Sample Preparation Expectations

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Biological Tests Sample Preparation

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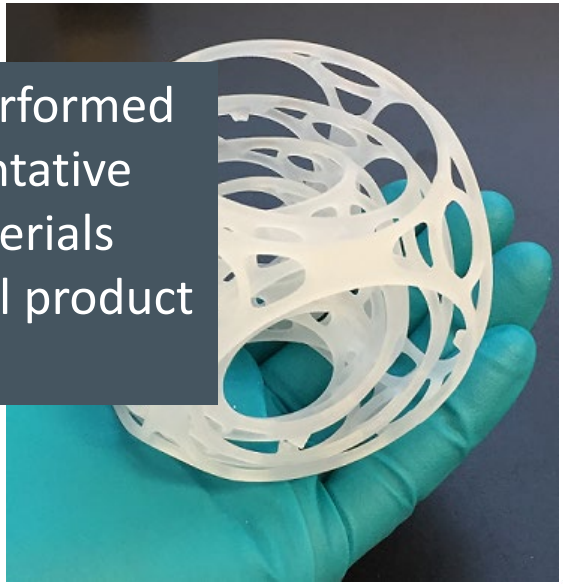
Biological Tests

Test Sample Selection

Raw Material

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).”



Finished Device

Biological Evaluation Plan (BEP)

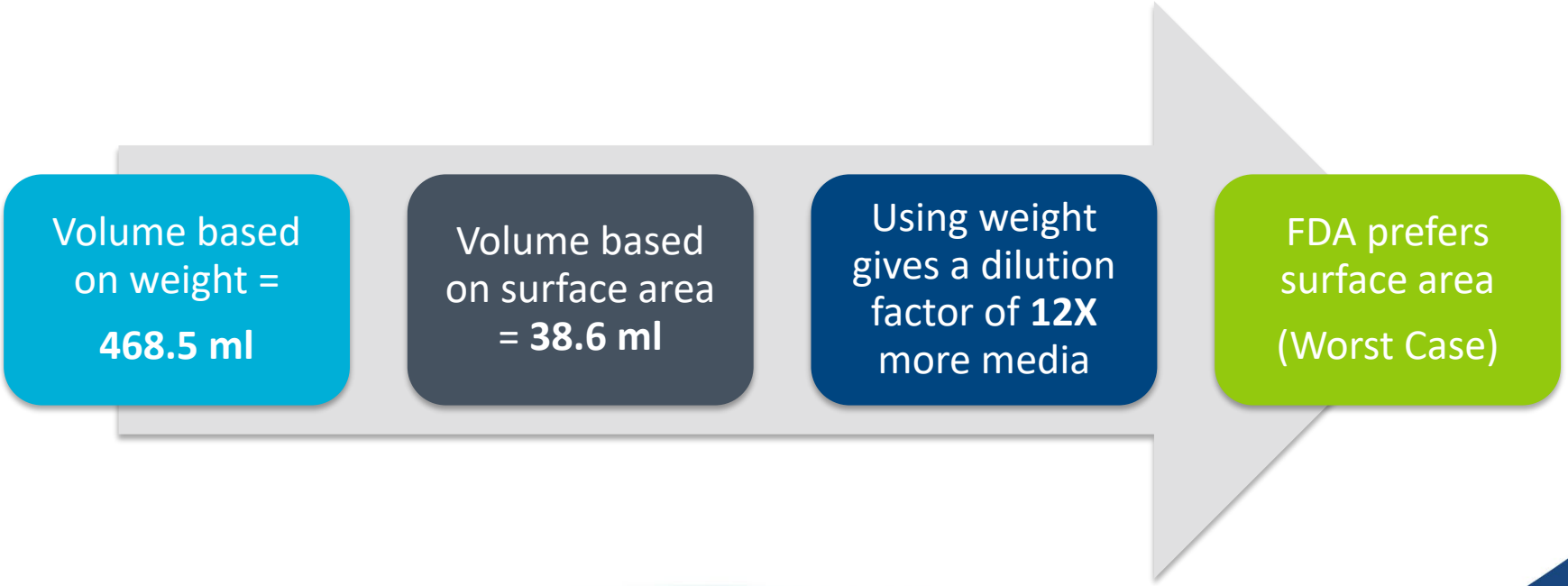
Extraction Ratio

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

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

Biological Evaluation Plan (BEP)

Test Sample Preparation



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Biological Evaluation Plan (BEP)

Test Sample Preparation

- Coupons
- Representative samples
- Multiple components

Extraction Ratios

Table 1 — Standard surface areas and extract liquid volumes

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

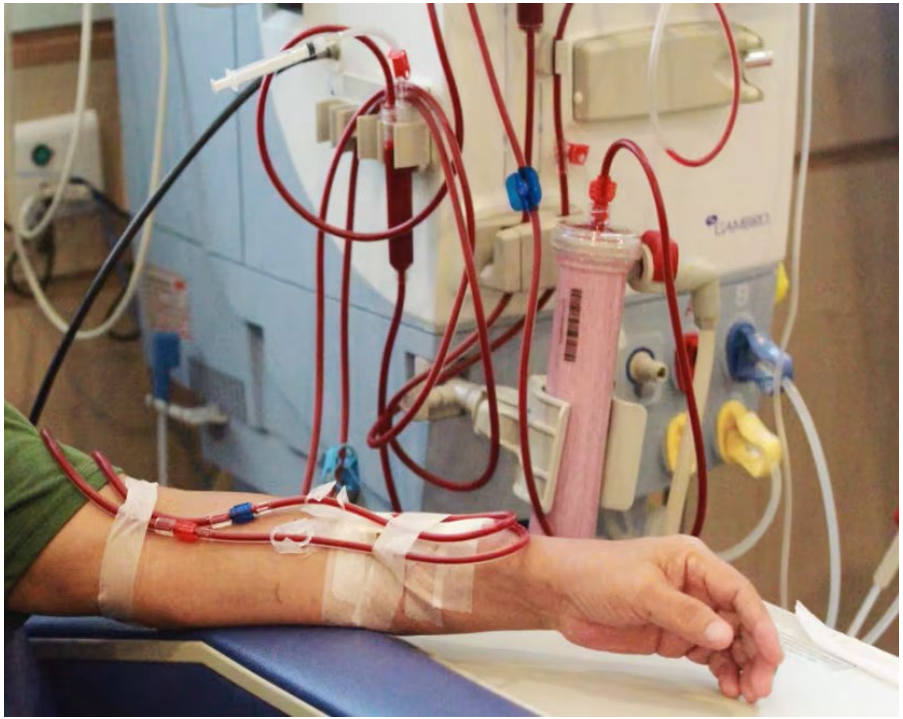
[a] If the medical device includes multiple tissue contacting components with different thicknesses, the extraction ratio should be justified. One way to do this is to base the ratio on the thinnest material layer of that component.

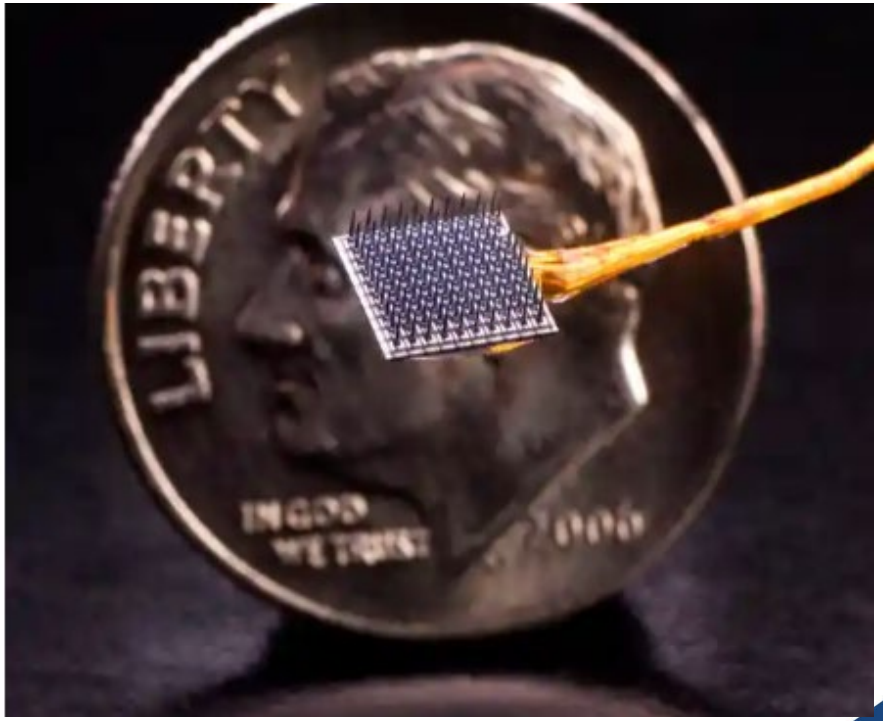
NOTE While there are no standardized methods available at present for testing solvent absorbing polymer materials (e.g. absorbents and hydrocolloids), a suggested protocol is as follows:

— determine the volume of extraction vehicle that each 0,1 g or 1,0 cm^2 of material absorbs;

— then, in performing the material extraction, add this additional volume to each 0,1 g or 1,0 cm^2 in an extraction mixture.

Possible Concern





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 (typically)

How do I choose?

Does it matter?

Biological Evaluation Plan (BEP)

Extraction Vehicle	Per ISO 10993-12 for biocompatibility tests
Polar	water, physiological saline, culture media without serum;
Non-polar	freshly refined vegetable oil (e.g. cottonseed or sesame oil) of the quality defined in various pharmacopoeias;
Additional options	ethanol/water, ethanol/saline, polyethylene glycol 400 (diluted to a physiological osmotic pressure), dimethyl-sulfoxide and culture media with serum.

Extractable and Leachable Tests Sample Preparation

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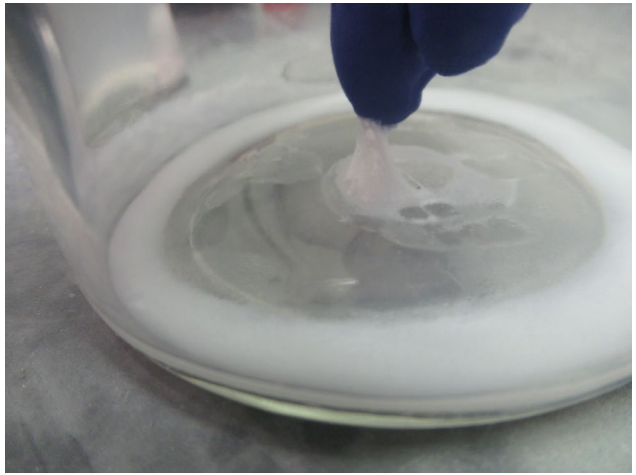
- First step should be solvent compatibility screen



Exhaustive Extractions

Test Method Summary: Gravimetric NVR

Gravimetric NVR

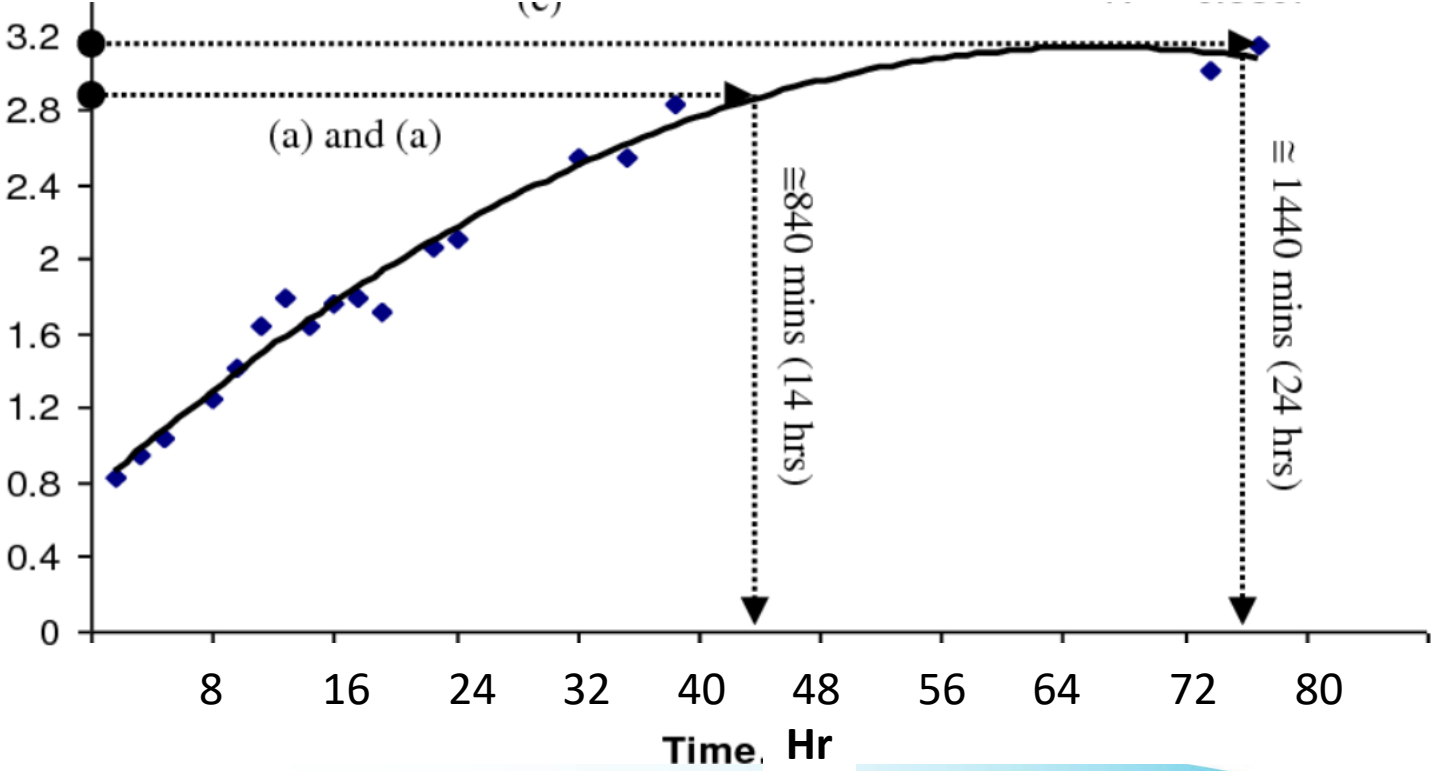
- Measures contaminants by weight after solvent evaporates away
- Can be used with polar and non-polar solvent, non-specific
- Recovery efficiencies ensure the extraction parameters are appropriate for device material and residue
- ASTM F2459: *Standard Test Method for Extracting Residue from Metallic Medical Components and Quantifying via Gravimetric Analysis*

Exhaustive Extraction

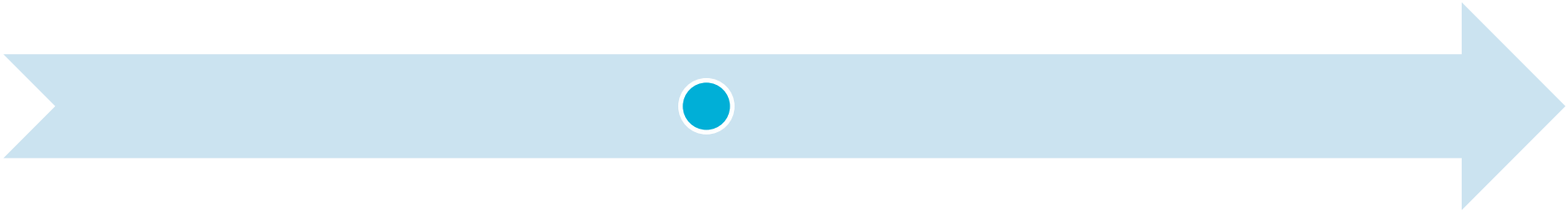
Keep going until the amount of measurable compounds in a subsequent extraction is less than 10 % of that detected in the first extraction, or until there is no analytically significant increase in the cumulative residue levels detected.

Extractions should be performed in the same method (time, temperature, and solvents as the testing

Exhaustive Extraction



Differences Between Biologic and E&L



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BIOLOGIC SAMPLE PREP

- Standard temperature and solvents
  - 50° for 72 hrs (37 for cyto)
  - Saline, vegetable oil, cell culture media
- Dose to animal or cells are surface area dependent
- Results are pass or fail and very subjective

E&L SAMPLE PREP

- Standard temperatures and solvents
  - 50° for 72 hrs
  - Water, alcohol, Hexane, combination
- Extracted amount is determined by exhaustive extraction
- Results are specific to population and intended use

Whats Next?

Some concern that E&L extractions are too worse case and inhibitive

Is exhaustive realistic to clinical exposure?

Is surface area relevant to dose?

Thank You

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