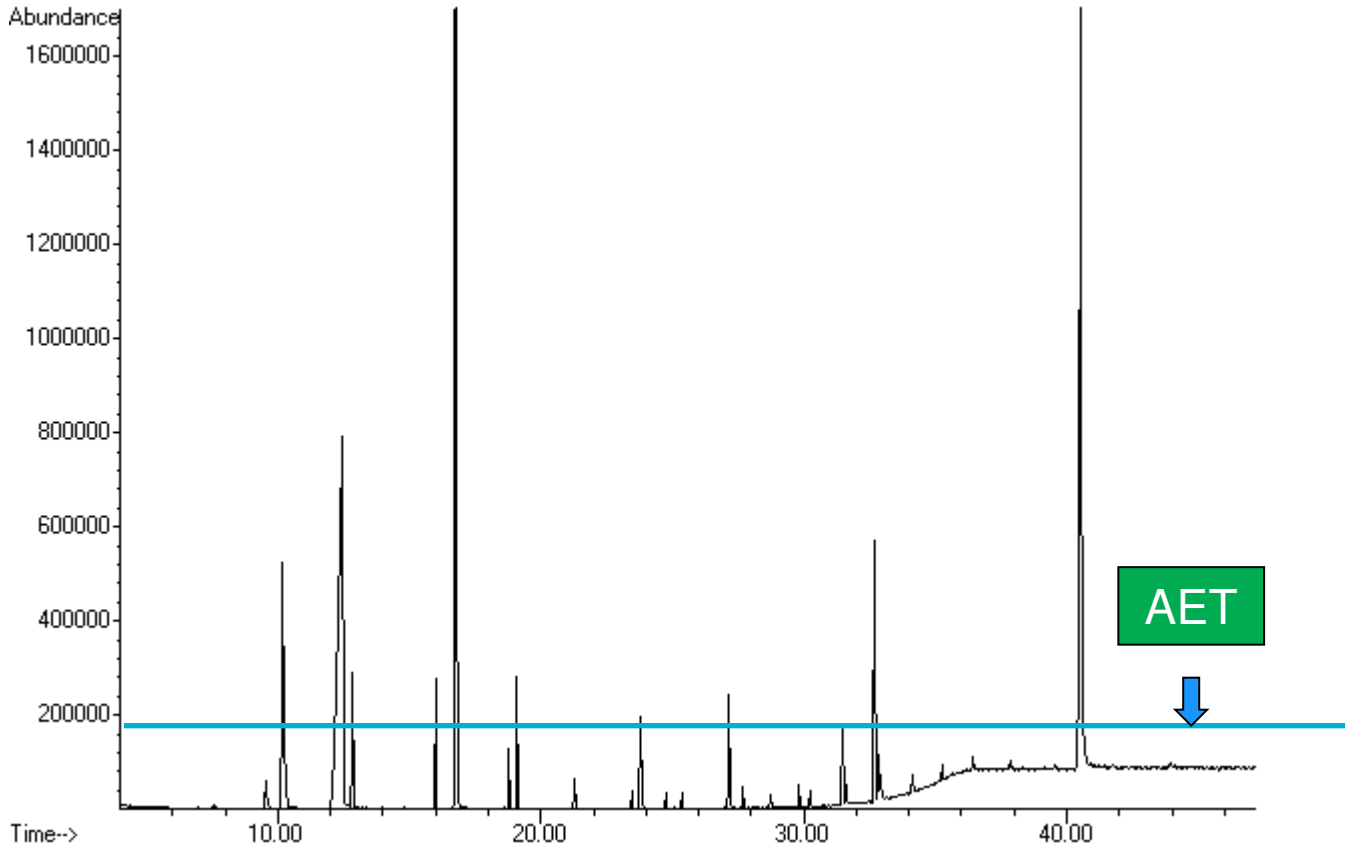
Long term contact

E&L testing: Analysis of the extracts

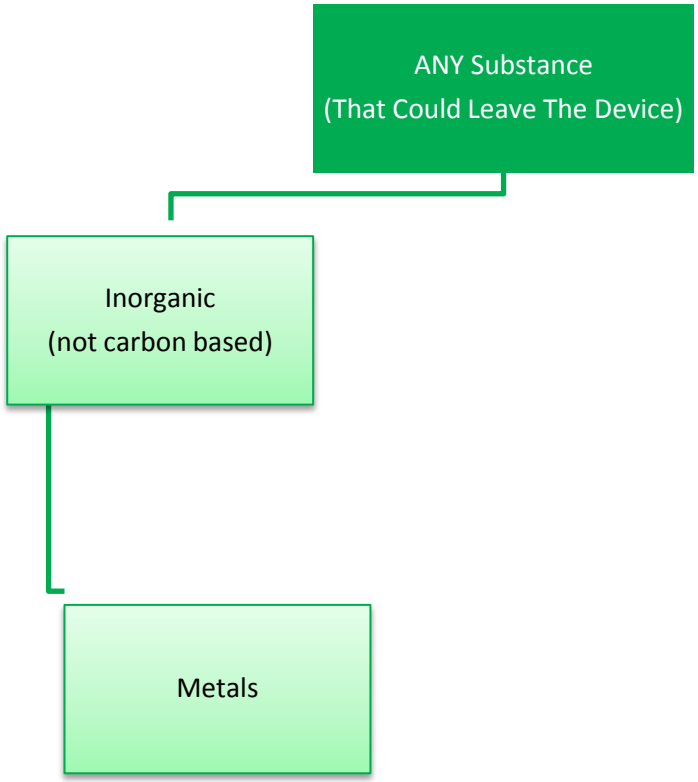
Organic
(carbon based)

Evaluation?

ISI



Metals

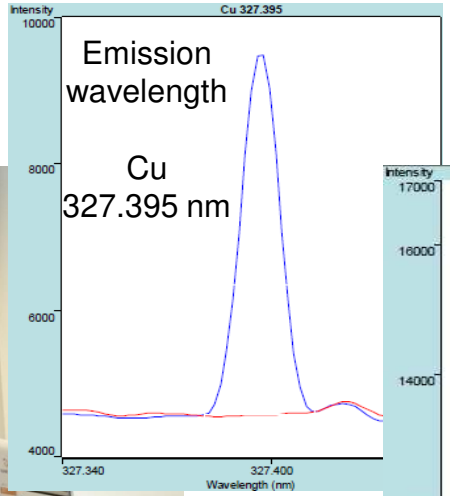

ANY Substance
(That Could Leave The Device)
Inorganic
(not carbon based)
Metals

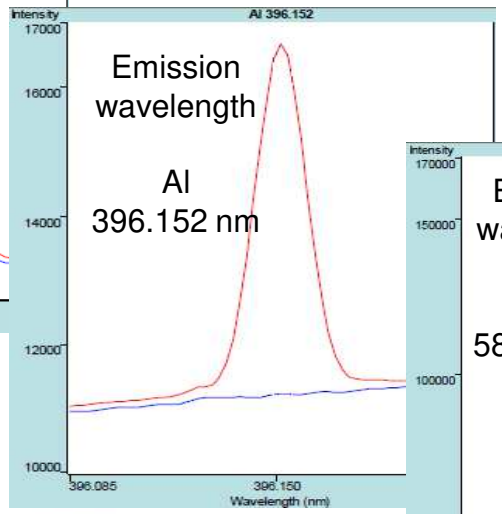
ICP-OES or ICP-MS:

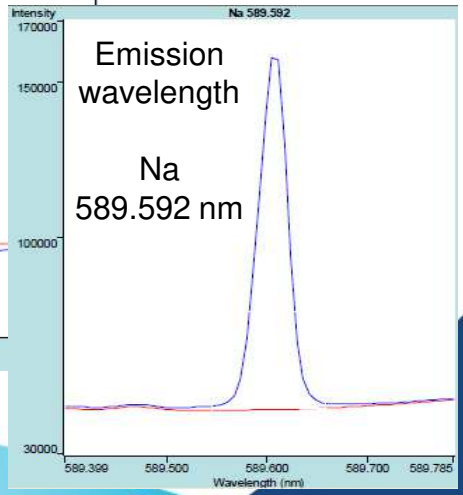
- Metals from Glass
- Metals from Rubbers
- Catalysts, used on the polymerization
- Fillers, added to Polymers
- Acid Scavengers
- Activator systems for Rubbers
- ...

Metals

Inductively coupled plasma optical emission spectroscopy (ICP-OES), is a spectroscopic technique used for the detection of trace metals. By means of an inductively coupled plasma, atoms and ions are excited and emit electromagnetic radiation at wavelengths specific for each element. The intensity of the emission is a measure for the concentration of an element.







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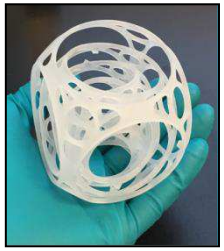
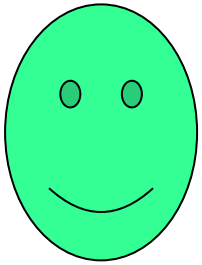
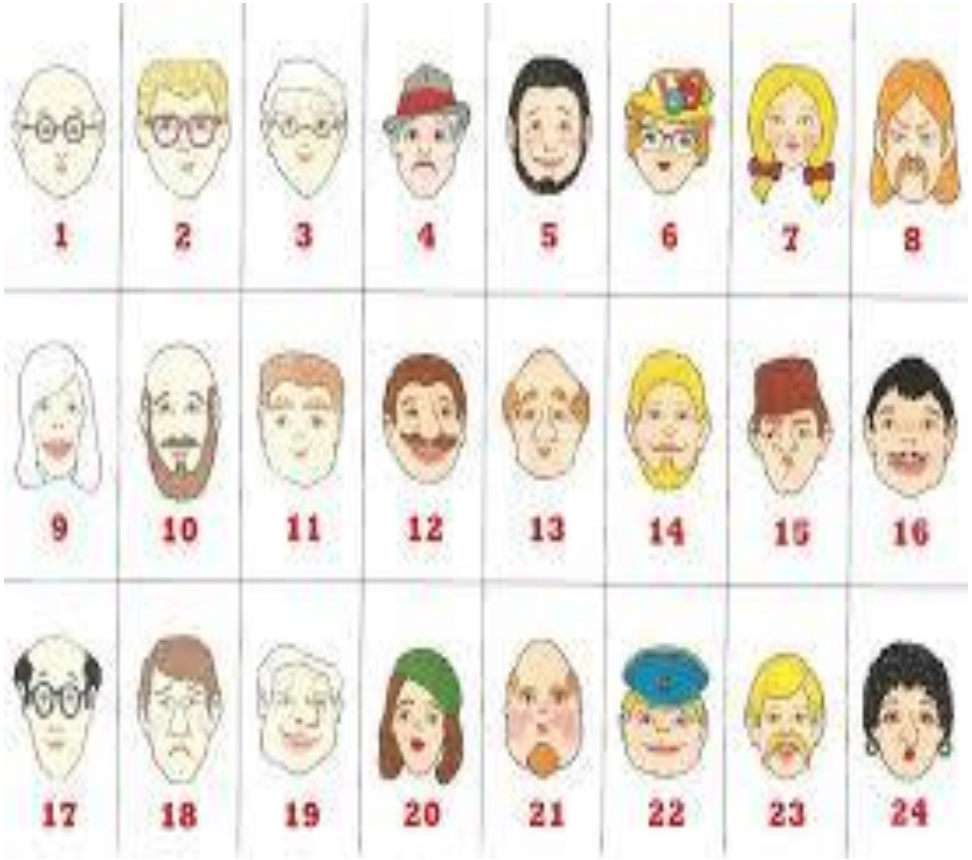
E&L testing: Goal





Safe

Not Safe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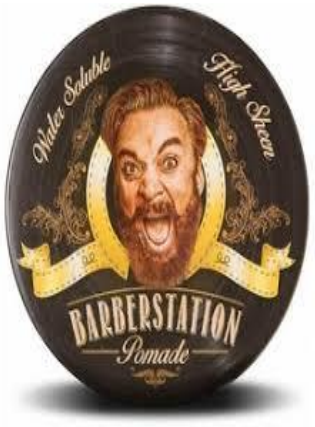
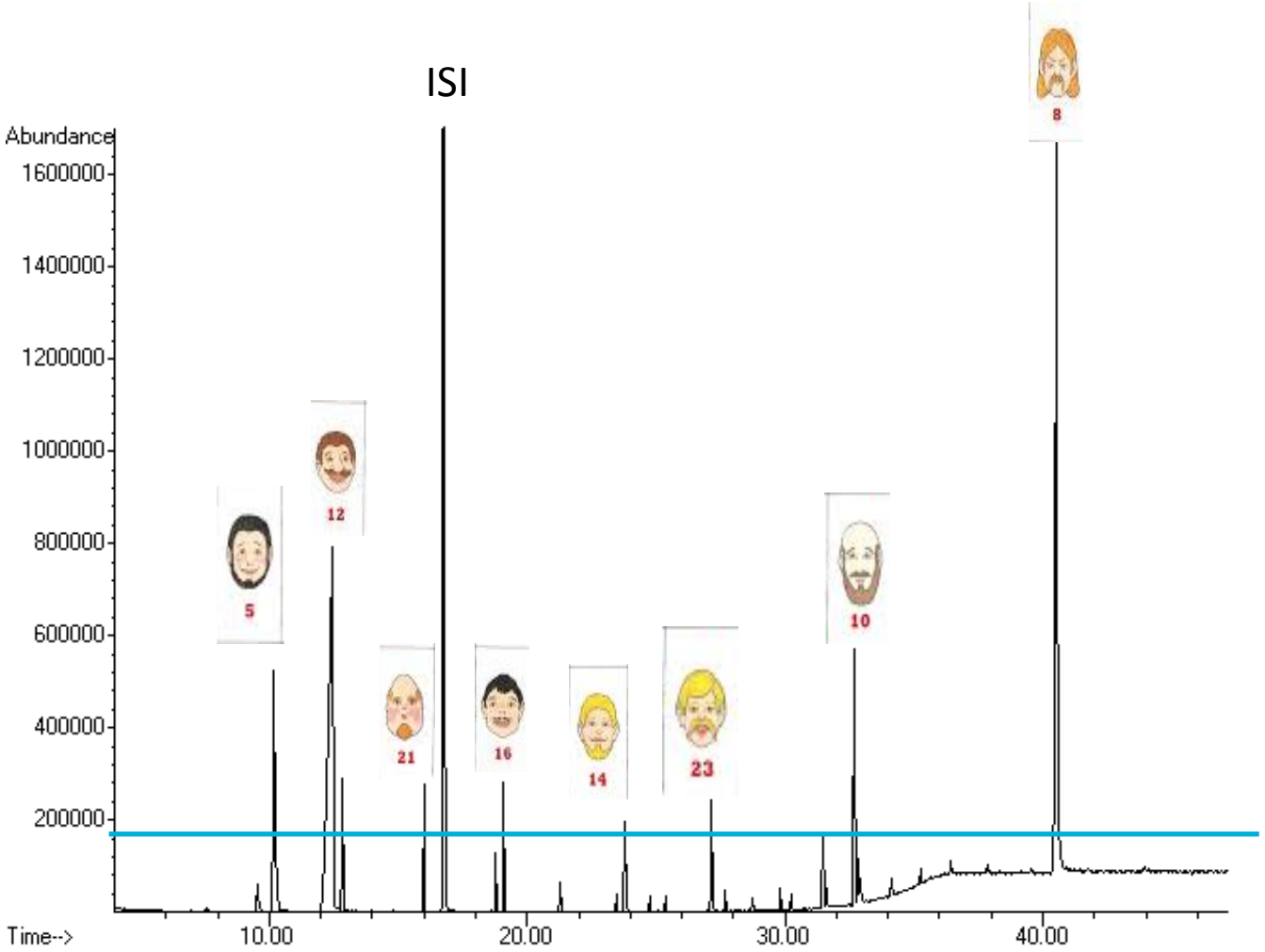
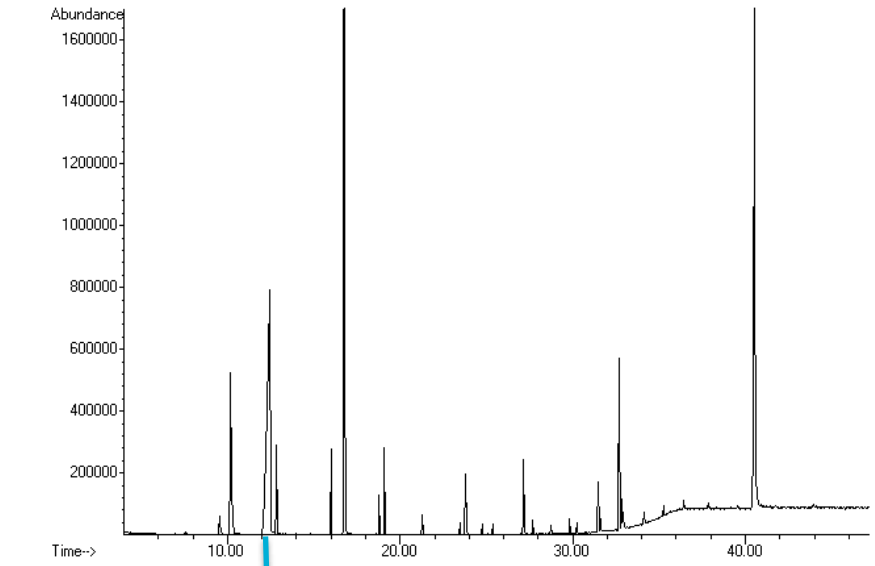


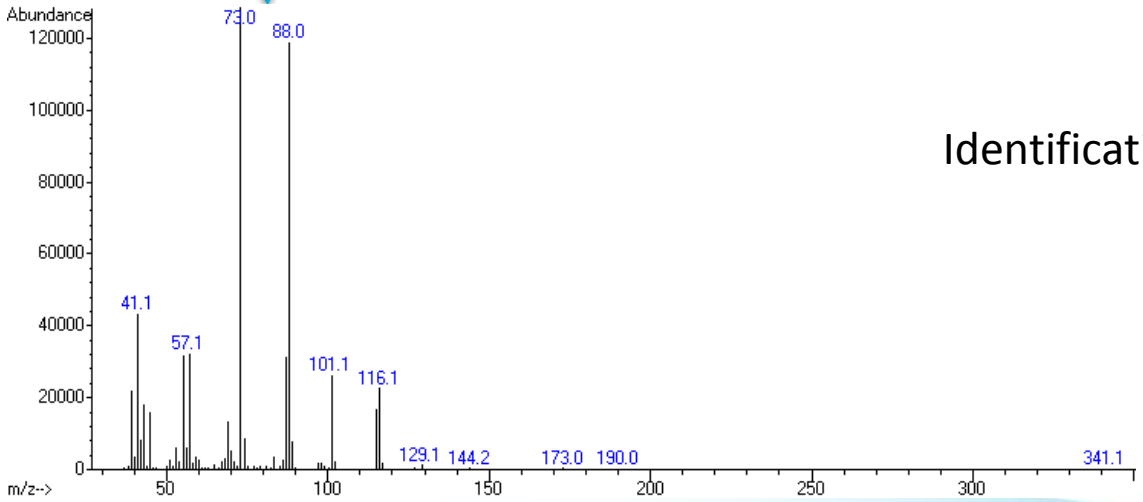
Semi-volatile compounds : separation with Gas Chromatography

ISI



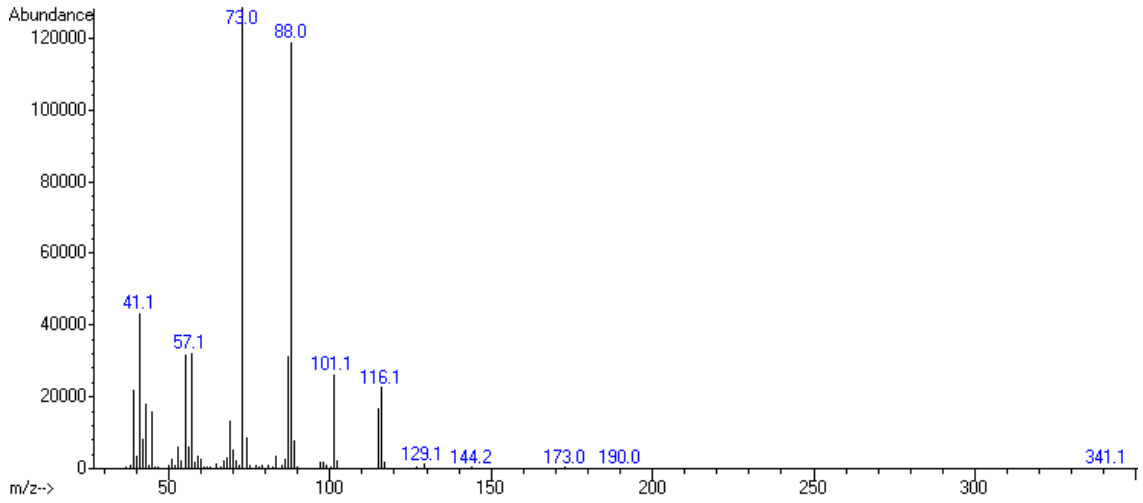
E&L testing: Analysis of the extracts: Identifying the compounds





Identification with mass spectrometry

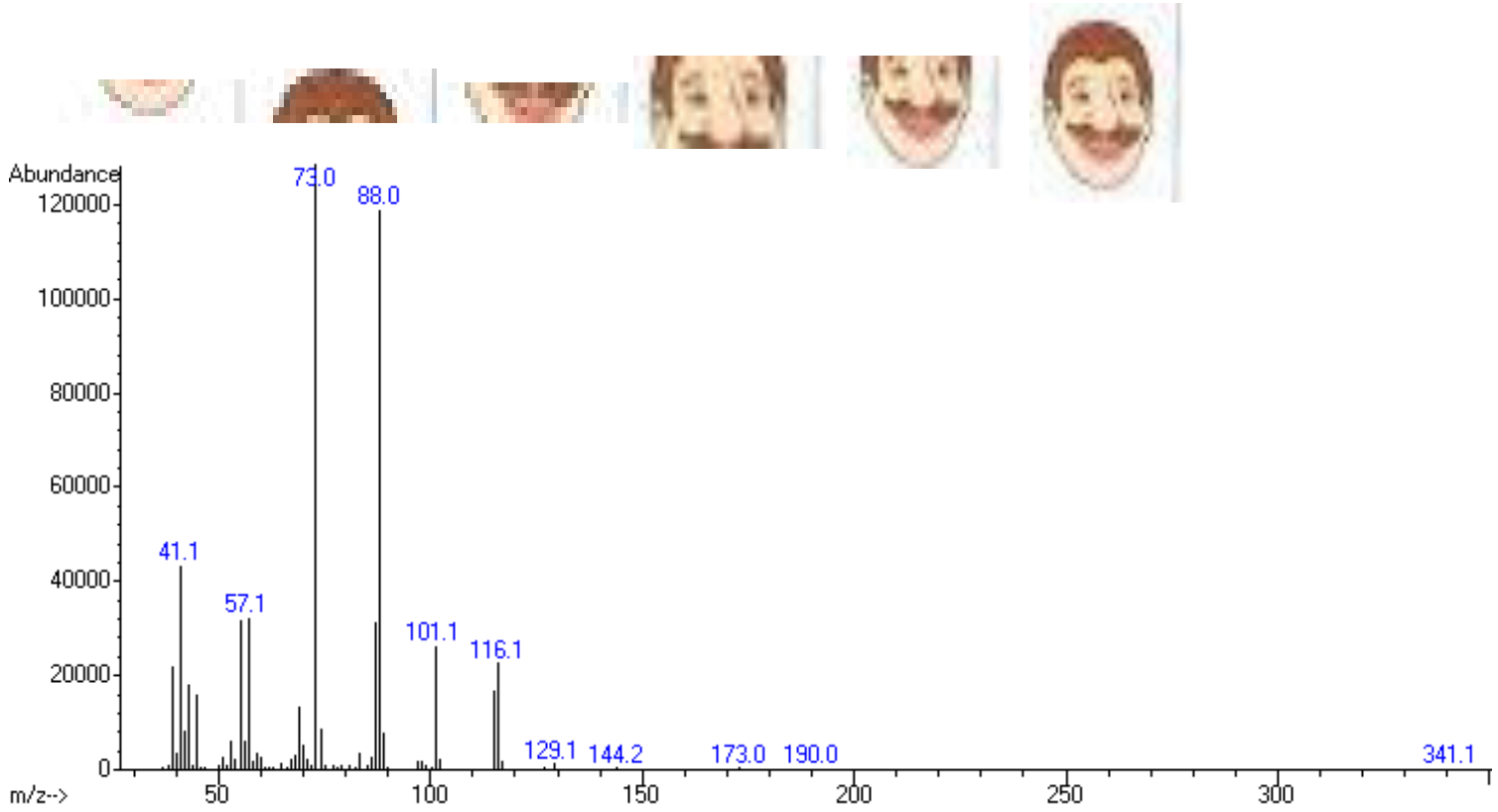
E&L testing: Analysis of the extracts: Identifying the compounds



E&L testing: Analysis of the extracts: Identifying the compounds

Chemical compound is fragmented in a unique combination of masses with specific abundance

E&L testing: Analysis of the extracts: Identifying the compounds



E&L testing: Analysis of the extracts: Identifying the compounds

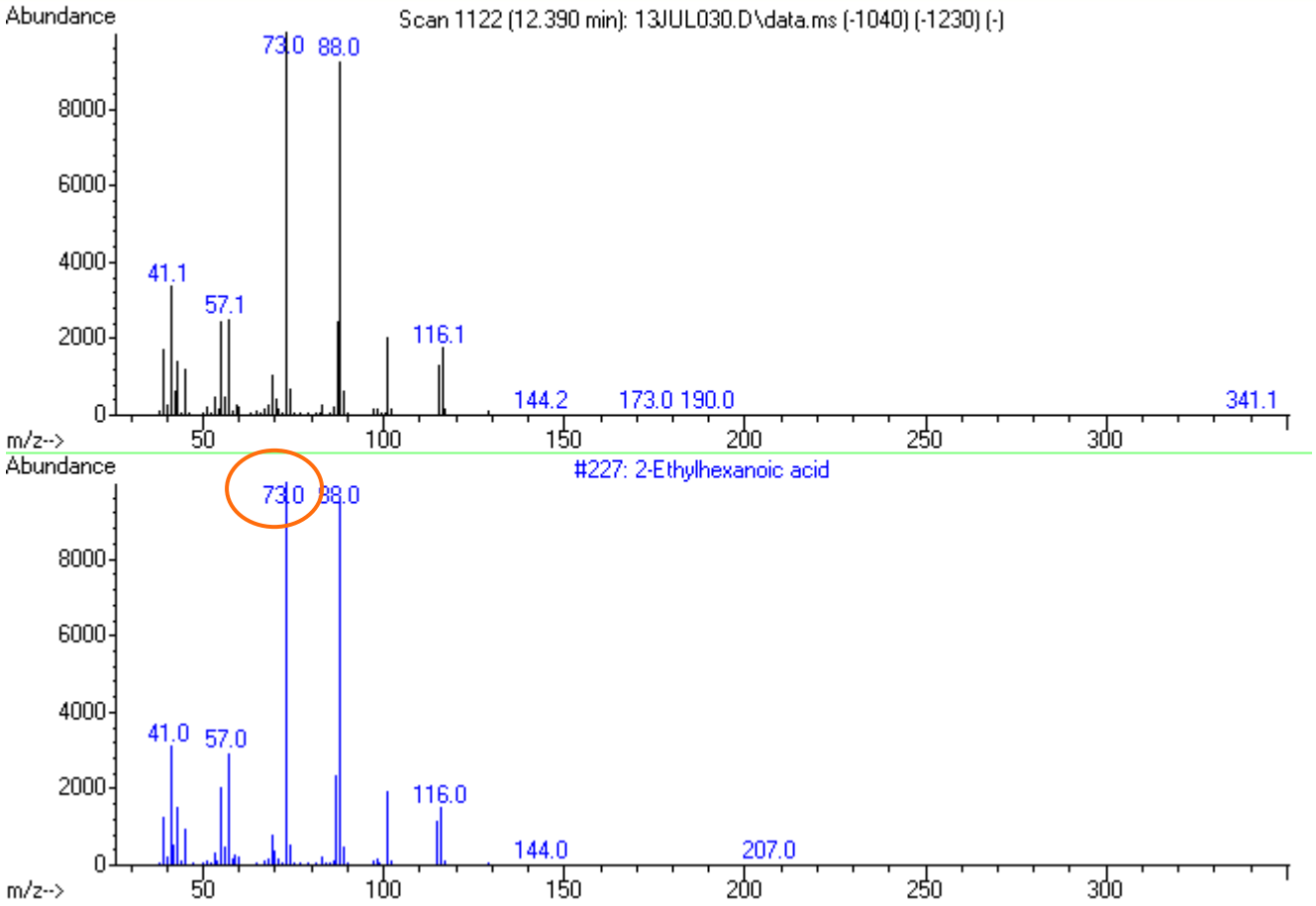
Look for similar combination of masses and abundance in existing library

E&L testing: Analysis of the extracts: Identifying the compounds

MAX

Unique identification

E&L testing: Analysis of the extracts: Identifying the compounds



Compound = 2-Ethylhexanoic acid

E&L testing: Analysis of the extracts: Identifying the compounds

- **Look at match factor and similarities beween your spectrum and library spectrum**

Toxicological Risk Assessments

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Octoberfest!!

- Oktoberfest 2017 7.5 million liters of beer was consumed by 6.2 million visitors so that's 1.2 liters per person.

Toxicological Risk Assessments

Applying chemistry to the biocompatibility or biological safety of your device

Great - you have your chemistry data. Now what?

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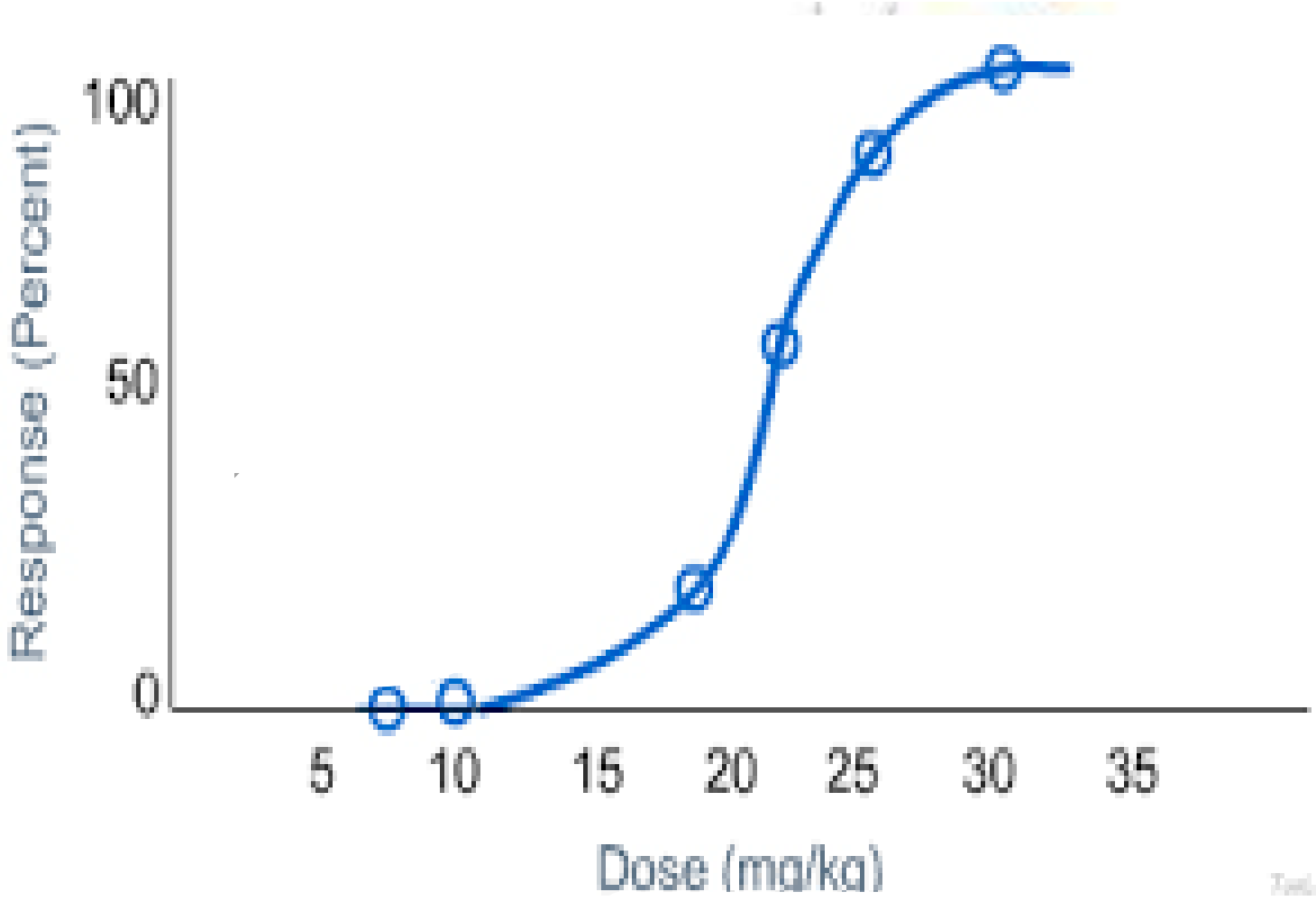
Toxicological Risk Assessments



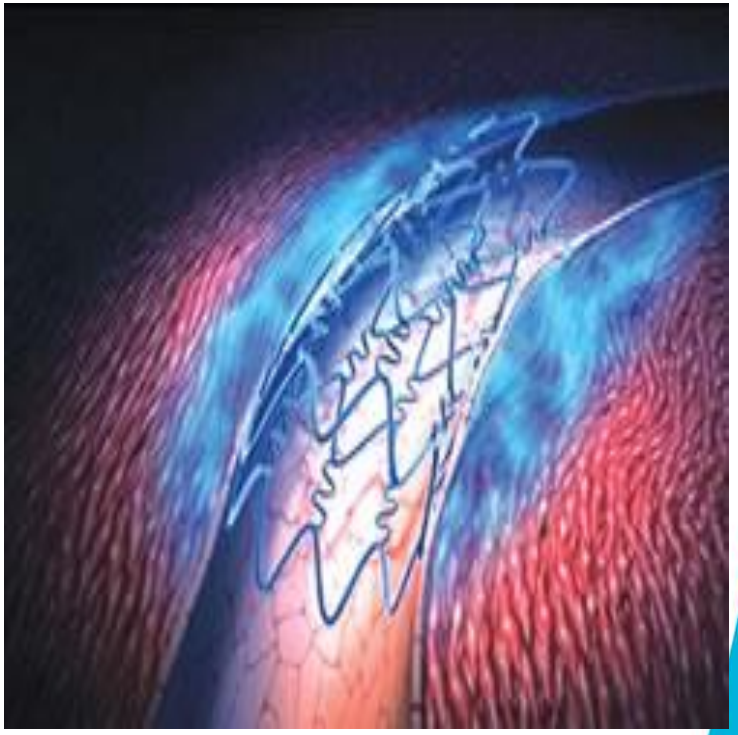
E&L Results: Interpretation of the Toxicological Risk

Recognize the **requirements** of a toxicologist to conduct a suitable **Toxicology Risk Assessment**

Apply appropriate **Thresholds of Toxicolgical Concern (TTC)** to E&L data

Understand the risks to the patient

Perform Tolerable Intake (TI), Tolerable Exposure (TE), and Margin of Safety calculations



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Toxicological Risk Assessment

Determine E&L results in mg/device

Research the tox data available for each compound (*NOAEL* or *LOAEL*)

Per ISO 10993-17, calculate *TI* → *TE* → *MOS*

NOAEL/LOAEL: No Adverse Effect Level / Lowest Adverse Effect Level
TI/TE: Tolerable Intake
MOS: Margin of Safety

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E&L Results and Example Calculations

Result: Cyclohexanone detected at 3.2 mg/device

Determine an appropriate NOAEL

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Hazardous Substances Data Bank

HSDB

Next Item | Search Results | Basic Search | Details | Other Files | Modify Search

Download | Limits | Browse Index | Help

TOXNET Home

NATIONAL LIBRARY OF MEDICINE

Item 1 of 118

Table of Contents

Contract all categories
Expand all categories
Select Clear

- FULL RECORD
- Human Health Effects
  - Evidence for Carcinogenicity
  - Human Toxicity Excerpts
  - Skin, Eye and Respiratory Irritations
  - Medical Surveillance
  - Probable Routes of Human Exposure
  - Body Burden
- Emergency Medical Treatment
  - Emergency Medical Treatment
- Animal Toxicity Studies
  - Evidence for Carcinogenicity
  - Non-Human Toxicity Excerpts
  - Ecotoxicity Values
  - Ongoing Test Status
  - TSCA Test Submissions
- Metabolism/Pharmacokinetics
  - Metabolism/Metabolites
  - Absorption, Distribution & Excretion

gave a lace-work of spider-web appearance of the periphery of the lenses against the pink fundus reflex. (In parallel experiments with acetone and dimethyl sulfoxide a similar appearance developed, but in higher incidence.)
[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 296] **PEER REVIEWED**

Exposure of rabbits by inhalation to about 12,000 mg/cu m **cyclohexanone** for 6 hour per day on five days per week for three weeks and to 1,200-5,560 mg/cu m for ten weeks induced /CNS depression/, loss of coordination and death (2/4 animals) only in the highest exposure group; slight conjunctival irritation was seen at doses of 1,200-3,000 mg/cu m. No toxic effect was observed with exposure to 750 mg/cu m.
[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work). Available at: http://monographs.iarc.fr/index.php p. V47 162 (1989)] **PEER REVIEWED**

Intravenous administration of 50 or 100 mg/kg body weight **cyclohexanone** to rats for 28 consecutive days caused no significant ophthalmological or hematological toxicity or alterations in clinical chemistry, gross pathology or histopathology.
[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work). Available at: http://monographs.iarc.fr/index.php p. V47 162 (1989)] **PEER REVIEWED**

Guinea pigs and rabbits were administered 0.5 or 5 mg/kg body weight **cyclohexanone** intravenously or 0.5 ml percutaneously three times a week for three consecutive weeks; lenticular alterations (anterior subcapsular vacuoles) were observed in all groups of guinea pigs but not in rabbits.
[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization,

Example Calculations

$$TI = \frac{NOAEL \text{ or } LOAEL}{(UF1 \times UF2 \times UF3)}$$

UF1: Inter-individual variation among humans (default 10)
UF2: Extrapolation of effects between animals and humans (default 10)
UF3: Quality and relevance of experimental data

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Example Calculations

Calculate the TI

$$TI = \frac{\frac{100\ \text{mg}}{\text{kg} \cdot \text{day}}}{(10 \times 10 \times 1)} = 1\ \text{mg/kg} \cdot \text{day}$$

UF1: Inter-individual variation among humans (default 10)
UF2: Extrapolation of effects between animals and humans (default 10)
UF3: Quality and relevance of experimental data

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Example Calculations

$$TE = TI \times mB \times UTF$$

$$(UTF = CEF \times PEF)$$

m_B: Body weight (default adult male 70 kg; adult female 58 kg)
UTF: Utilization Factor
CEF: Concomitant Exposure Factor (default 0.2)
PEF: Proportional Exposure Factor (default 1)

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Calculate the TE

$$TE = \frac{1\ \text{mg}}{\text{kg}\cdot\text{day}} \times 70\ \text{kg} \times 0.2 = \underline{14\ \text{mg/day}}$$

m_B: Body weight (default adult male 70 kg; adult female 58 kg)
UTF: Utilization Factor
CEF: Concomitant Exposure Factor (default 0.2)
PEF: Proportional Exposure Factor (default 1)

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Example Calculations

$$MOS = \frac{TE}{E\&L\ Device\ Result}$$

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Calculate the MOS

$$MOS = \frac{14\ mg/day}{3.2\ mg/device} = \underline{4.3}$$

A MOS greater than a value of 1 is indicative of low toxicological hazard for the evaluated substance

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Is Octoberfest Lethal?

- Oktoberfest 2017 7.5 million liters of beer was consumed by 6.2 million visitors so that's 1.2 liters per person.
- 5.5% alcohol per beer so that's 66 ml or 51816.6 mg per day
- NOAEL for repeat dose toxicity =1730mg/kg* (male rats).
- *ECHA Dossier Ethanol EC number: 200-578-6 | CAS number: 64-17-5

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Example Calculations

$$TI = \frac{NOAEL \text{ or } LOAEL}{(UF1 \times UF2 \times UF3)}$$

UF1: Inter-individual variation among humans (default 10)
UF2: Extrapolation of effects between animals and humans (default 10)
UF3: Quality and relevance of experimental data

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Example Calculations

$$TI = (1730mg/kg)/10X10X1$$
$$= 17.3mg/kg/day$$

UF1: Inter-individual variation among humans (default 10)
UF2: Extrapolation of effects between animals and humans (default 10)
UF3: Quality and relevance of experimental data

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Example Calculations

$$TE = TI \times mB \times UTF$$

$$(UTF = CEF \times PEF)$$

m_B: Body weight (default adult male 70 kg; adult female 58 kg)
UTF: Utilization Factor
CEF: Concomitant Exposure Factor (default 0.2)
PEF: Proportional Exposure Factor (default 1)

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Example Calculations

TE= 17.3mg/kg/day X 70 kg X 0.2 =

242.2 mg/day

m_B: Body weight (default adult male 70 kg; adult female 58 kg)
UTF: Utilization Factor
CEF: Concomitant Exposure Factor (default 0.2)
PEF: Proportional Exposure Factor (default 1)

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Example Calculations

$$MOS = \frac{TE}{E\&L\ Device\ Result}$$

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Example Calculations

MOS=(242.2 mg/day)/(51816.6 mg/day) =0.005

A MOS greater than a value of 1 is indicative of low toxicological hazard for the evaluated substance

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Side Note

- From witnesses at Oktoberfest “A typical German at Oktoberfest will easily have 3 steins per session each at a liter- that makes 130.2 grams per day. Maybe the average of 1.2 L takes into account the light-weight Americans that go there.

Conclusion

This risk assessment was supported by information gathered from **extractable and leachable** chemical characterization testing data on the system, **published literature**, and the **derived margins of safety** of the compounds extracted from the system.

This risk assessment indicates that the likelihood of adverse effects from the device is considered low for all compounds.

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Conclusion on Toxicological Assessments

- Biocompatibility evaluations must be strategic & science based
- ***Material Characterization***: Thorough understanding of the device materials and processing can help to minimize biocompatibility testing
- ***Chemical Characterization (E&L)***: Provides the key information needed to conduct a proper risk toxicological assessment
- Goals: Save animal life, save time, save money, and **IMPROVE PATIENT CARE**!

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Medical Device Regulations

Potential Synergies when Applying for FDA

Thor Rollins BS RM(NRCM)
Director of Toxicology
Nelson Laboratories
trollins@nelsonlabs.com

22 MAY 2019

The Past

Early 2000s to recently companies preferred Europe

- US companies would target CE mark before FDA clearance
  - 65% of devices were CE marked before FDA Clearance
  - Up to 80% initially approached Notified Bodies for Clearance(Newswire 2011)

Limited biocompatibility testing was needed for CE mark compared to “check box” approach for FDA

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Then Everything Changed….

More Governance

More Clinical Data

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Now the Clock is Ticking

- Are we going to be ready?

MedTech Europe

Our industry is prepared to submit product files to comply with the new Medical Device Regulation (MDR). However, we cannot do so. The new regulatory system is not ready to function. The deadline for the system to be fully operational is not 26 May 2020, the date of MDR application as the Commission continues to suggest. The deadline for the system to be ready for our industry to comply is now.

Re: Open letter on the implementation and readiness status of the new Medical Device Regulation 745/2017 (MDR)

Dear Vice-President Katainen,

I am writing to you regarding an issue of absolute urgency for patient care across Europe and for the internal market at large. The medical device industry in Europe confirms that without immediate action by the European Commission, the new regulatory system will not be ready on time to ensure continued access of patients and healthcare systems to life-saving and life-transforming devices.

Our industry is prepared to submit product files to comply with the new Medical Device Regulation (MDR). However, we cannot do so. The new regulatory system is not ready to function. The deadline for the system to be fully operational is not 26 May 2020, the date of MDR application as the Commission continues to suggest. The deadline for the system to be ready for our industry to comply is now.

One of the critical concerns is the designation and capacity of Notified Bodies, which the European Commission and Member States are still assessing to the new rules. It is only after being designated that

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What About the FDA?

No-predicate submissions for lower risk devices

The De Novo Program

The ASCA Program

- Accreditation Scheme for Conformity Assessment

MDSAP

- Emerging Global Consensus on device Quality Systems and Audit

*https://www.fda.gov/medical-devices/standards-and-conformity-assessment-program/accreditation-scheme-conformity-assessment-asca

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The Outcom

510(k) Clearances by Country of Origin			EMERGO
Country	2014	2015	2016
Canada	1.0%	1.3%	1.6%
China	5.9%	7.0%	6.6%
France	1.0%	2.5%	2.1%
Germany	2.3%	3.7%	4.5%
Israel	1.4%	1.5%	2.8%
Italy	0.8%	1.5%	1.6%
Japan	0.8%	2.3%	2.9%
South Korea	1.1%	2.9%	4.4%
Switzerland	0.5%	1.6%	1.9%
Taiwan	1.3%	2.4%	1.8%
UK	1.4%	1.8%	1.9%
USA	78.1%	63.3%	59.7%

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The Timing is Horrendous

New ISO 10993-1 (from X to E)

New ISO 18562 (March 2017)

New 10993-18 Final Draft

Meet the New Standard: Table A.1 from ISO 10993-1

Table A.1 — Endpoints to be addressed in a biological risk assessment

Medical device categorization by			Endpoints of biological evaluation														
Nature of body contact		Contact duration															
Category	Contact	A - limited (≤24 h) B - prolonged (>24 h to 30 d) C - Long term (>30 d)	Physical and/or chemical information	Cytotoxicity		Irritation or intracutaneous reactivity	Material mediated pyrogenicity[a]	Acute systemic toxicity[b]	Subacute toxicity[b]	Subchronic toxicity[b]	Chronic toxicity[b]	Implantation effects[b,c]	Hemocompatibility	Genotoxicity[d]	Carcinogenicity[d]	Reproductive/ developmental toxicity[d,e]	Degradation[f]
Surface medical device	Intact skin	A	X[g]	E[h]	E	E											
		B	X	E	E	E											
		C	X	E	E	E											
	Mucosal membrane	A	X	E	E	E											
		B	X	E	E	E		E	E			E					
		C	X	E	E	E		E	E	E	E	E		E			
	Breached or compromised surface	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E					
		C	X	E	E	E	E	E	E	E	E	E		E	E		
Externally communicating medical device	Blood path, indirect	A	X	E	E	E	E	E					E				
		B	X	E	E	E	E	E	E				E				
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
	Tissue/ bone/ dentin[i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Circulating blood	A	X	E	E	E	E	E					E	E[j]			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

- **Issued August 2018**
- **Replaced 2009 version**

Summary Actions

MARKET STRATEGY	REGULATORY STRATEGY	DIRECTIONS

What Markets Matter?

What Products Matter?

Family Groupings?

Communicate

- Internally
- Customers
- Investors

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Start Family Groupings

Set of Devices:

- 4 different plate sizes
- 5 different screw sizes
- Each screw comes in two colors
- Each plate available in cpTi or 316SS
- Each plate and screw equivalently available from 2 suppliers

- 36 line items to be considered
- 80 different possible patient contacting configurations

More Information

Irritation and sensitization *in vitro* developments	• Sensitization working on bringing laboratories together to collaborate on a procedure.
"How Chemical Characterization Can Supplement & Support Biocompatibility Testing"	• Authors - Sarah Campbell, Thor Rollins, Audrey Turley http://directory.qmed.com/download-this-whitepaper-to-examine-the-various-file060395.html
FDA Guidance Document on ISO 10993-1	• http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf • Effective September 14, 2016

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QUESTIONS?

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