Validation of Sterilizing Filtration Operations Using Quality by Design Principles

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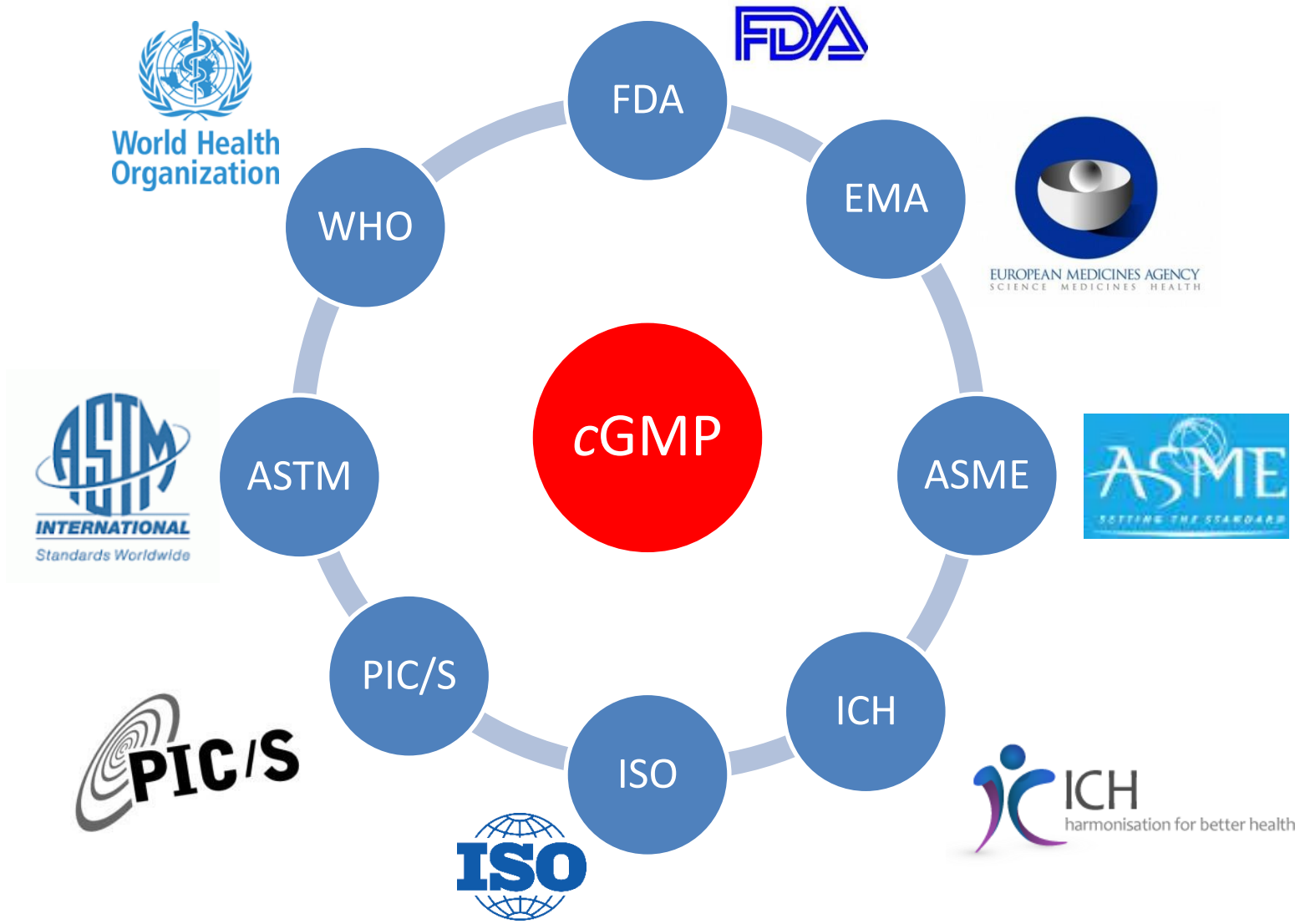
Validation Overview

1. Regulatory and Reference Guidelines
2. General Considerations
3. Deliverables
4. When to Consider Validation

1. Regulatory And Reference Guidelines



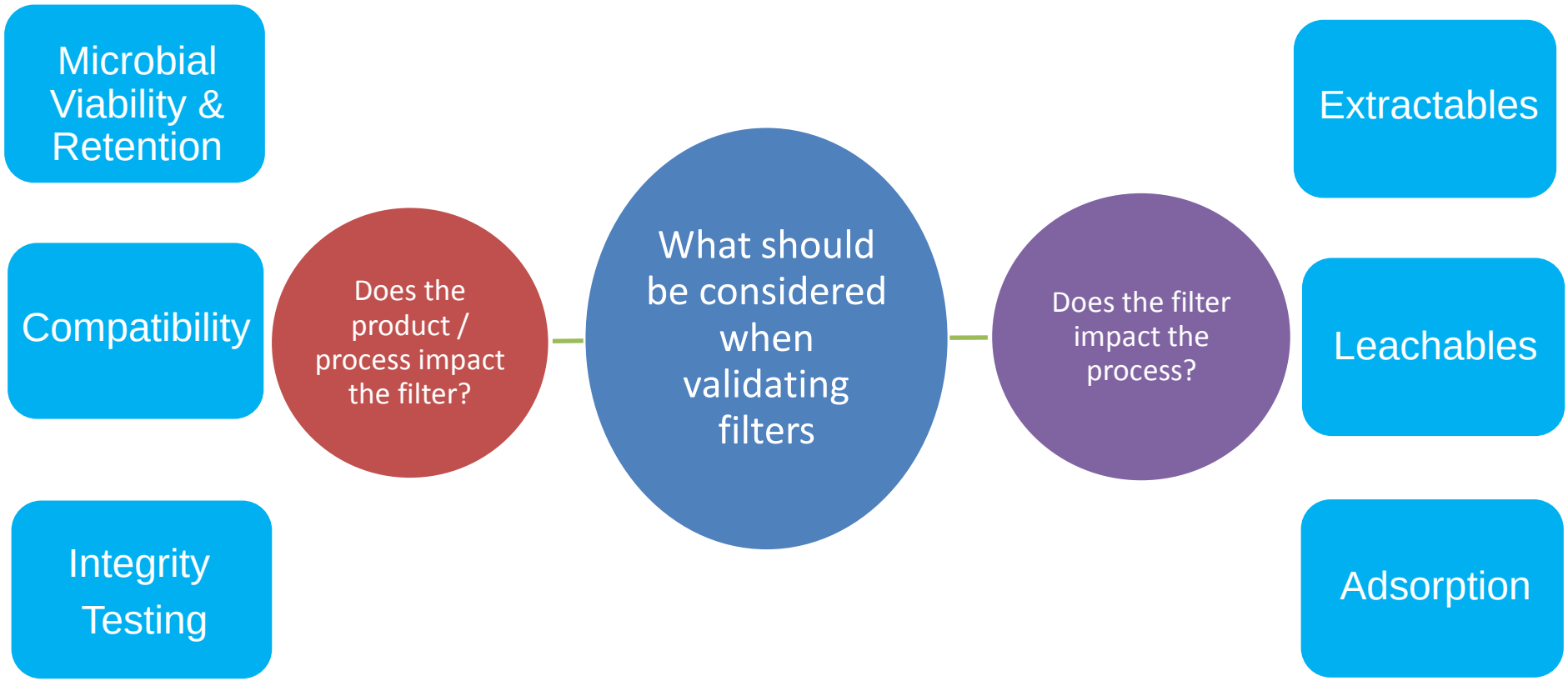
1. Regulatory Perspective

FDA Definitions[1]

- Sterilizing Filter
  - "A filter that, when appropriately validated, will remove all microorganisms from a fluid stream, producing a sterile effluent"
- Validation
  - "Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes"
- Validation studies assure product quality and patient safety requirements are satisfied under worst case conditions

1: FDA Guidance for Industry –Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice September, 2004, p 58

2. General Considerations: Process Specific Validation



2. General Considerations: Supplier's Data

What are the validation needs for the specific application?

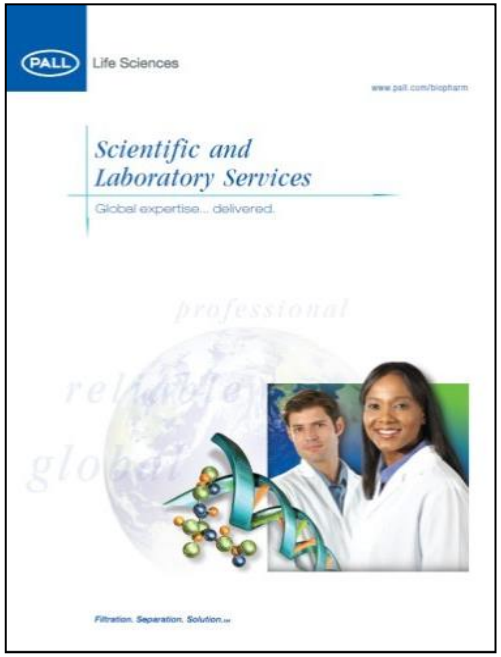
Is the supplier data sufficient, high-quality and brackets process conditions?

Data can be used for process validation

User-specific process validation must be performed

2. General Considerations: Validation Services

- Considers:
  - Critical product attributes
  - Process parameters
  - Scientific rationale
  - Worst-case conditions
  - Use of actual products wherever possible



- Complies with:
  - Regulatory expectations
  - Standard test methods (e.g. ASTM F838)
  - Guidelines of Parenteral Drug Association Technical Report 26 and 66

3. Deliverables: Description of Tests

- **Viability**
  - Establishes fluid and/or process conditions as bactericidal, moderately bactericidal or non-bactericidal (this must be known before challenge)
- **Bacterial Challenge**
  - Qualifies that filter produces sterile filtrate (using 3 membrane lots – at least one filter lot at or near the minimum filter manufacturing specification - Concentration > 1 x 10^7 CFU/cm^2 with *B. diminuta*)
- **Test Parameters Determination***
  - Product Wet Integrity Test establishes filter integrity test values for process filter wet with process fluid

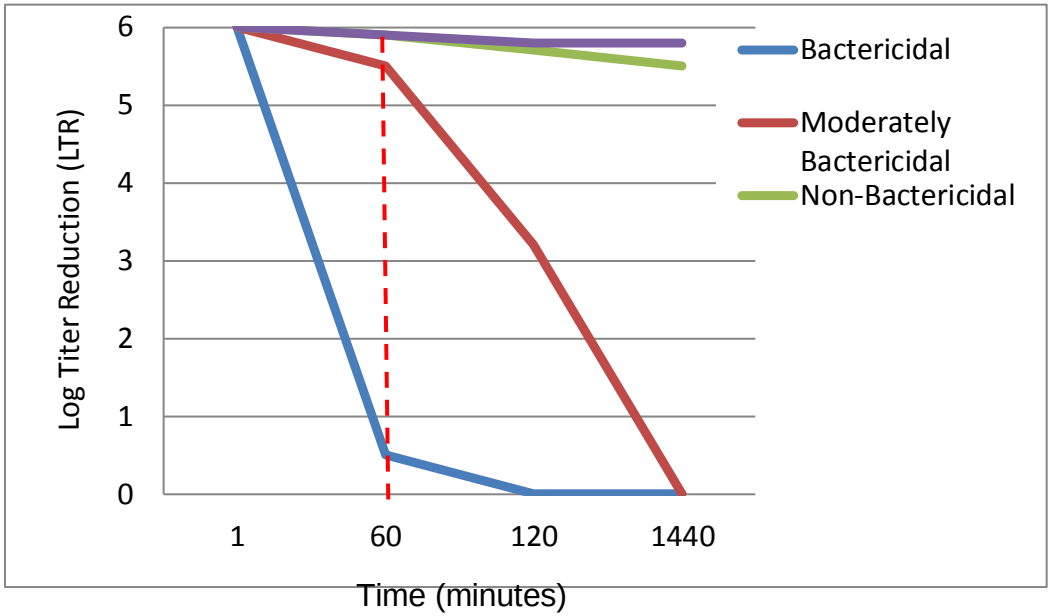
*optional not considered a regulatory requirement for submission

- **Compatibility**
  - Evaluates filter integrity before and after exposure to "worst-case" conditions
- **Adsorption**
  - Quantifies components adsorbed onto filter membrane – helps with filter selection – minimizes product loss/adsorption
- **Extractables**
  - Produces quantitative and qualitative information under worst case conditions (GC/LC/ICP/MS, NVR/FTIR)
- **Leachables#**
  - Produces quantitative and qualitative information using actual process fluid (or placebo) under actual or slightly worst case conditions, including filter/system flush (NVR/FTIR, GC/LC/ICP/MS)

optional based on extractables risk assessment

3. Deliverables: Bacterial Viability and Flush Testing

- Determine the viability of *Brevundimonas diminuta* (or other test bacterium) in process fluid
  - Process time
  - Temperature



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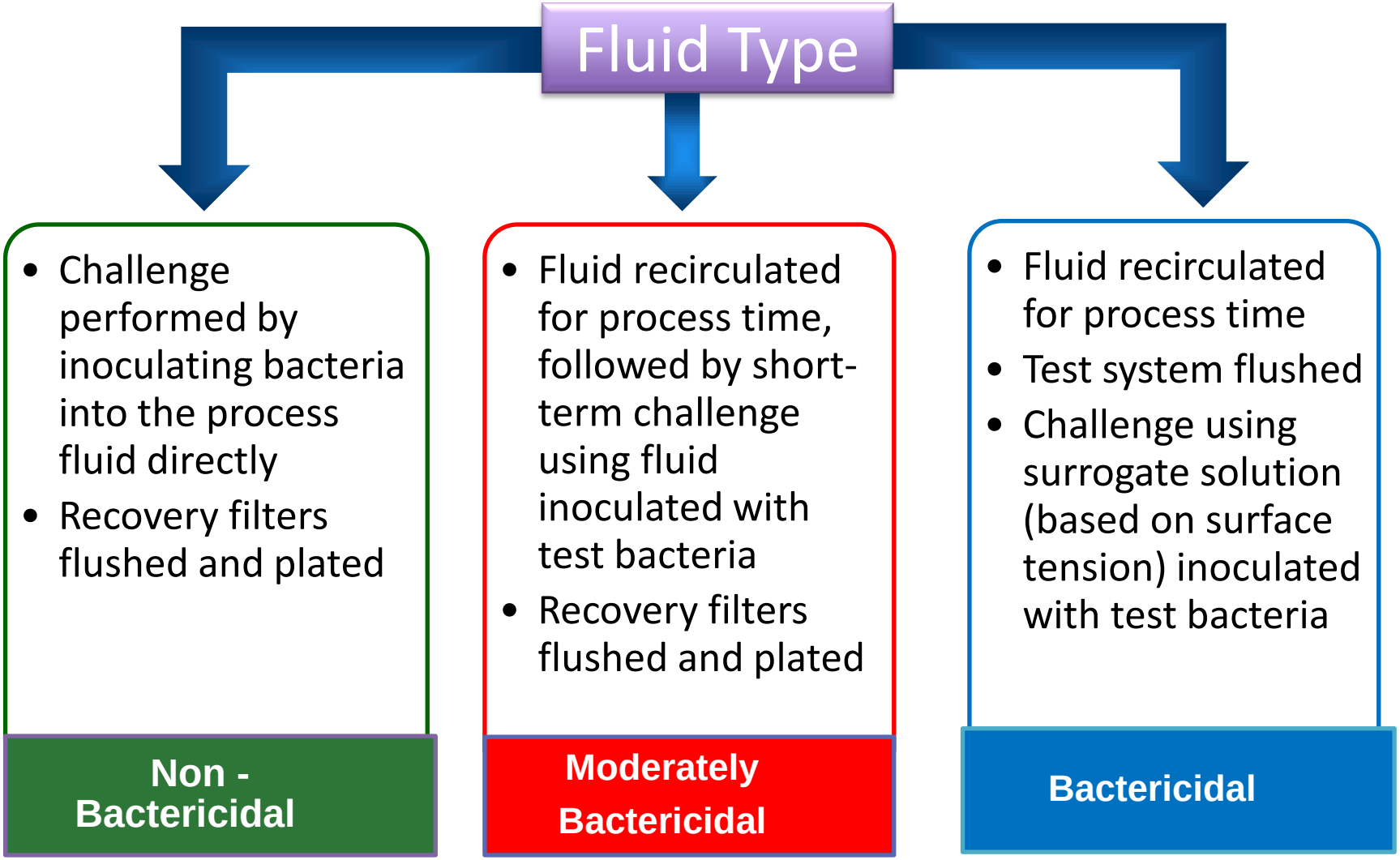
3. Deliverables: Options For Bacterial Retention Test



3. Deliverables: Bacterial Retention Test

- *Brevundimonas diminuta* (ATCC 19146) or other "worst-case" bioburden isolate
- Includes three test filters from three different lots
  - Including one minimum specification filter membrane lot
- Controlled culture conditions (ASTM F838-05)
- Demonstrate penetration of 0.45 µm rated control filter
  - Minimal size (*B. diminuta* 0.3 x 0.8 µm)
  - Monodispersed
- Simulate "worst-case" process conditions
  - Process time
  - Temperature
  - Pressure or flowrate
- Total challenge $\geq 1 \times 10^7$ CFU/cm^2
- Analyze total effluent for sterility

3. Deliverables: Studies With Process Isolates

- "In certain cases, when justified as equivalent or better than use of *B. diminuta*, it may be appropriate to conduct bacterial retention studies with a bioburden isolate".[1]
  - Process isolates eg. waterborne bacteria
  - Developing customized microbiological procedures
  - Challenging filters using specific process isolates

1: FDA Guidance for Industry –Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice September, 2004, p 27

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3. Deliverables: Product-Wet Integrity Test Values

- Establishes filter integrity test values for process filtration assembly wet with process fluid
- Values are determined for filter wet with customer fluid and correlated to reference fluid-wet value (typically water)
  - Filter wetted with water then perform FF test at increasing test pressures
  - Ratio applied to reference wet parameters to determine product wetted parameters
- Product-wet values derived from test data

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3. Deliverables: Compatibility Assessment

- Confirms maintenance of filter integrity after exposure to “worst-case” fluid and process conditions:
  - Filter sterilization conditions
    - Gamma irradiation
    - Steam sterilized
  - Process temperature
  - Duration

- Compatibility determined by performing integrity tests on filter pre- and post-fluid exposure and visual examination of filter

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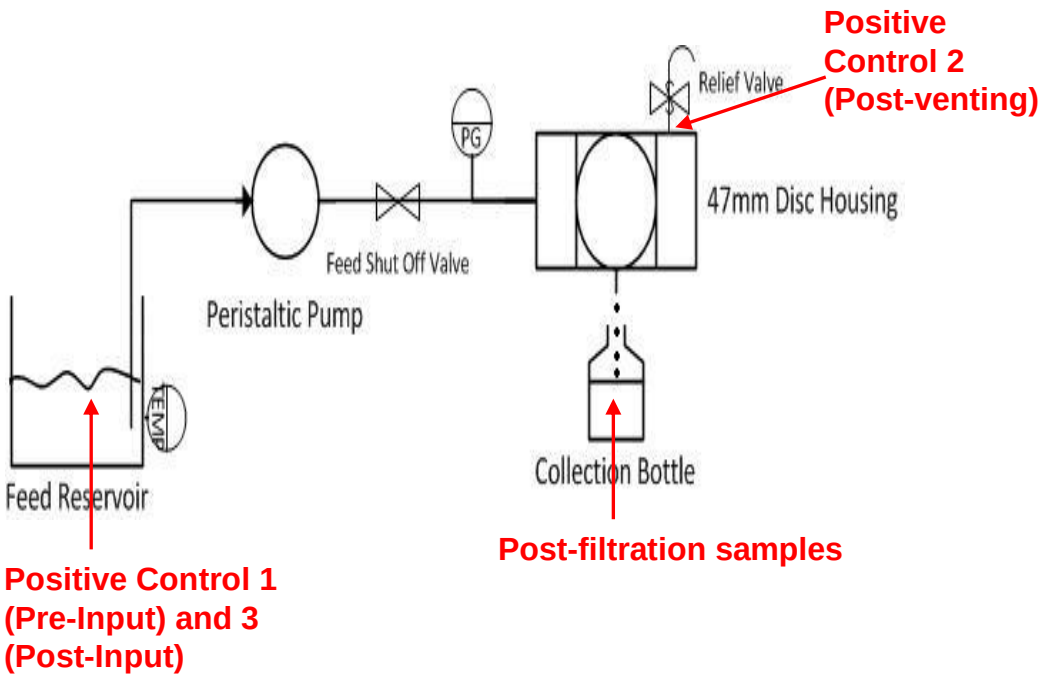
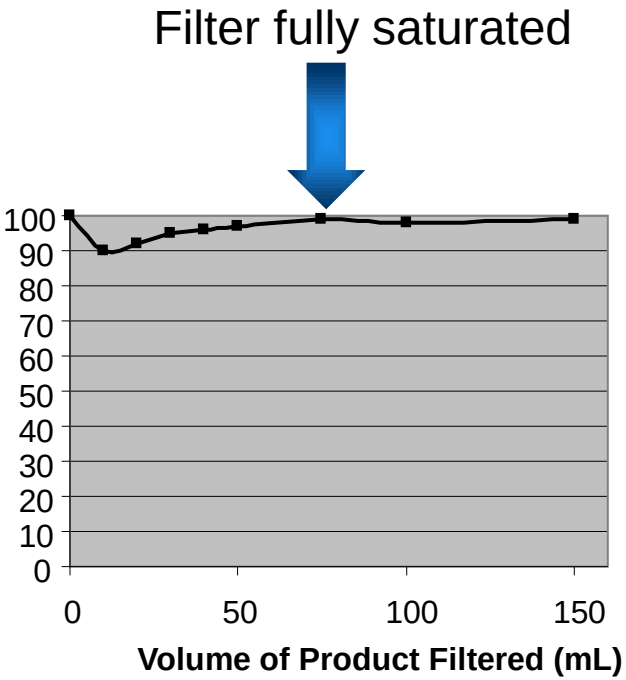
3. Deliverables: Adsorption Testing

- To quantify the amount of component(s) adsorbed from the product onto the filter membrane under processing conditions
- To enable calculation of volume of product which should be flushed through process filter to ensure saturation





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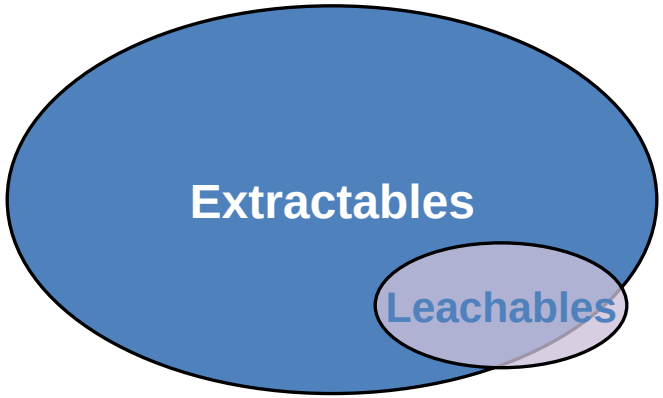
3. Deliverables: Definitions (BPSA) of Extractables/Leachables

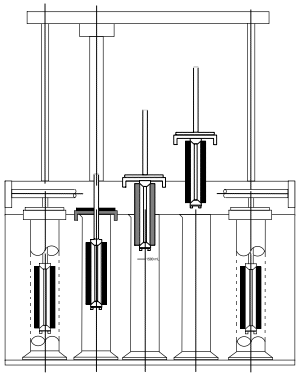
Chemical compounds that migrate from any product contact material, when exposed to an **appropriate solvent under exaggerated conditions** of time and temperature

Chemical compounds, **typically a subset of extractables**, that migrate into the **drug formulation** from any product contact material, as a result of direct contact with the drug formulation **under normal process conditions** or accelerated storage conditions and are found in the final drug product.



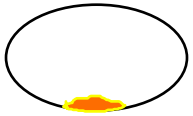
Reference: BPSA (Bio-Process Systems Alliance) "Recommendations for Extractables and Leachables from Single-Use Systems"

3. Deliverables : Extractables Testing – Test Methods



Filter capsules extracted via recirculation
Filter cartridges extracted via reciprocation

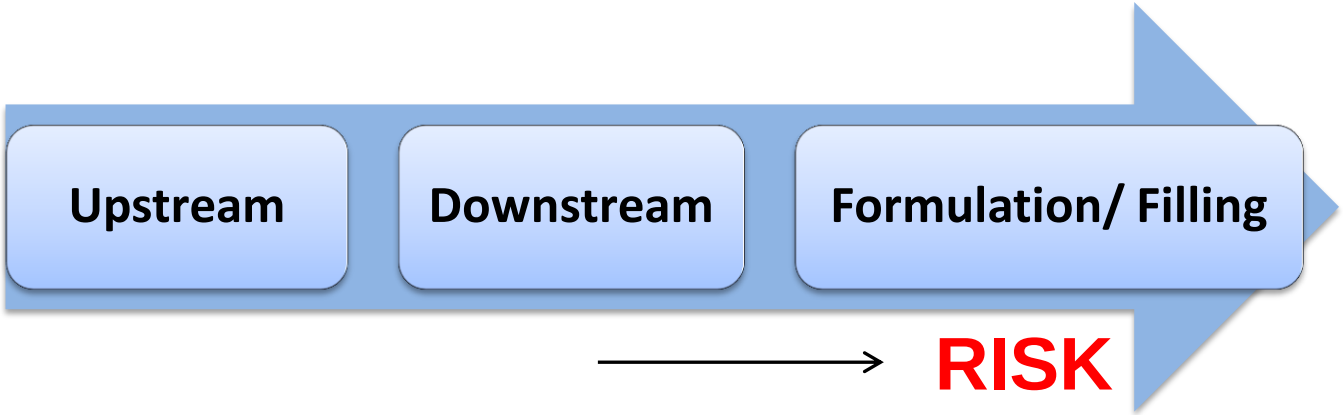
Solvent transferred to rotary evaporator



Solvent/extractables mixture placed in vacuum oven and dried

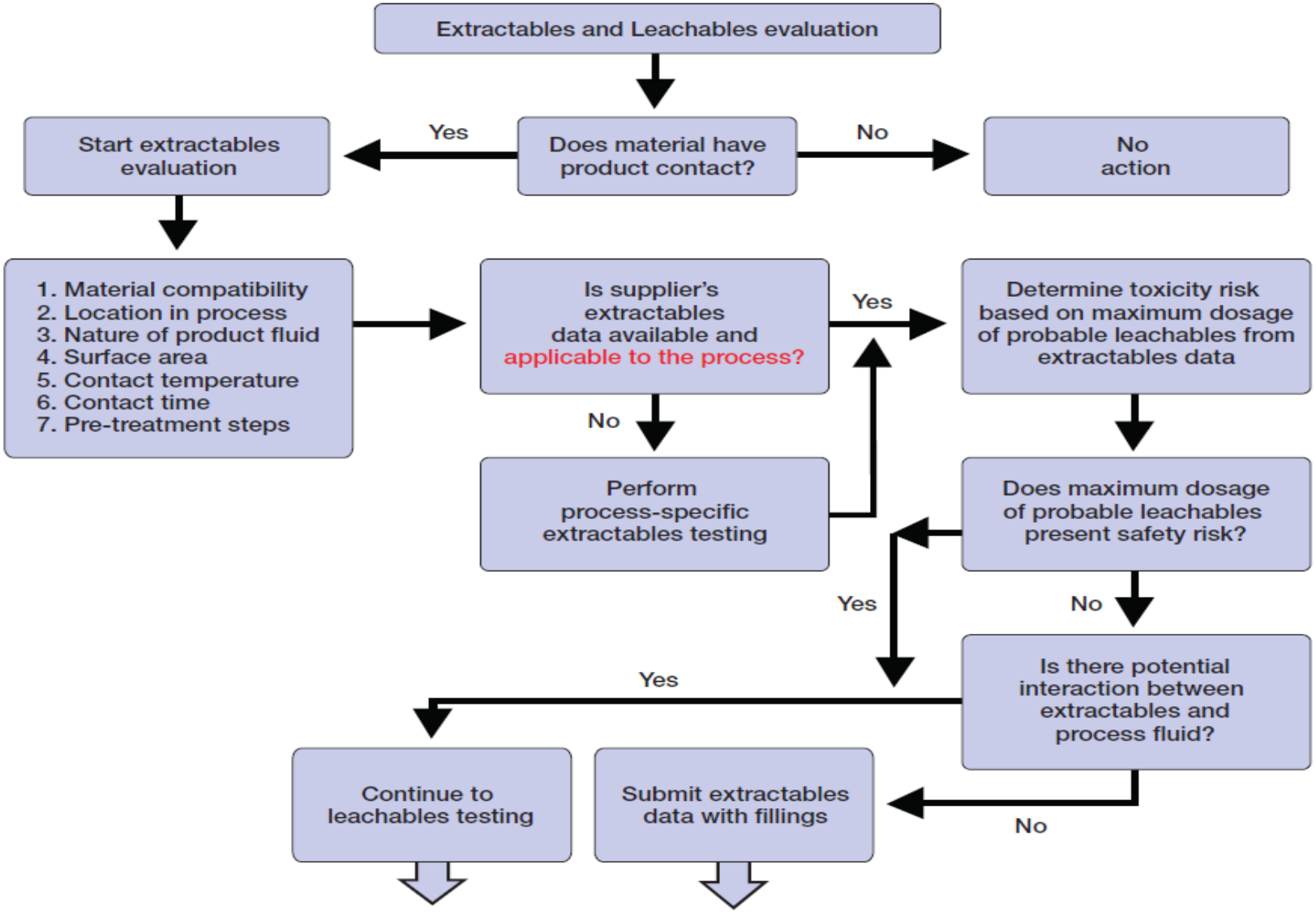
- **LC/MS (Liquid Chromatography)** → Semi-volatile and non-volatile, heat sensitive organic compounds
- **GC/MS (Direct Injection)** → Semi-volatile organic compounds
- **GC/MS (Head Space Analysis)** → Volatile organic compounds
- **ICP/MS (Metal Ions)** → Metal Ions
- **Non-Volatile Residue (NVR)** → Quantitative
- **Fourier Transform Infra-Red Spectroscopy (FTIR)** → Qualitative

3. Deliverables: Assessing Process Application Risk for E&L

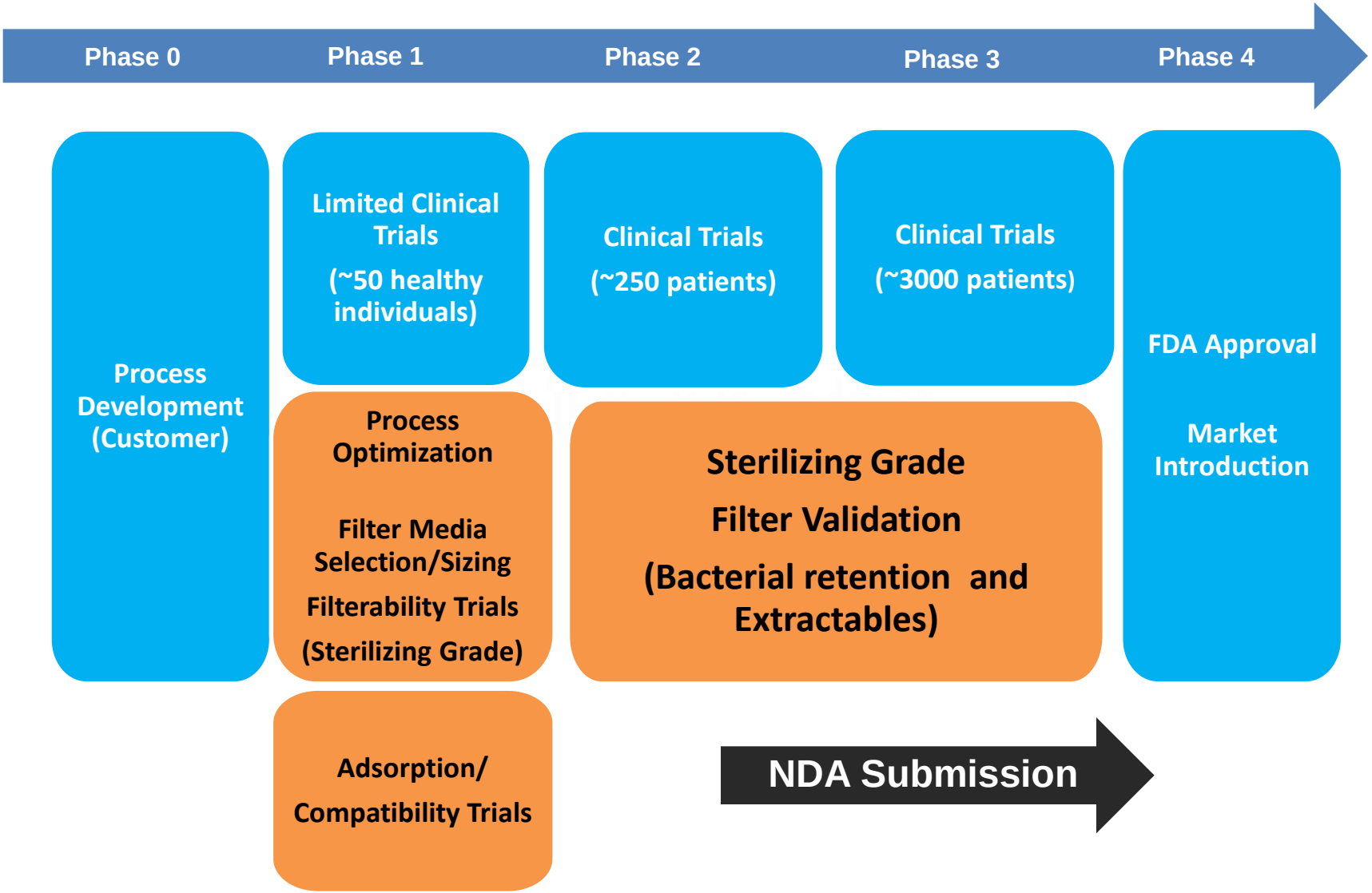


- Upstream - media preparation
  - Cytotoxicity, protein reactivity
- Downstream – protein reactivity
  - Leachables removed at UF/DF step
  - Buffer preparation
  - Ultrafiltration / diafiltration
- Formulation – patient safety, stability
  - API / bulk drug sterilization
  - Final product formulation, sterilization, filling

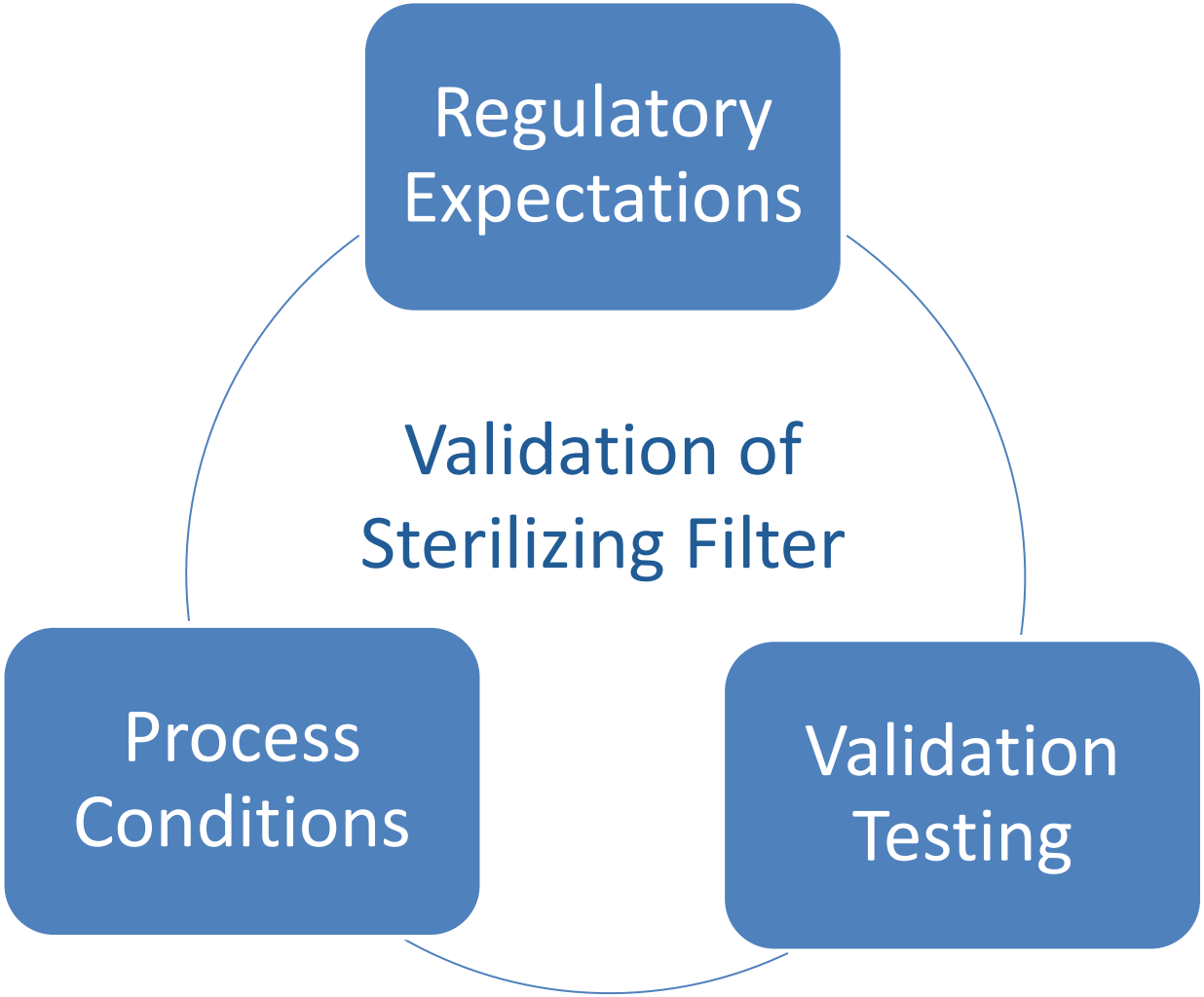
3. Deliverables: Risk Assessment Decision Tree



4. When to Consider Validation



Summary


Regulatory Expectations
Validation of Sterilizing Filter
Process Conditions
Validation Testing