ISO 10993-18 in the MDR :

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Understanding the restrictions and risk assessment for substances which are Carcinogenic, Mutagenic, toxic to Reproduction (CMR) or have Endocrine-Disrupting (ED) properties (**section 10.4, Annex I MDR**)

Annelies Vertommen, PhD

4 MARCH 2020

2020: The Year Of Change for the Medical Device Industry

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Outline

- **MDR**: section 10.4, Annex I, Chapter II

- **ISO 10993-18**:
  - a screening vs a targeted analytical approach
  - three levels of quantification

- **ISO 10993-18 in the MDR**

- **Conclusion**: proposed workflow

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MDR Annex I (GSPR)

Design and manufacture of devices to reduce **risks** posed by substances or particles that may be released from the device

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MDR Annex I, Chapter II, Section 10.4.

Risk justification and labelling for substances

- *10.4.1*: when? Design and manufacture of devices
- *10.4.2*: how *justification*?
  - Section 10.4.3: guideline on phthalates
  - Section 10.4.4: guideline on other CMR & ED substances
- *10.4.5*: how *labelling*?

10.4.1 When?

1. What type of test items?

Device, part or material

- Invasive & direct contact with human body
- (Re)administering medicines or other substances to/from body
- Transport or storing medicines or other substances

10.4.1 When?

2. Cannot contain CMR 1A, CMR 1B or ED substance > 0.1 % weight/weight unless justification & labelling

- *CMR: Carcinogenic, mutagenic, or reprotoxic*
  - *CMR 1A: Known human CMR*
  - *CMR 1B: Presumed human CMR*
  - CMR 1A/1B: As per Annex VI CLP Regulation
- ED substance: Endocrine disruptor (human health)
  - *Article 59, EC 1907/2006 (REACH)*
  - *Article 5(3) EC 528/2012 (biocidal)*

Why 0.1% w/w ?

- Analysis of (patient & user) exposure

ICS › 11 › 11.100 › 11.100.20

ISO 10993-18:2020

BIOLOGICAL EVALUATION OF MEDICAL DEVICES — PART 18: CHEMICAL CHARACTERIZATION OF MEDICAL DEVICE MATERIALS WITHIN A RISK MANAGEMENT PROCESS

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- Analysis of (patient & user) exposure

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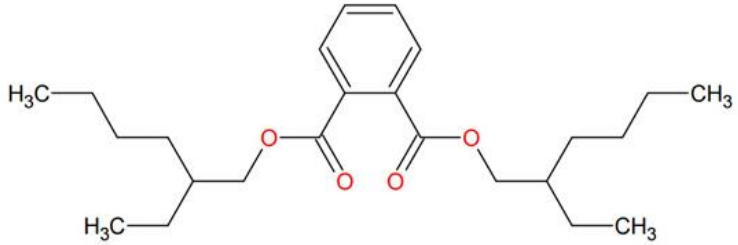
- Analysis of (patient & user) exposure

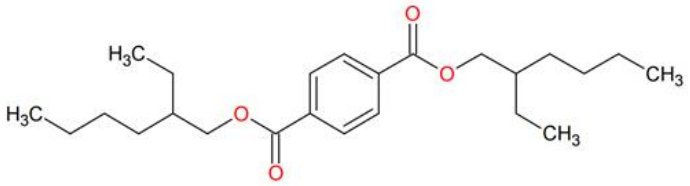
  = risk assessment : ISO 10993-18

- Analysis of alternative substances, materials, designs



DEHP

Isophthalate
Endocrine-disruptor



DEHT

Terephthalate
No endocrine-disruptor

- Benefit-risk assessment

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- 10.4.3: Guideline on phthalates (Scheer, 2019)

Scientific Committee on Health, Environmental and Emerging Risks

SCHEER

GUIDELINES

on the benefit-risk assessment of the presence of phthalates in certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to reproduction (CMR) or have endocrine-disrupting (ED) properties

- 10.4.4: Guideline on other CMR and endocrine-disrupting substances

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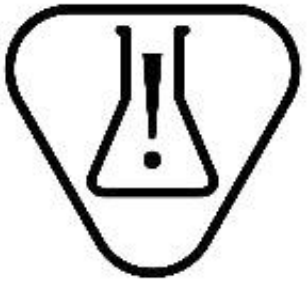
Where?

- on the device itself and/or
- on the packaging for each unit or,
- on the sales packaging



The missing link?

> 0.1 % weight/weight: HOW?

ISO 10993-18?

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Test my device for all substances??

0.1 % w/w = a lot !

Test my device for all substances??

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Test for all substances??

- Polycarbonate – Bisphenol A (BPA)
- PVC - Phthtalates
- Supplier: intentionally added

Only those substances that can be present > 0.1% w/w

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Test for all substances??

Polycarbonate – Bisphenol A (BPA)

PVC - Phthtalates

Supplier: intentionally added

Only those substances that can be present > 0.1% w/w

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ISO 10993-18:

- Answer for > 0.1 % w/w?

- Tool for risk assessment/justification

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ISO 10993-18:

- Answer for > 0.1 % w/w?

- Tool for risk assessment/justification

➡ **a screening versus a targeted approach**

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Screening

- No predefined target: **screen for all**
- General techniques:
  - HS-GC/MS: volatile organic compounds (VOC)
  - GC/MS: semi-volatile organic compounds (SVOC)
  - LC/MS: non-volatile organic compounds (NVOC)
- **No LOD, LOQ** for each compound

Targeted

- A limited number of **known targets**
- Selective technique:
  - ICP/OES: **elements**
  - IC: **anions**
  - Validated method: **specific organic compound**, e.g. Bisphenol A: GC/MS method
- **LOD, LOQ** for each compound

ISO 10993-18: three levels of quantification

- A screening versus a targeted analytical approach :
  three levels of quantification in ISO 10993-18

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ISO 10993-18: three levels of quantification

- A screening versus a targeted analytical approach :
  three levels of quantification in ISO 10993-18:

1. Estimated quantification
2. Semi-quantification

} Screening approach

3. Full quantification — Targeted approach

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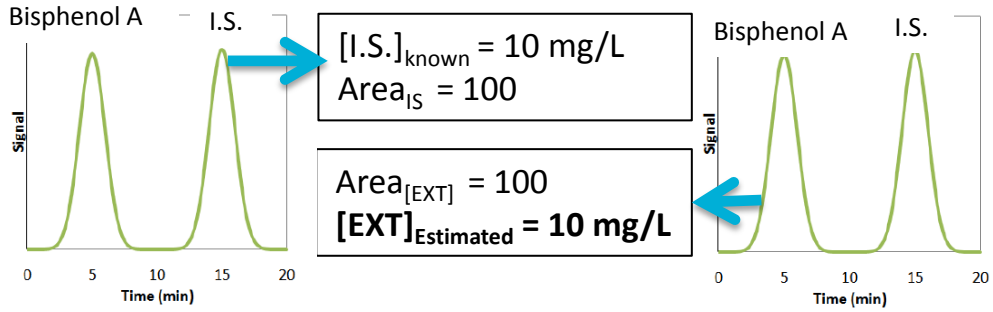
ISO 10993-18: three levels of quantification

3.30.1
estimated quantitative analysis
analytical approach which estimates an analyte's concentration by using the response from a surrogate substance chosen without specifically addressing or considering the relative responses of the analyte and the surrogate

ISO 10993-18: three levels of quantification

ESTIMATED QUANTITATIVE ANALYSIS

Assuming
$RF_{IS} = RF_{[EXT]}$



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ISO 10993-18: three levels of quantification

Bisphenol A

=

Internal Standard (IS)

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ISO 10993-18: three levels of quantification

3.30.2
semi-quantitative analysis
analytical approach which provides an analyte's concentration by using the response from a surrogate substance (or substances), specifically accounting for the relative responses of the analyte and the surrogate

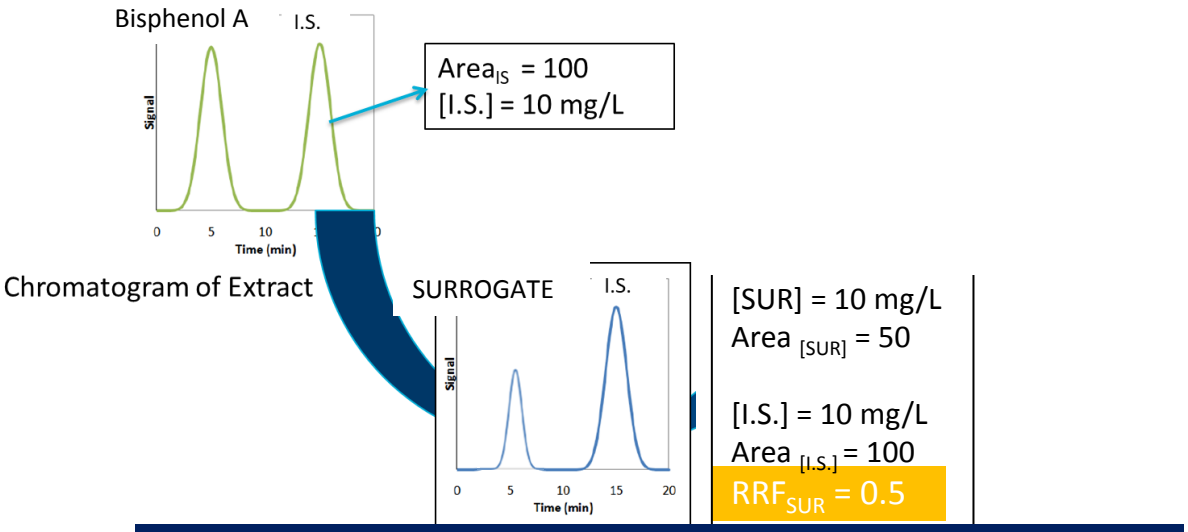
a. Semi-quantitative analysis via surrogate compound

b. Semi-quantitative analysis via individual RRF correction

a. SEMI-QUANTITATIVE ANALYSIS VIA SURROGATE RRF CORRECTION

ISO 10993-18: three levels of quantification

a. SEMI-QUANTITATIVE ANALYSIS VIA SURROGATE RRF CORRECTION



Surrogate compound: compound similar to target compound
BUT: many variation, e.g. Bisphenol A_d_{16}, Naphthalene_d_4

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Surrogate compound

>>>

IS

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ISO 10993-18: three levels of quantification

Bisphenol A

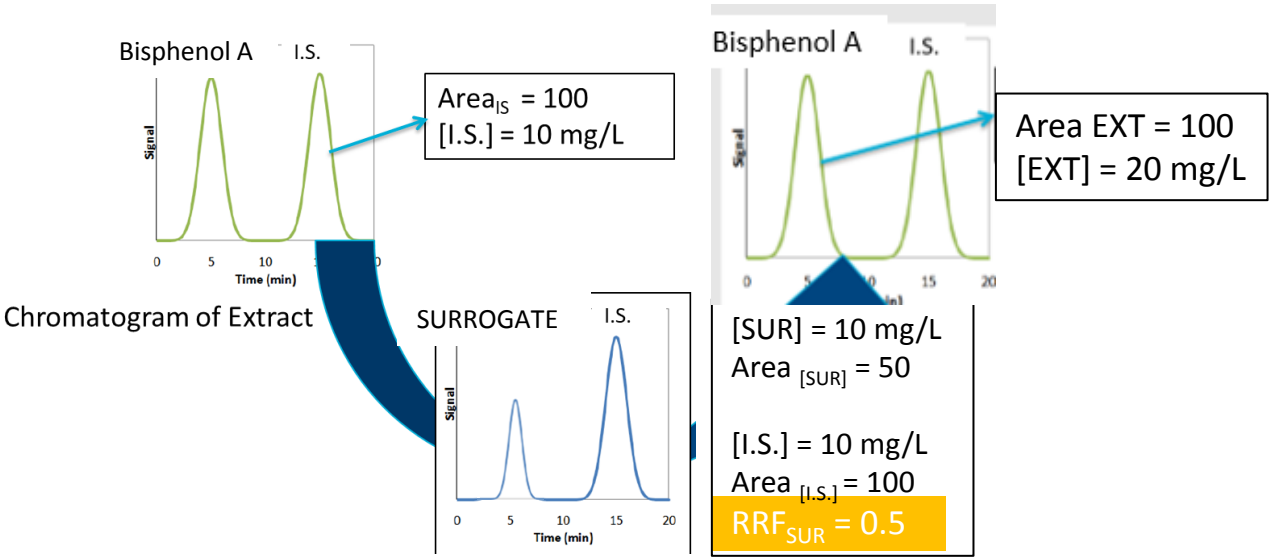
=

Surrogate compound

>>>

IS

a. SEMI-QUANTITATIVE ANALYSIS VIA SURROGATE RRF CORRECTION



b. SEMI-QUANTITATIVE ANALYSIS VIA INDIVIDUAL RRF CORRECTION

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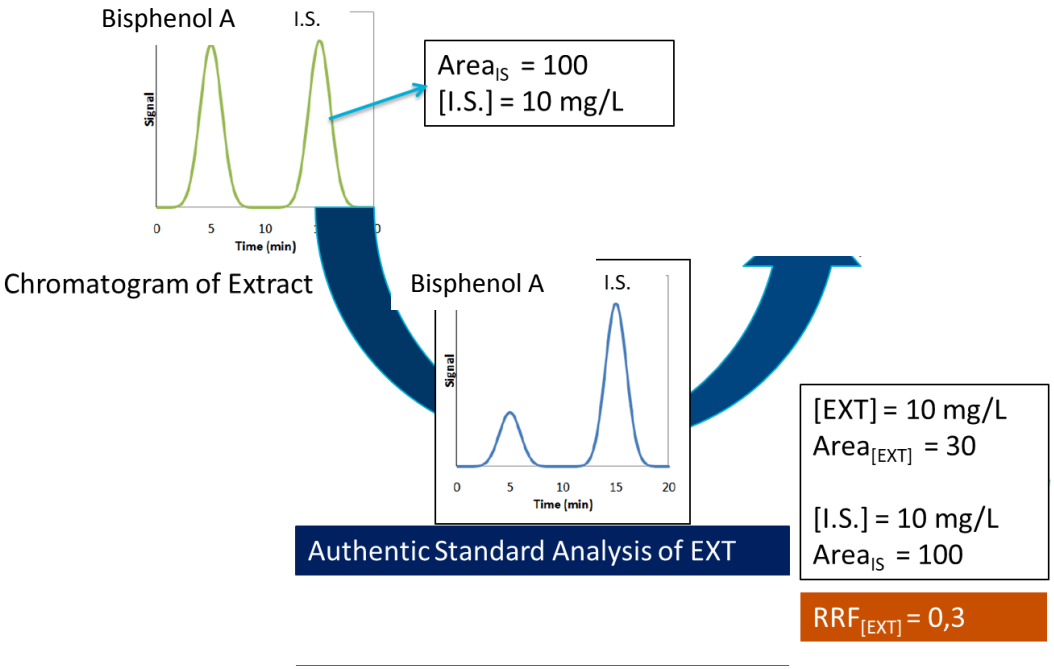

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ISO 10993-18: three levels of quantification

Bisphenol A

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IS

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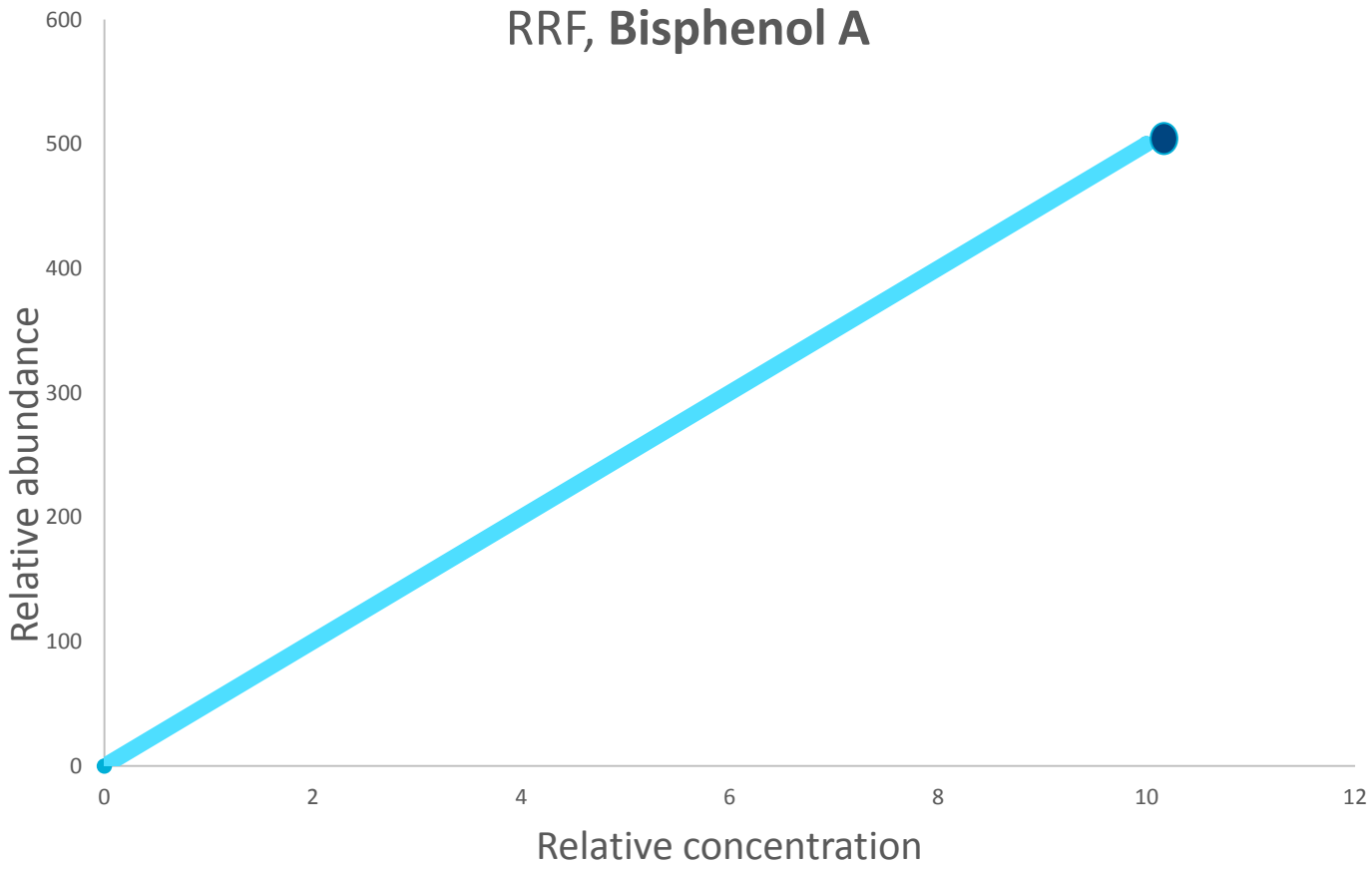
ISO 10993-18: three levels of quantification



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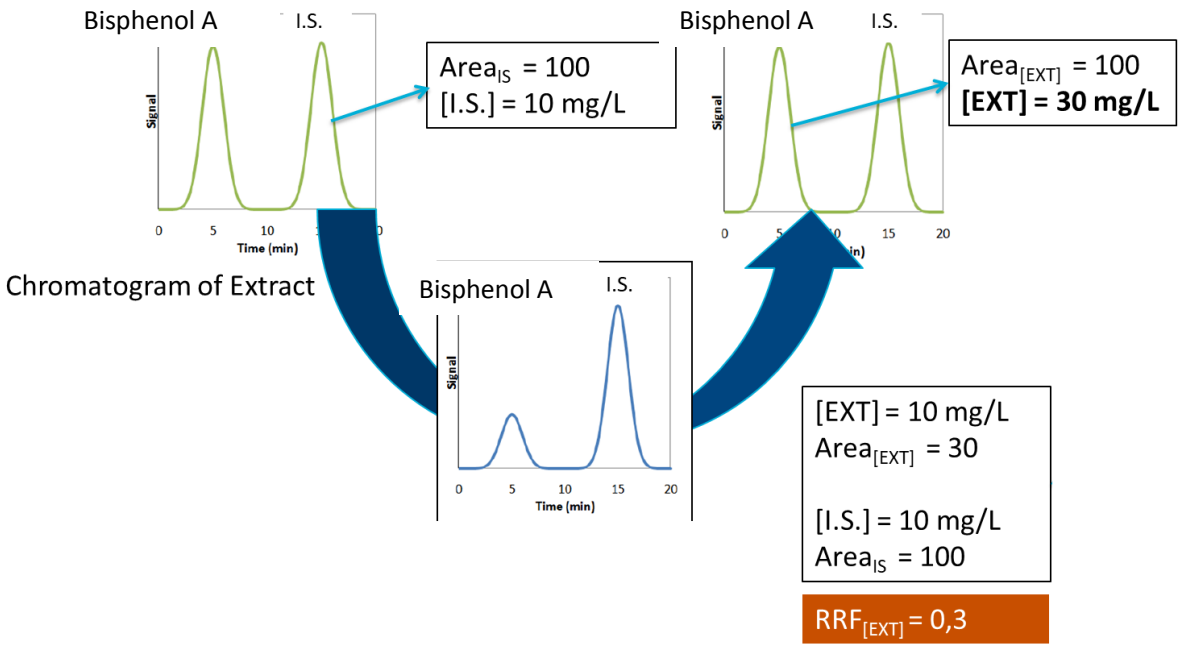

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ISO 10993-18: three levels of quantification

3.30.3
quantitative analysis
analytical approach which establishes the most accurate estimate of an analyte's concentration by using a response function (calibration curve) generated specifically for the analyte via the use of a reference standard

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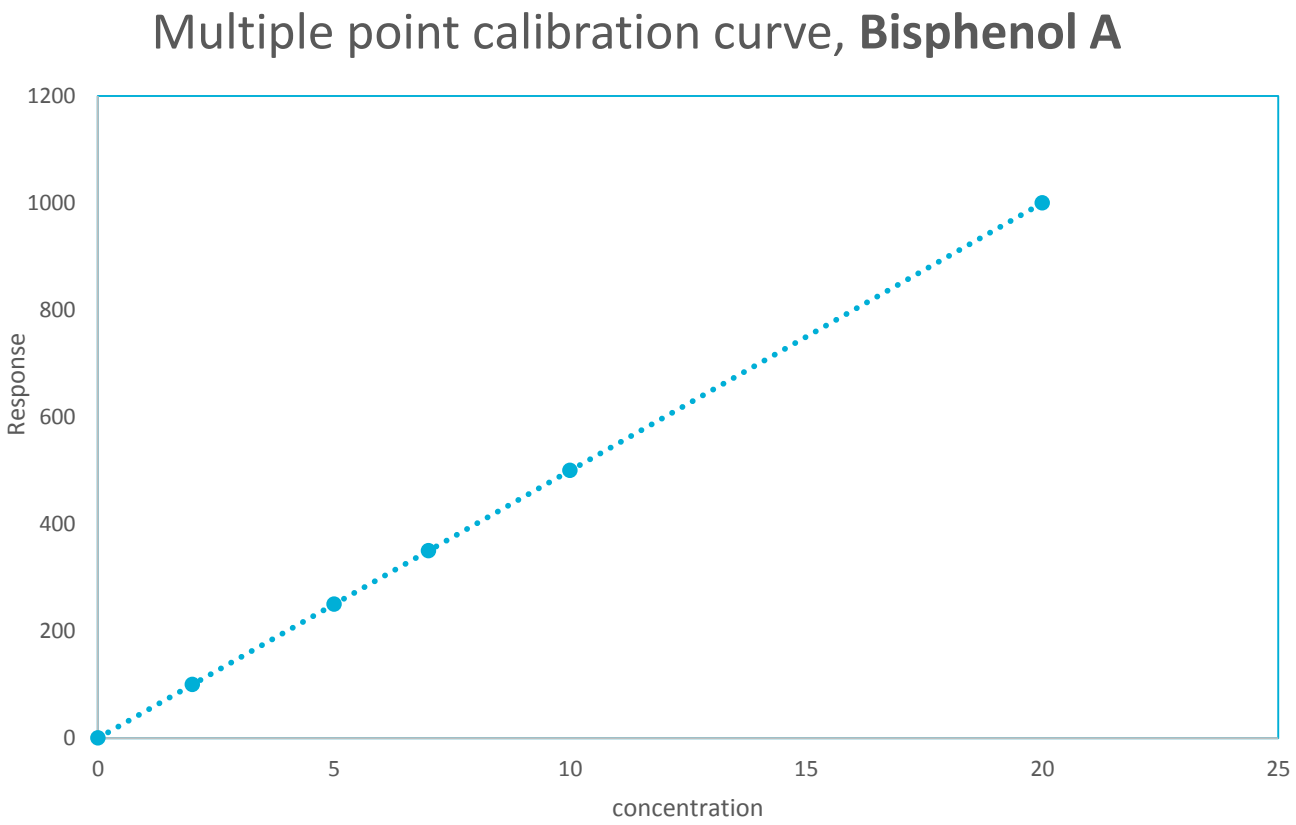
ISO 10993-18: three levels of quantification



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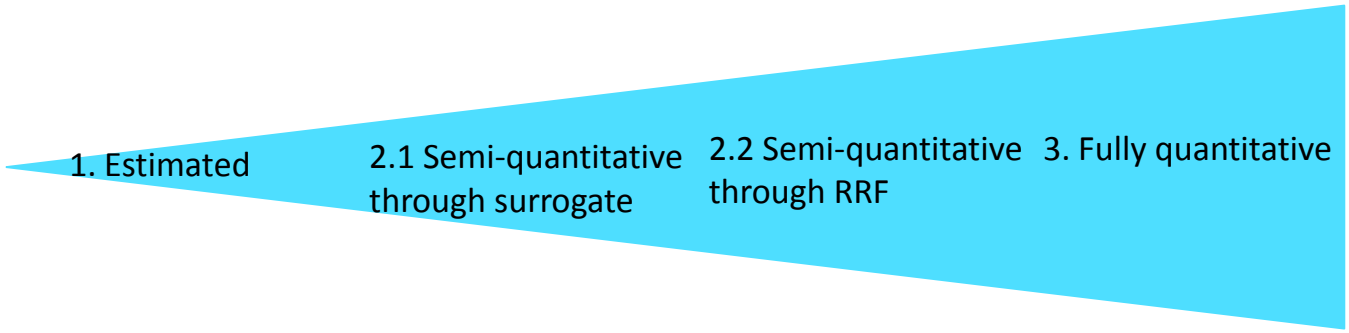
ISO 10993-18: three levels of quantification



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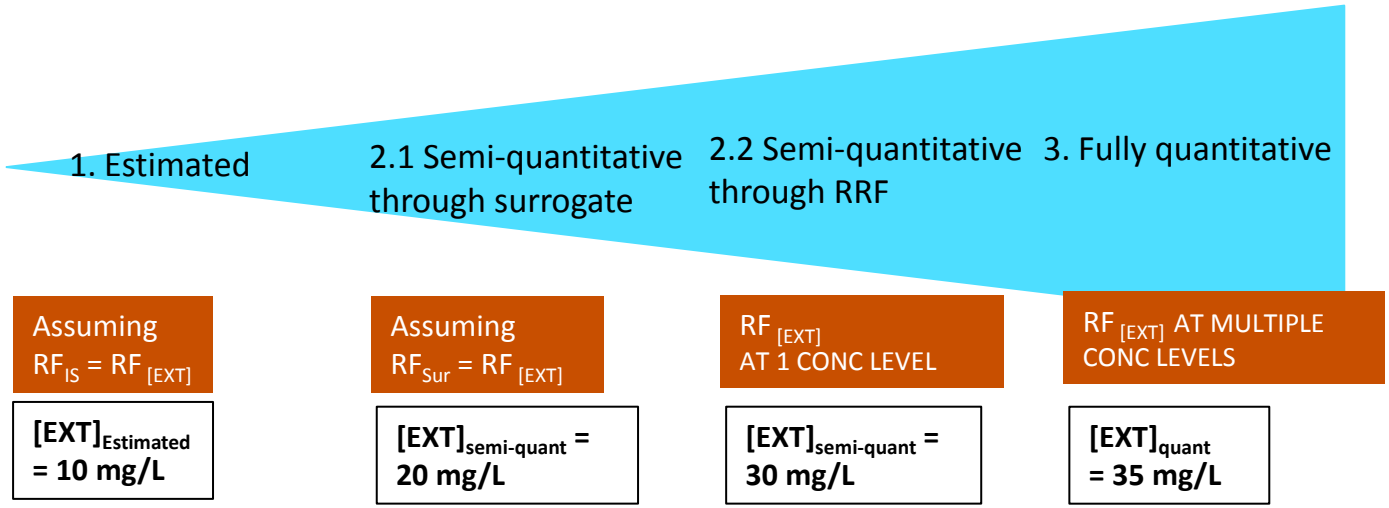
ISO 10993-18: three levels of quantification



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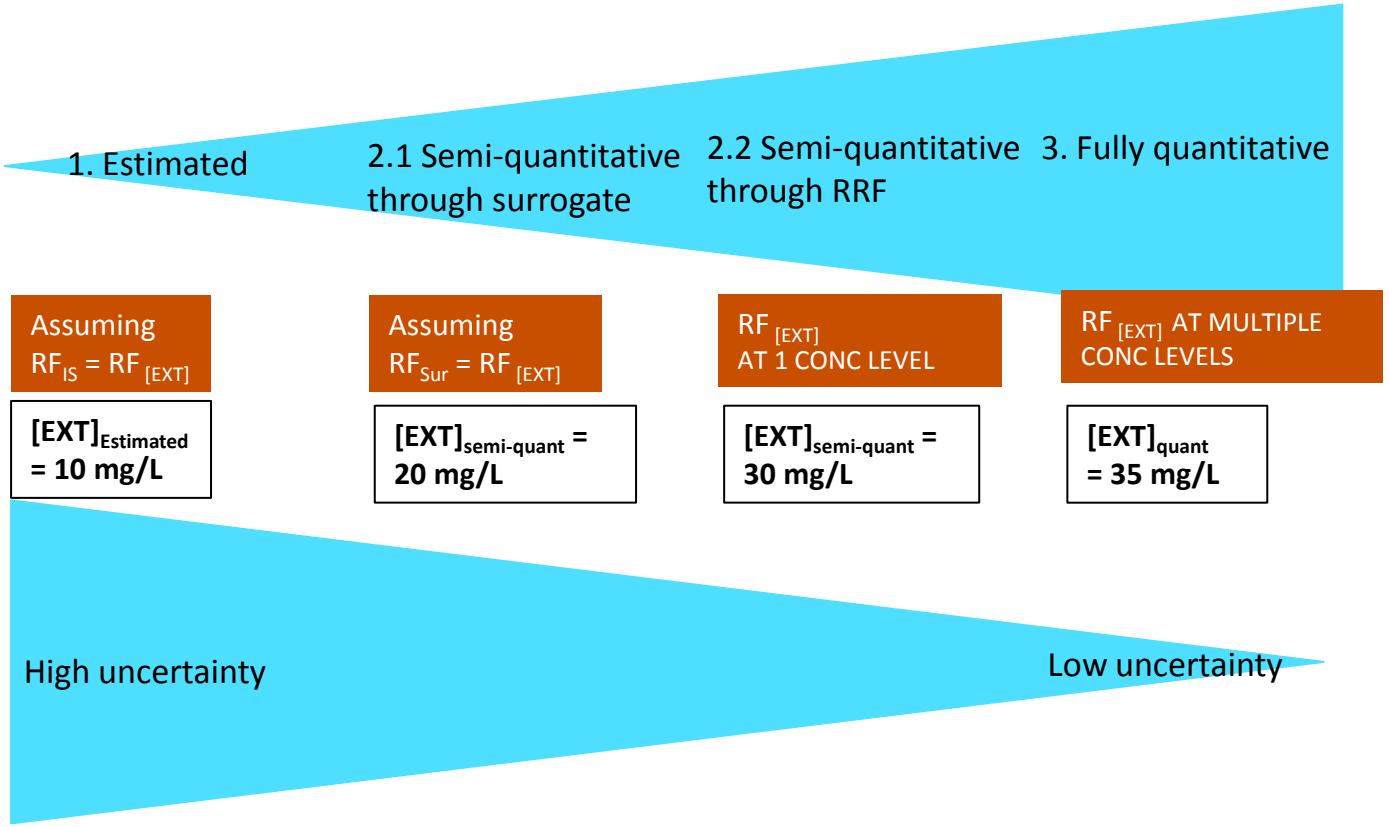
ISO 10993-18: three levels of quantification



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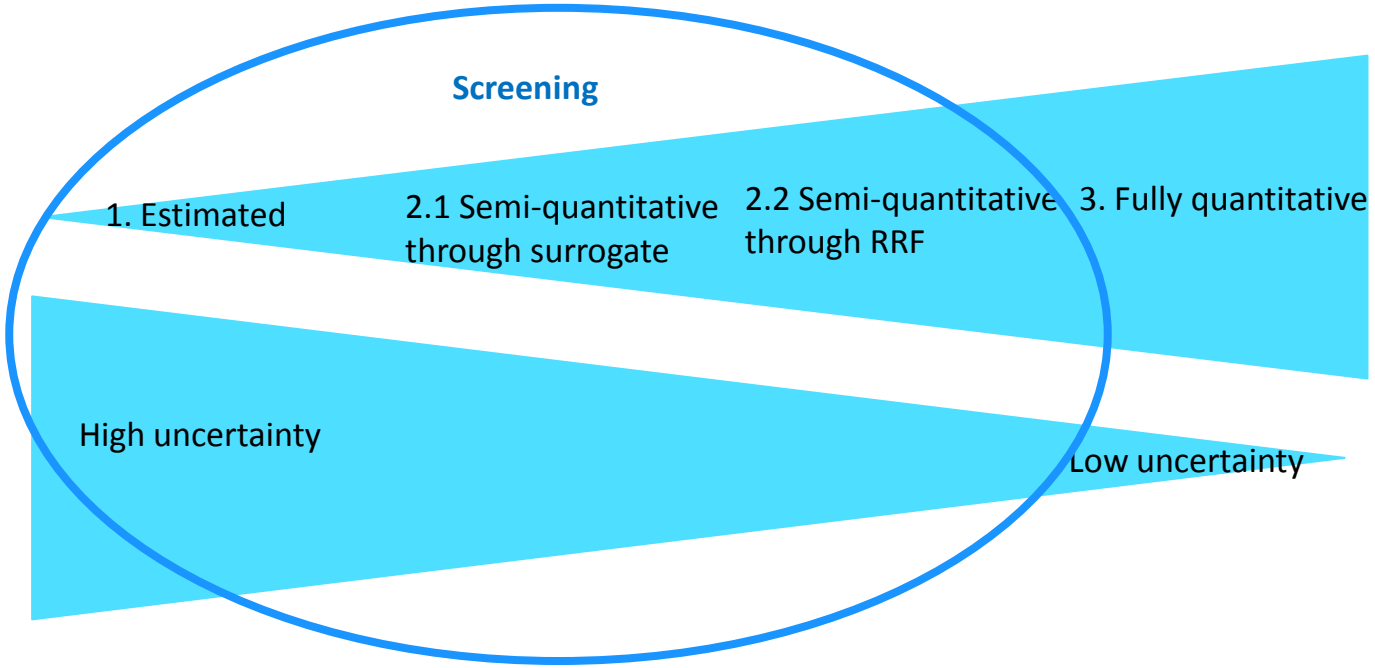
ISO 10993-18: three levels of quantification



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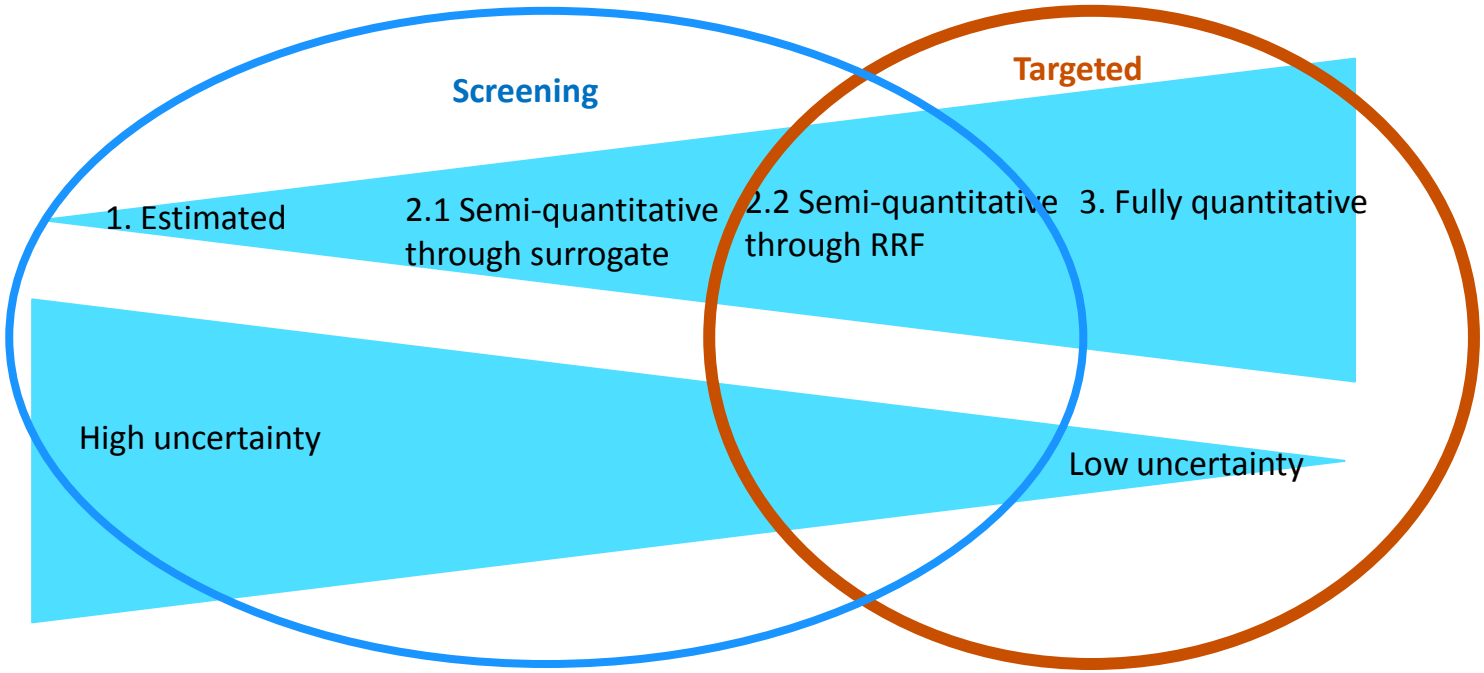
ISO 10993-18: three levels of quantification



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ISO 10993-18:

- **Answer for 0.1 % w/w?**

- **Tool for risk assessment**

→ a screening versus a targeted approach: three levels of quantification

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Test for all substances??

Polycarbonate – Bisphenol A (BPA)

PVC - Phthtalates

Supplier: intentionally added

Only those substances that can be present > 0.1% w/w

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> 0.1 % weight/weight: HOW?

ISO 10993-18?

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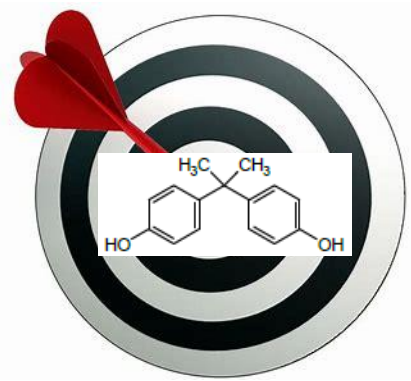
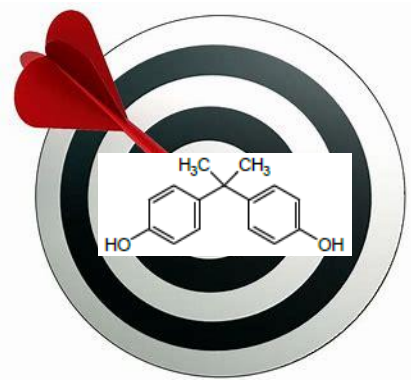
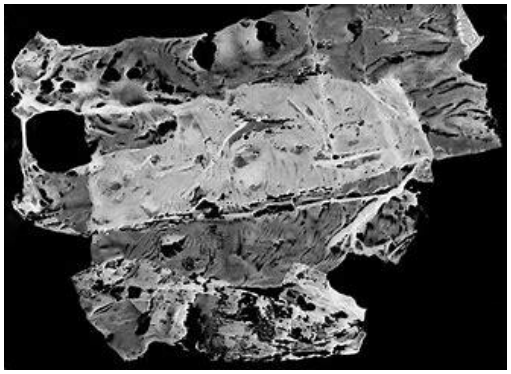


- Target the substance that is expected : BPA



- Target the substance that is expected : BPA
- Knowledge on total amount BPA needed

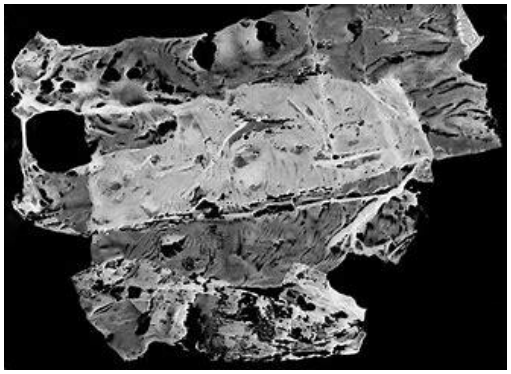


- Extract the **total amount BPA**: “digest the material”:
  Use solvent that best solubilizes the target substance

3.12
digestion
process of completely solubilizing a medical device, one or more of its components or one or more of its materials of construction by breaking it down into its fundamental structural units, including its elemental constituents or monomeric units

3.24
material composition
listing of the constituents that are contained in a material (qualitative) and the amount of each substance in the material (quantitative)

Note 1 to entry: A material's composition establishes the hypothetical situation in which the total amount of all substances present in a medical device are released during clinical use. These amounts can be derived directly from known composition; experimentally, they can be derived from digestion, dissolution, and, in many cases, exhaustive extraction studies.



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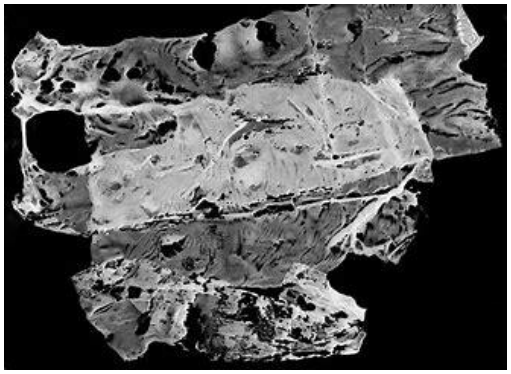
USP 661.1

ISO 10993-18 in the MDR



- Extract the **total amount BPA**: “digest the material”:
  Use solvent that best solubilizes the target substance

- Use 1 analytical technique (GC/MS)

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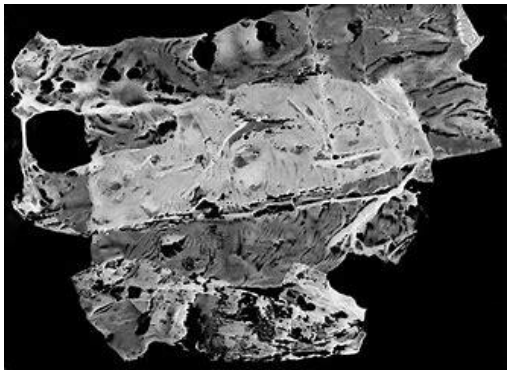
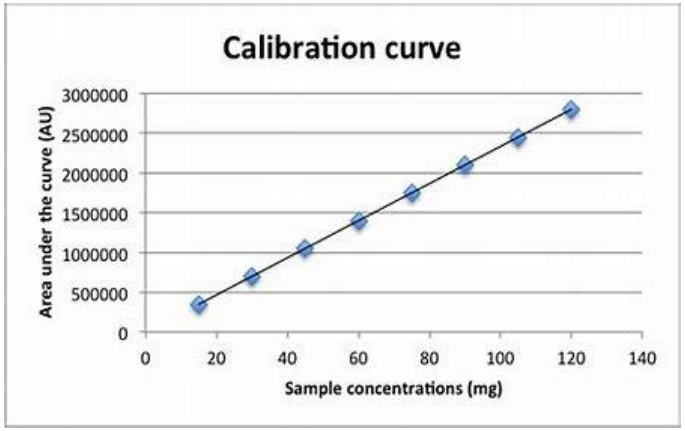


- Extract the **total amount BPA**: “digest the material”: Use solvent that best solubilizes the target substance
- Use 1 analytical technique (GC/MS)
- Include calibration curve: quantitative result



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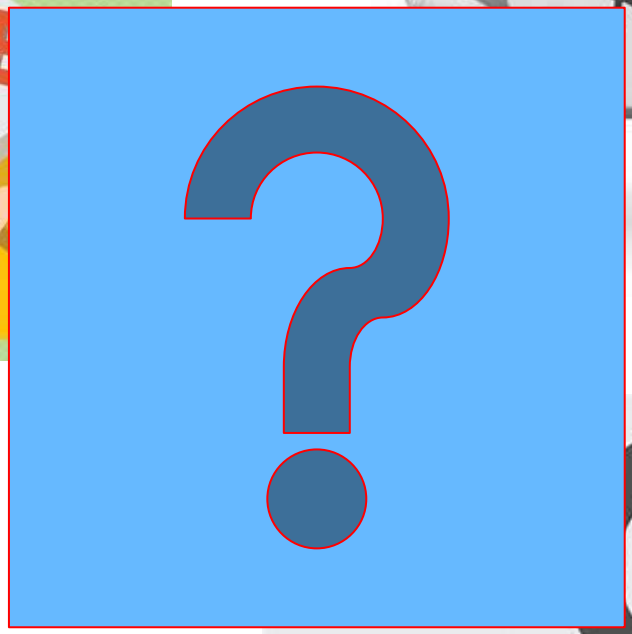
ISO 10993-18:

➡ **Answer for 0.1 % w/w**

(= Material characterization)

ISO 10993-18 in the MDR



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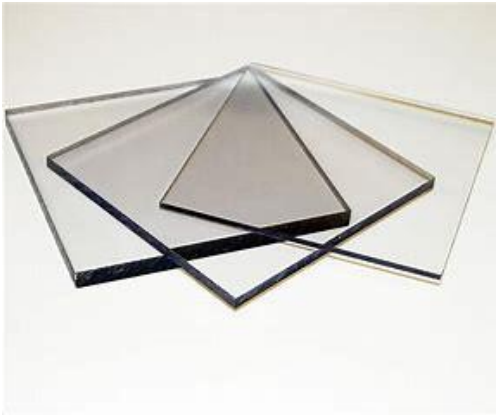
Screen for all possible target substances



Keep device/material/part intact during extraction:

- Extraction conditions: ISO 10993-18

- CMR/ED substance: different sizes, different nature

➡ Different extraction solvents, different analytical techniques

- CMR/ED not known: no calibration curve of target substance

➡ Screening: estimated/semi-quantitative concentration

ISO 10993-18 in the MDR

no.	ID Level	ORGANIC COMPOUND	CAS-No. / ToxID / Spectrum	t_R (min)	Result (µg/g)
1	IC	Cyclohexylamine	108-91-8	6.69	56
2	IC	2-Ethyl-1-hexanol	104-76-7	10.37	350
3	IC	Thioisocyanatocyclohexane	1122-82-3	14.44	40
4	TIC	Amide	-	19.22	88
5	IC	Palmitic acid	57-10-3	25.13	120
6	IC	1,3-Dicyclohexylurea	2387-23-7	26.40	190
7	MPC	2-Ethylhexyl methyl isophthalate	ToxID 664	27.11	74
8	IC	Stearic acid	57-11-4	27.47	110
9	**TIC**	**2-ethylhexyl propyl (iso or tere-) phthalate**	-	**28.33**	**1400**
10	IC	*N,N*-Dimethylhexadecanamide	3886-91-7	28.49	79
11	IC	Acetyl tributylcitrate	77-90-7	28.60	350
12	U	Masses: 141, 200, 56, 60, 154, 98, 281	Figure 8	28.93	37
13	IC	Bis(2-ethylhexyl) adipate	103-23-1	29.99	130
14	IC	Antioxidant 2246	119-47-1	30.30	180
15	IC	*N,N*-Dimethyloctadecanamide	3886-90-6	30.62	87
16	U/TIC	Sum of Masses: 141, 228, 56, 154 & Compound related to Antioxidant 2246	Figure 8 / -	31.08	200
17	MPC	3,5-Bis[4-(1,1-dimethylethyl)phenyl]-2,3-dihydro-1*H*-indene-1-one	357941-12-9	31.37	52
18	IC	DEHP	117-81-7	31.49	525
19	IC	Ziram	137-30-4	32.59	95
20	IC	Bis(2-ethylhexyl) isophthalate	137-89-3	32.87	220
21	U	Masses: 141, 154, 256, 56	Figure 8	33.08	170
22	**IC**	**Bis(2-ethylhexyl) terephthalate**	**6422-86-2**	**33.52**	**60000***
23	U	Masses: 141, 154, 284, 56	Figure 8	34.94	270
24	U	Masses: 173, 381, 366, 239, 155, 185	Figure 8	37.04	46

IC: Identified Compound; MPC: Most Probable Compound; TIC: Tentatively Identified Compound;
U: Unidentified;
&: co-eluting compounds;
*: 100x diluted to fall into MS detector range;
Reporting limit: 35 µg/g.

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ISO 10993-18 in the MDR

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U: Unidentified;
&: co-eluting compounds;
*: 100x diluted to fall into MS detector range;
Reporting limit: 35 µg/g.

CMR/ED substance detected?

Lists in MDR (> 2000 compounds)

Reduced lists
(MedTech Europe, proprietary, < 200)

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ISO 10993-18 in the MDR

no.	ID Level	ORGANIC COMPOUND	CAS-No. / ToxID / Spectrum	t_R (min)	Result (µg/g)
1	IC	Cyclohexylamine	108-91-8	6.69	56
2	IC	2-Ethyl-1-hexanol	104-76-7	10.37	350
3	IC	Thioisocyanatocyclohexane	1122-82-3	14.44	40
4	TIC	Amide	-	19.22	88
5	IC	Palmitic acid	57-10-3	25.13	120
6	IC	1,3-Dicyclohexylurea	2387-23-7	26.40	190
7	MPC	2-Ethylhexyl methyl isophthalate	ToxID 664	27.11	74
8	IC	Stearic acid	57-11-4	27.47	110
9	**TIC**	**2-ethylhexyl propyl (iso or tere-) phthalate**	-	**28.33**	**1400**
10	IC	*N,N*-Dimethylhexadecanamide	3886-91-7	28.49	79
11	IC	Acetyl tributylcitrate	77-90-7	28.60	350
12	U	Masses: 141, 200, 56, 60, 154, 98, 281	Figure 8	28.93	37
13	IC	Bis(2-ethylhexyl) adipate	103-23-1	29.99	130
14	IC	Antioxidant 2246	119-47-1	30.30	180
15	IC	*N,N*-Dimethyloctadecanamide	3886-90-6	30.62	87
16	U/TIC	Sum of Masses: 141, 228, 56, 154 & Compound related to Antioxidant 2246	Figure 8 / -	31.08	200
17	MPC	3,5-Bis[4-(1,1-dimethylethyl)phenyl]-2,3-dihydro-1*H*-indene-1-one	357941-12-9	31.37	52
18	IC	DEHP	117-81-7	31.49	525
19	IC	Ziram	137-30-4	32.59	95
20	IC	Bis(2-ethylhexyl) isophthalate	137-89-3	32.87	220
21	U	Masses: 141, 154, 256, 56	Figure 8	33.08	170
22	**IC**	**Bis(2-ethylhexyl) terephthalate**	**6422-86-2**	**33.52**	**60000***
23	U	Masses: 141, 154, 284, 56	Figure 8	34.94	270
24	U	Masses: 173, 381, 366, 239, 155, 185	Figure 8	37.04	46

IC: Identified Compound; MPC: Most Probable Compound; TIC: Tentatively Identified Compound;
U: Unidentified;
&: co-eluting compounds;
*: 100x diluted to fall into MS detector range;
Reporting limit: 35 µg/g.

CMR/ED substance detected?

DEHP: CMR 1B (toxic for reproduction), ED properties

Ziram: potential ED (under evaluation)

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Reporting limit: 35 µg/g.

No calibration curve!

ESTIMATED (semi-quantitative) concentration

→ close to 0.1 w/w %? (1000 µg/g)

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ISO 10993-18 in the MDR

- No calibration curve!
- ESTIMATED (semi-quantitative) concentration
- close to 0.1 w/w %? (1000 µg/g)

Include second step

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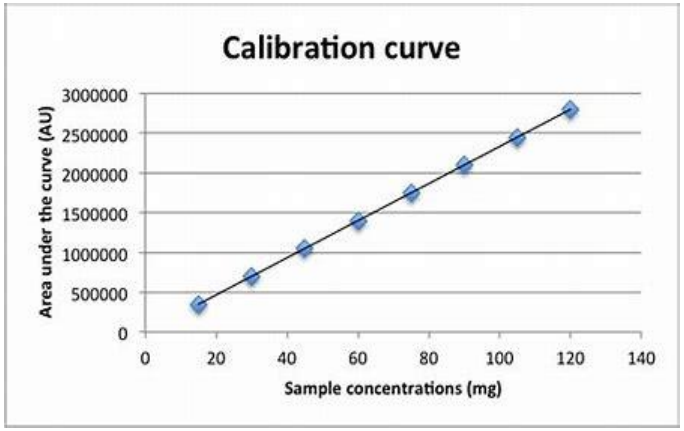
- No calibration curve!
- ESTIMATED (semi-quantitative) concentration
- close to 0.1 w/w %? (1000 µg/g)

Include second step

- Run same extract with calibration curve for detected CMR/ED (DEHP, Ziram)



Quantitative result!!!

ISO 10993-18 in the MDR

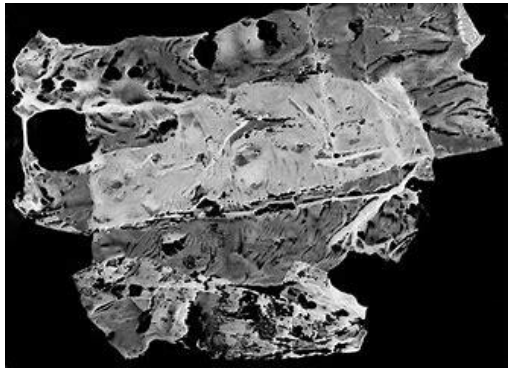
- calibration curve
- QUANTITATIVE concentration
- close to 0.1 w/w %? (1000 µg/g) → No

- calibration curve
- QUANTITATIVE concentration
- close to 0.1 w/w %? (1000 µg/g) → No

- calibration curve
- QUANTITATIVE concentration
- close to 0.1 w/w %? (1000 µg/g)

No → ISO 10993-17

Yes



- Extract the total amount: “digest the material”: Use solvent that best solubilizes the target substance
- Use 1 analytical technique
- Include calibration curve: quantitative result

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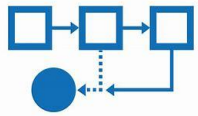
Using chemical characterization for CMR/ED substances in lack of information?

- Information on all substances that can be released from the device:
  Estimate overall risk to the patient (not only CMR/ED)
  Evaluation results: ISO 10993-17

- Justification in case conc CMR/ED substances > 0.1 % (w/w)

Conclusion: proposed workflow



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Conclusion: proposed workflow

STEP 1: ASK INFORMATION FROM SUPPLIERS
Information on nature of CMR/ED present (e.g. contains BPA)

YES

Information on concentration present
(e.g. conc. CMR/ED = 0.5% w/w)?

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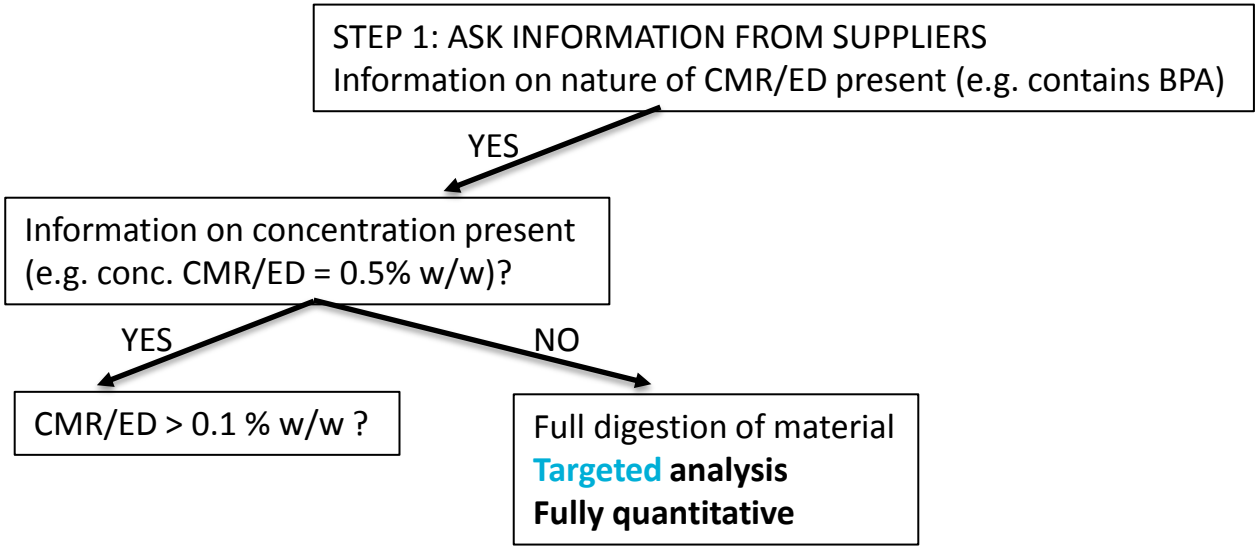
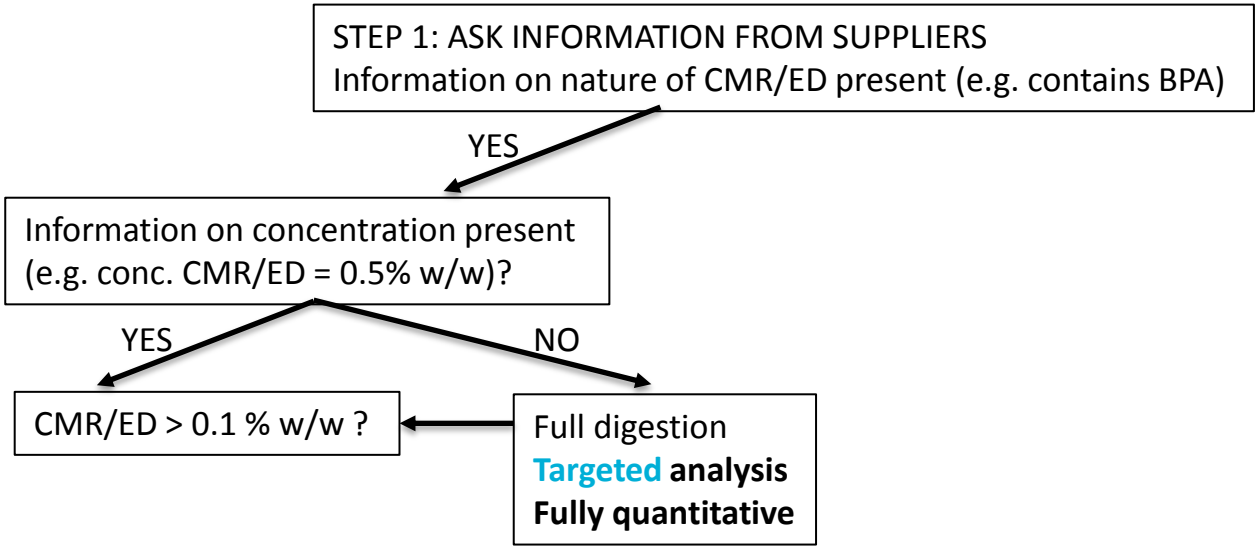
Conclusion: proposed workflow



Conclusion: proposed workflow



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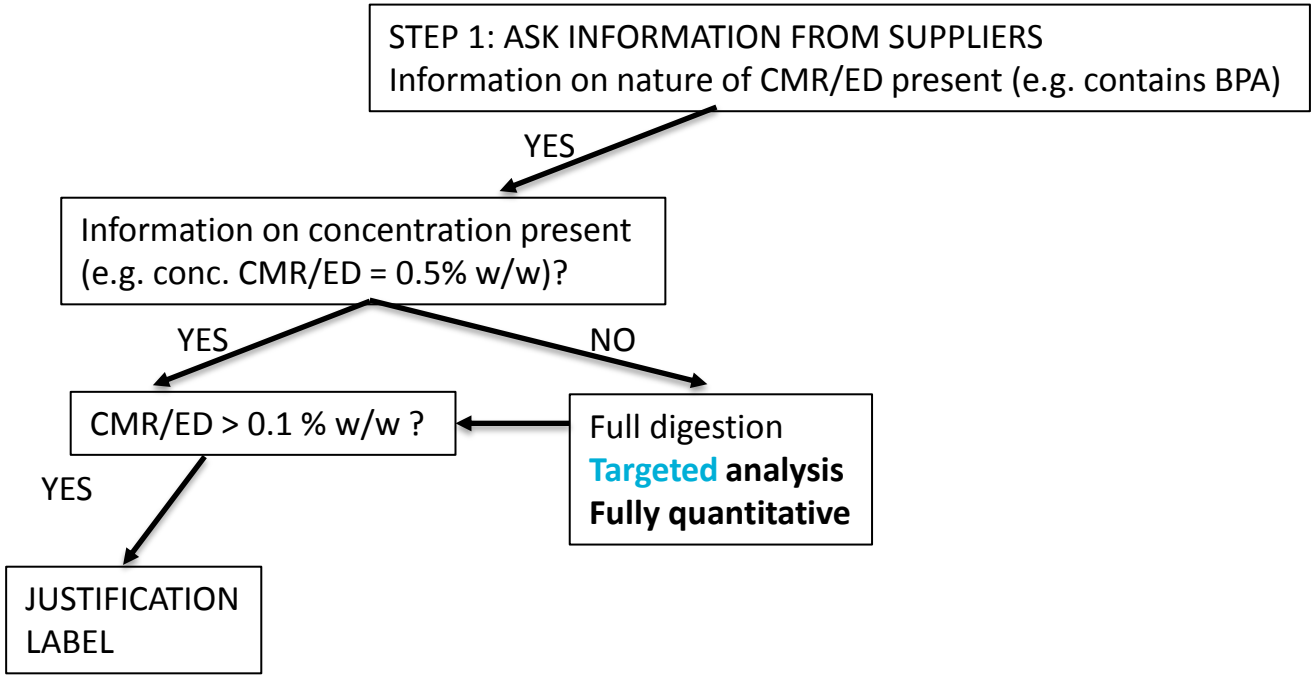
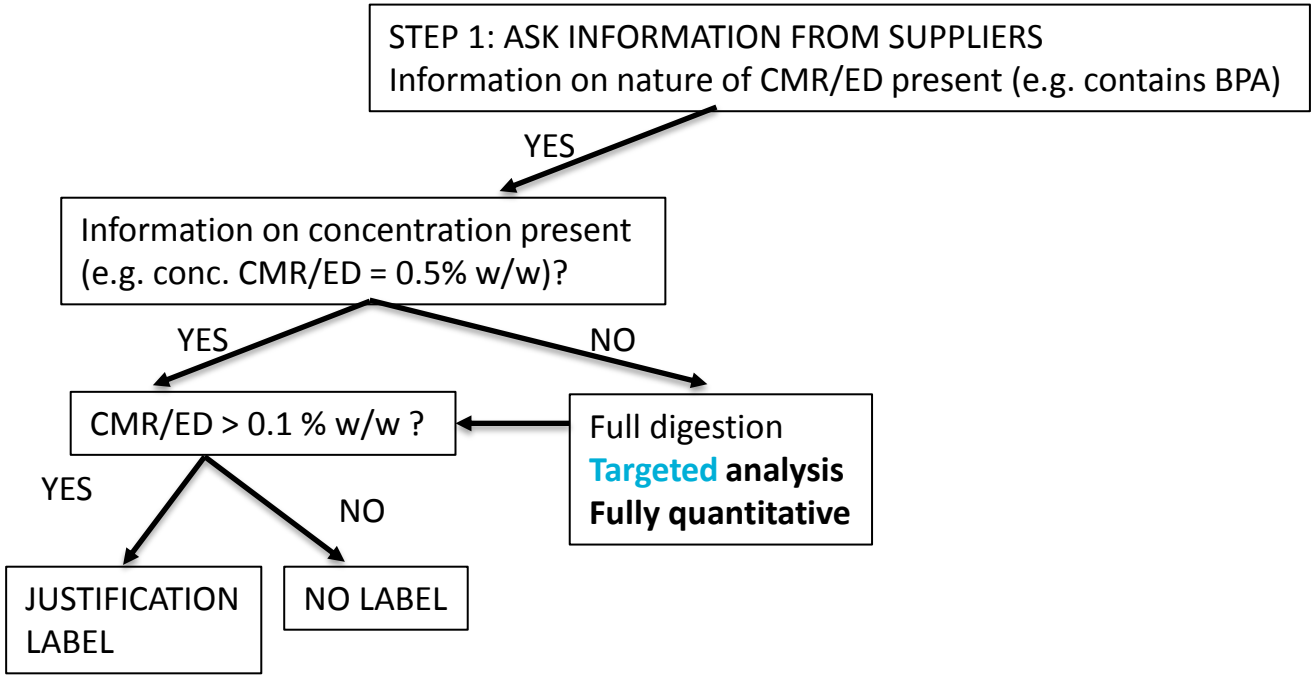
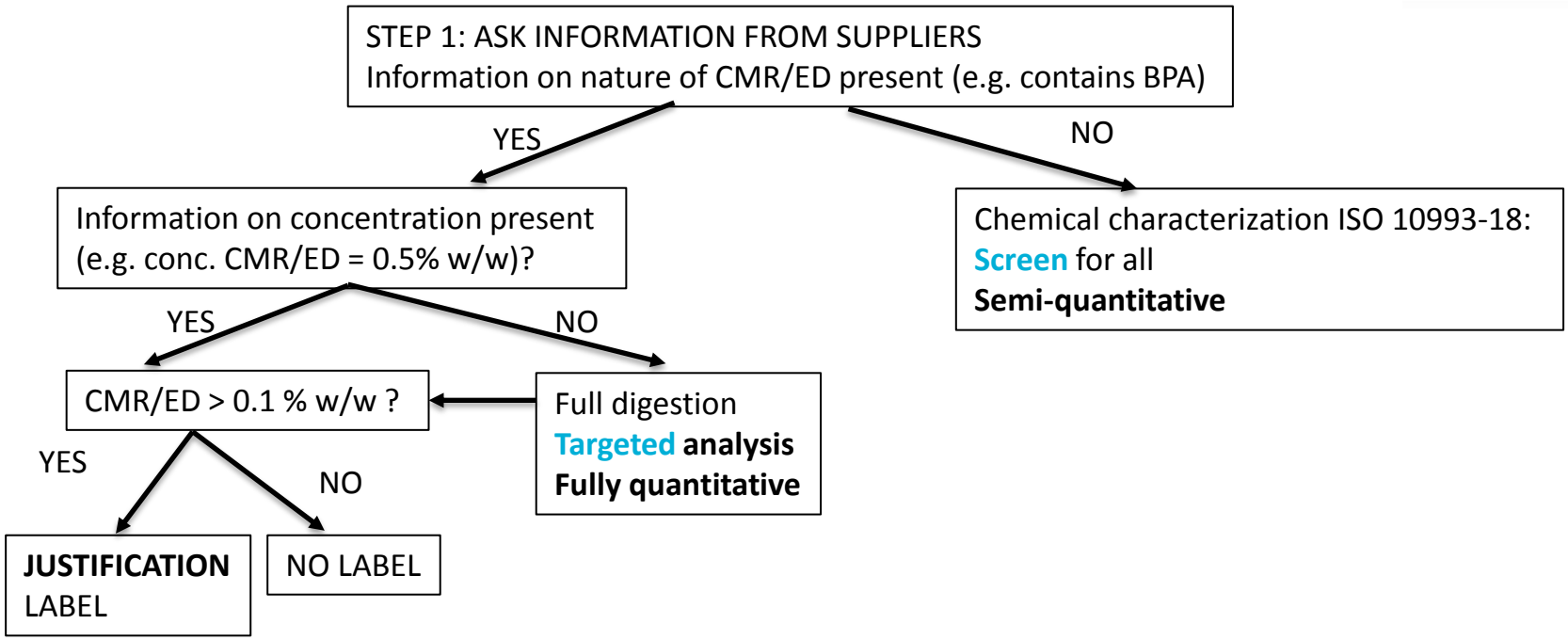
Conclusion: proposed workflow



Conclusion: proposed workflow



Conclusion: proposed workflow



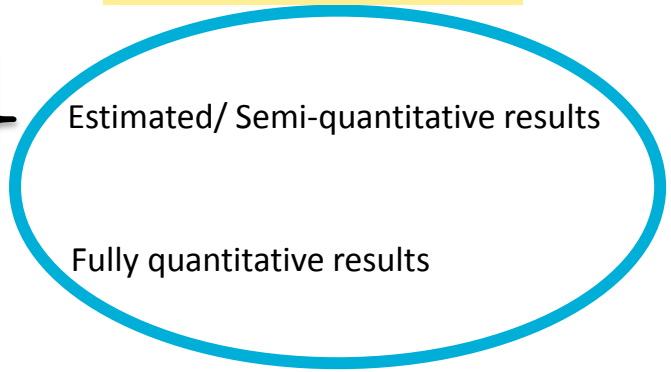
Set-up chemical characterization for safety risk assessment

1. Make extract
   72h -50°C, shaking incubation
   polar & non-polar solvent

2. Analytical techniques:
   VOC: HS-GC/MS screening
   SVOC: GC/MS screening
   NVOC: LC/MS screening

   Elements: ICP/OES

STEP 1. Gather all results



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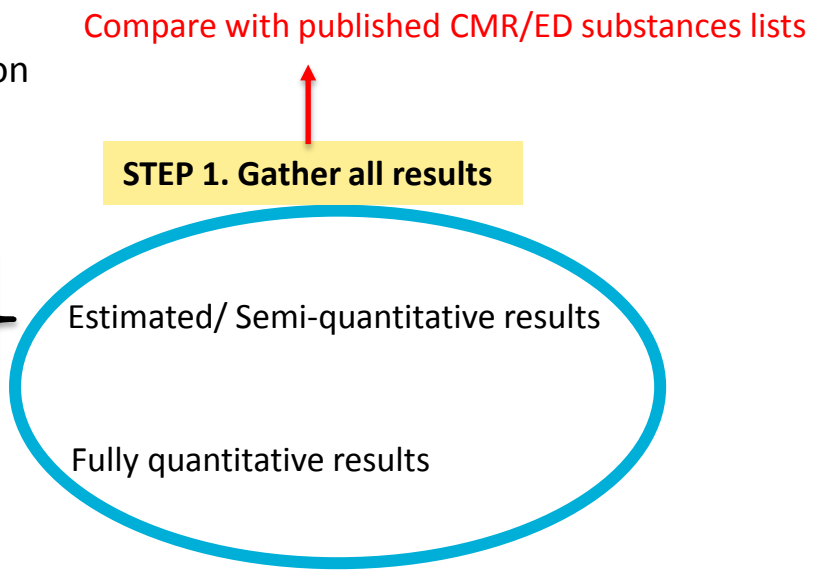

Conclusion: proposed workflow

Set-up chemical characterization for safety risk assessment

STEP 2. CALIBRATION CURVE:
more QUANTITATIVE
results for CMR/ED

Compare with published CMR/ED substances lists

STEP 1. Gather all results

Estimated/ Semi-quantitative results

Fully quantitative results

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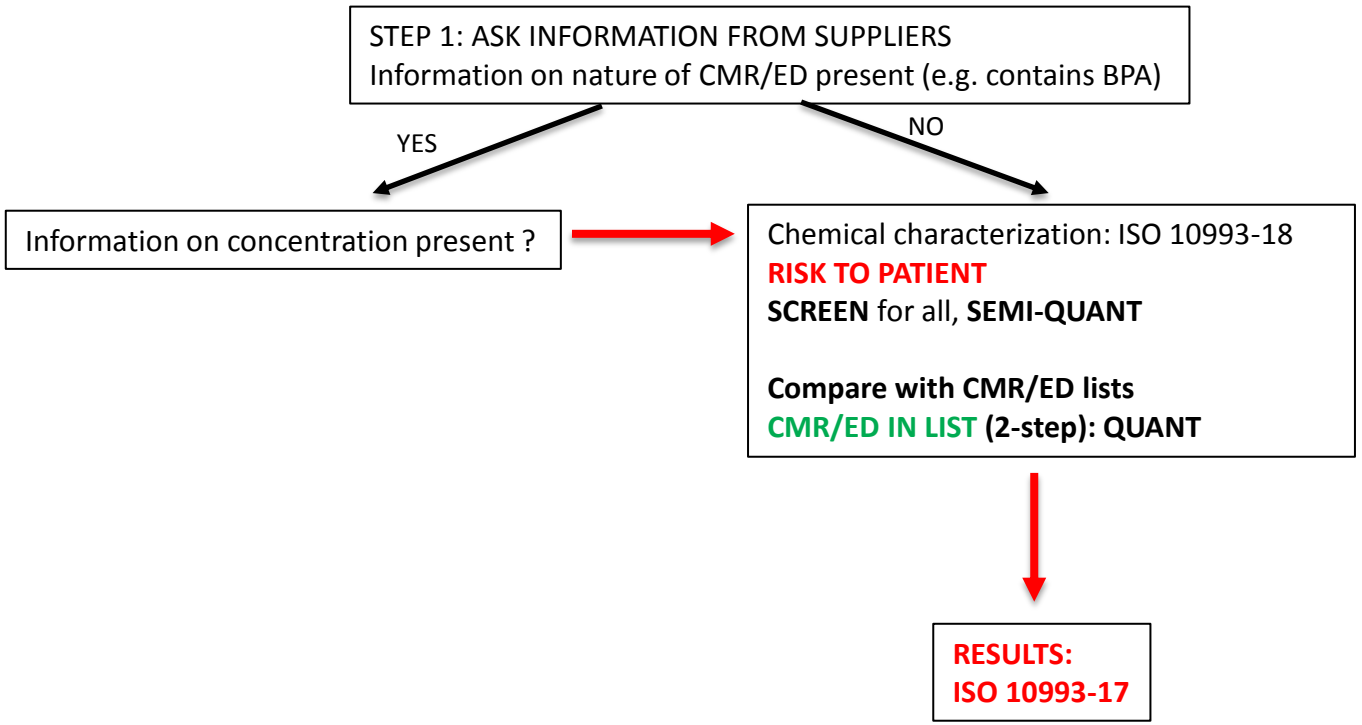
Conclusion: proposed workflow



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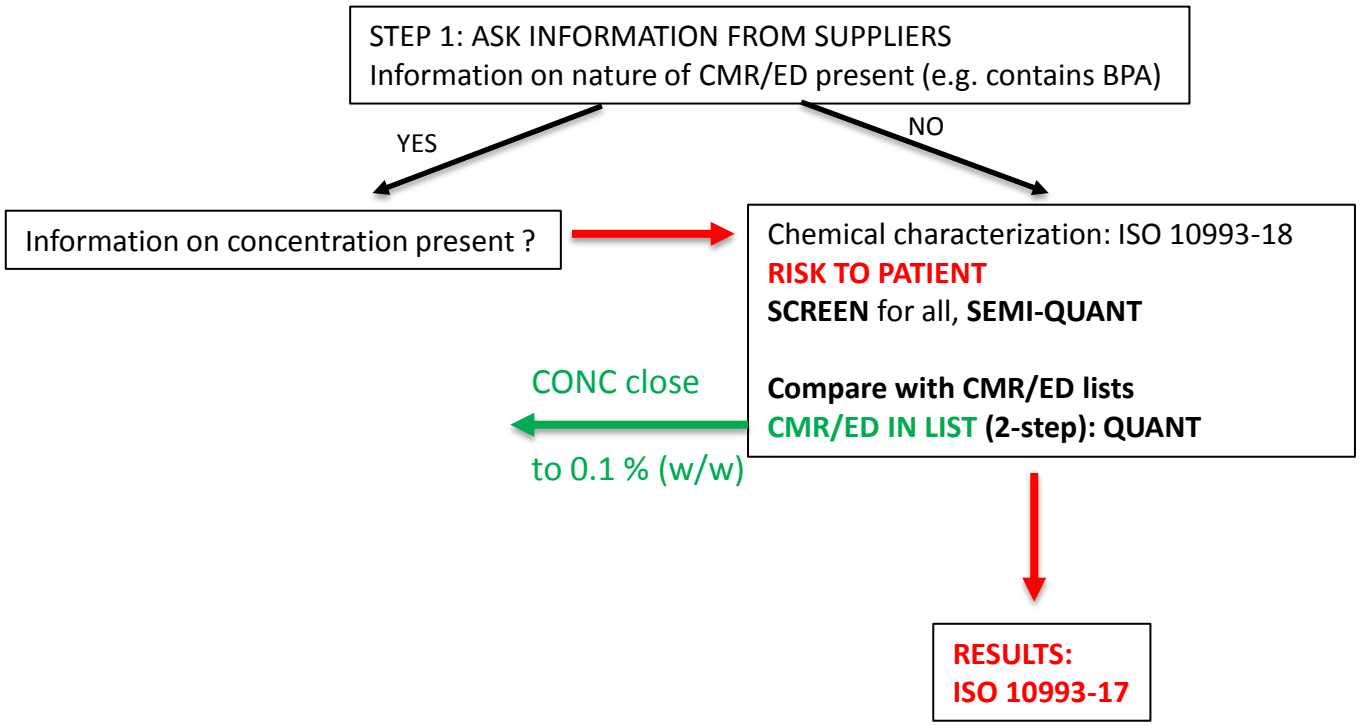
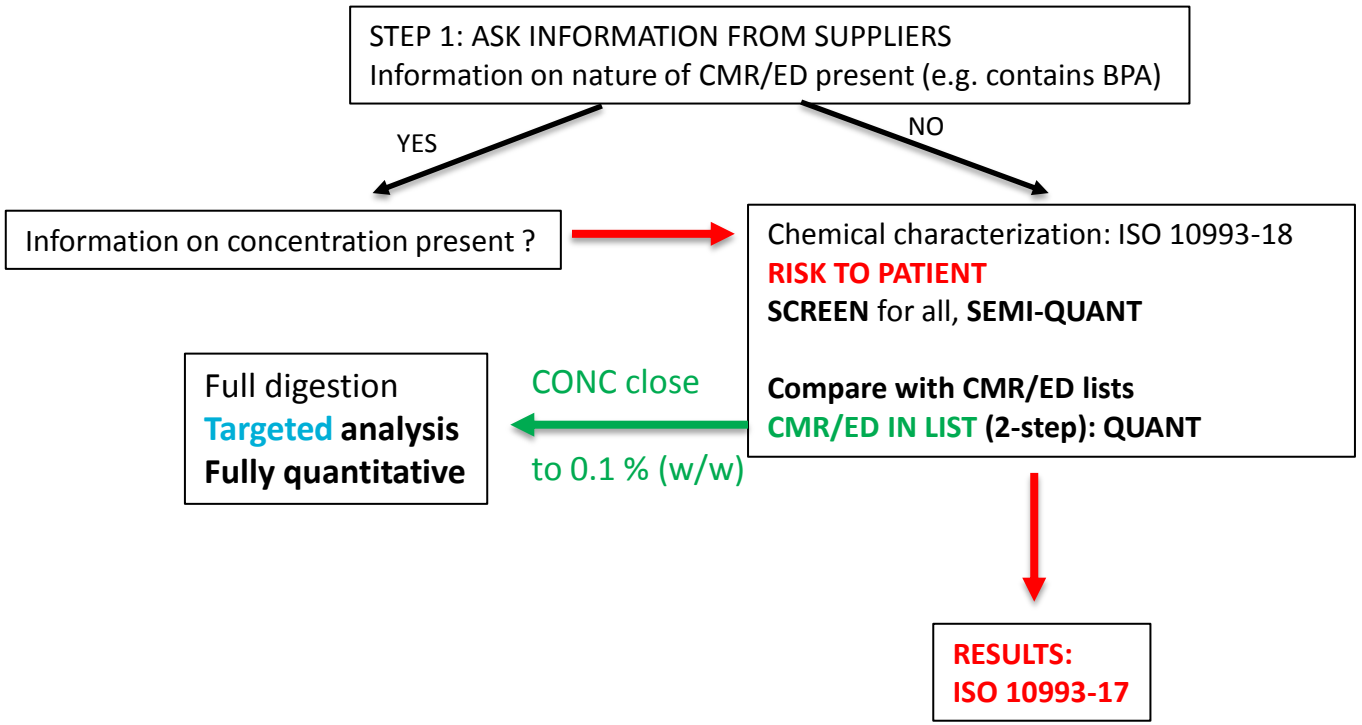
Conclusion: proposed workflow



Conclusion: proposed workflow



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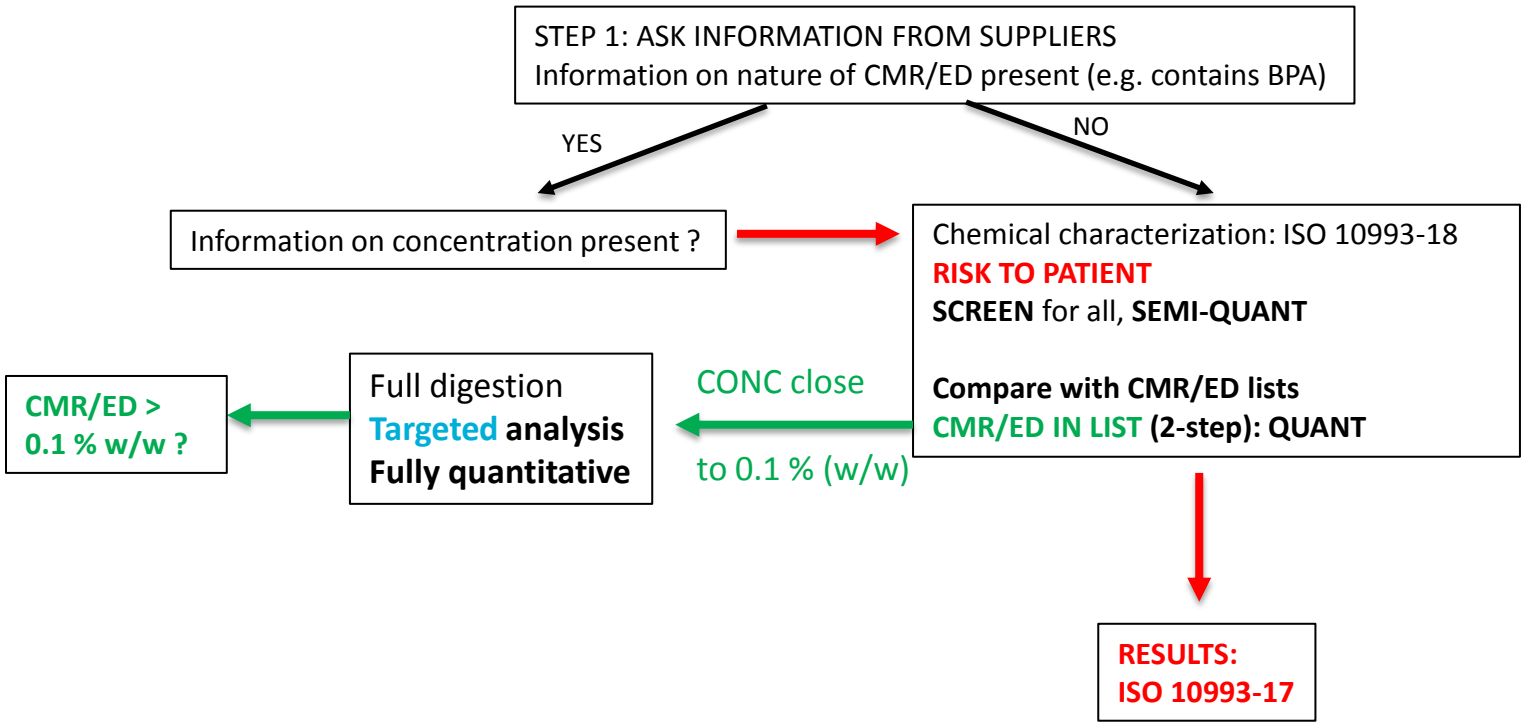
Conclusion: proposed workflow



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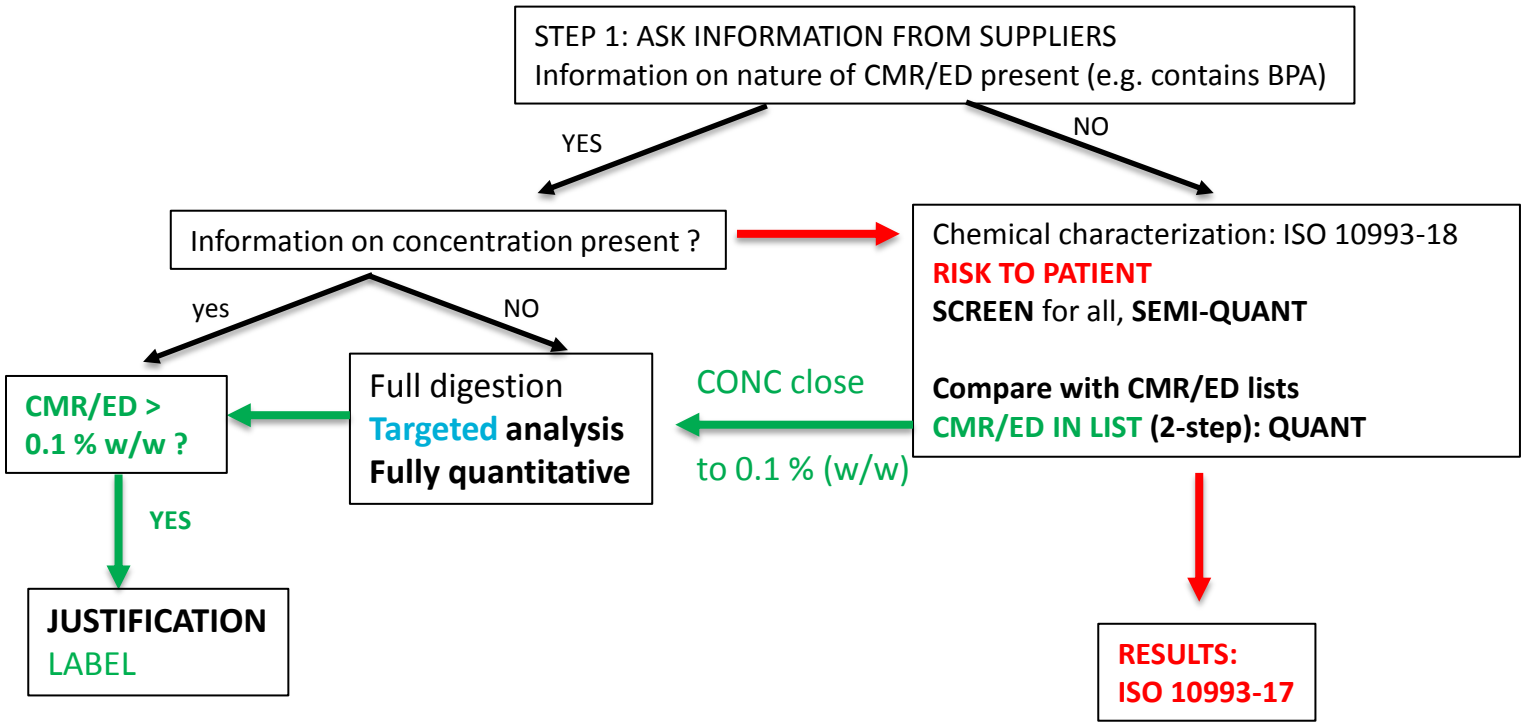

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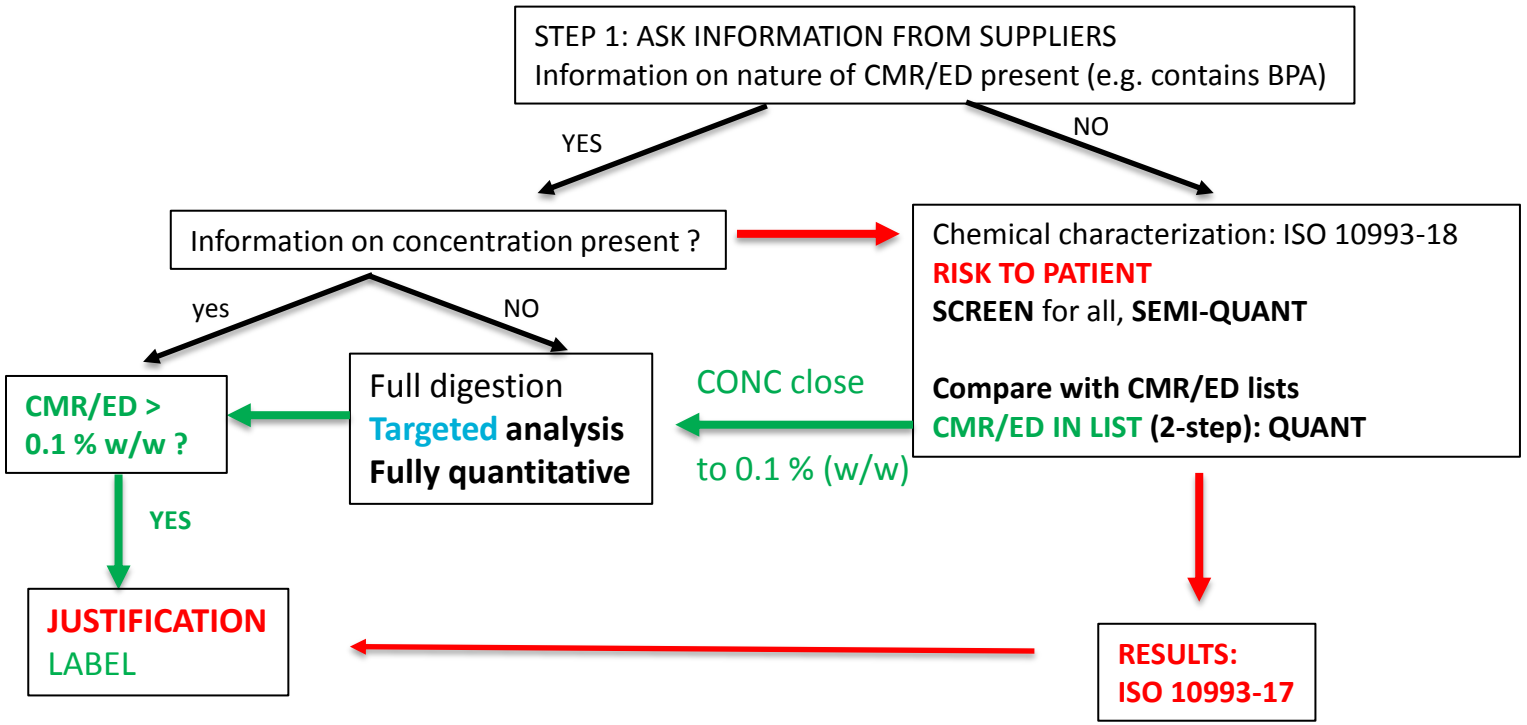

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2020: The Year Of Change for the Medical Device Industry

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