PDA Technical Report #26:

Implications on Liquid Filter Validation

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Filter Qualification

Tests for internal Validation Guides

- **Physical Tests**
  - flow rates/delta p
  - throughput
  - steam sterilizability
  - pressure and temperature resistance
  - autoclavibility
- **Biological Tests**
  - integrity test correlation to bacteria retention
  - bubble point
  - diffusion
  - bacteria retention after 1/20 steam cycles
- **Tests according to USP 24**
  - particle realease (asbestos release)
  - extractable substances/heavy metals
  - oxidizable substances
  - biosafety
  - endotoxin
- **Extractables Tests**
  - extractable analysis with NVR

FDA Regulatory Requirements

PDA Special Scientific Forum, Bethesda, MD; Validation of Microbial Retention of Sterilizing Filters, July 12 – 13, 1995

- Validation of filters should include microbiological challenges according to ASTM F838-83
- Challenge conditions should simulate "worst case" production conditions (pH, temp., flow rate, pressures etc.)
- Challenge fluid should simulate product as closely as in practice

FDA Regulatory Requirements

PDA Special Scientific Forum, Bethesda, MD; Validation of Microbial Retention of Sterilizing Filters, July 12 – 13, 1995

- It is not necessary to conduct validation studies on each individual product within a product group
- Acceptable to have tests conducted by filter manufacturers
- It is the responsibility of the filter user to have the test data available

New Requirements described in PDA T.R. 26

Reaction-Technical Report 26

The report was accomplished by members of the FDA, biopharmaceutical industry, consultants and filter manufacturer under the moderation of PDA.

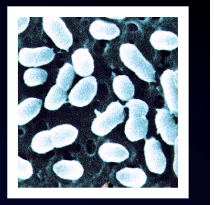
Main purpose:

„This document should be considered as a guide; it is not intended to establish any mandatory or implied standard“

6.11 Viability Testing

- ✓ evaluation of potential bactericidal effects of the product solution
  - ✓ adding of *Brevundimonas diminuta* main culture to product solution
  - ✓ sampling, filtration and colony counting after different exposure times (< 1 log reduction)
- ✓ necessary for product with unknown behavior
- ✓ determine the Bacteria Challenge test method

6.11 Viability Testing



- customers product solution
  - unknown toxicity
    - Viability Test in product solution
      - bactericidial
        - Bacteria Challenge Test with placebo solution (challenge without toxic components.)
          - 1 or 3 product lots with 3 filter lots
        - Bacteria Challenge Test with original solution (high volume challenge)
          - 1 or 3 product lots with 3 filter lots
        - Bacteria Challenge Test after filtration (challenge of used cartridges)
          - cartridges from customers process
          - cartridges from lab-filtration
      - not bactericidal
  - not bactericidal
    - Bacteria Challenge Test with original solution
      - 1 or 3 product lots with 3 filter lots
  - bactericidal
    - Viability Test in product solution
      - Bacteria Challenge Test with placebo solution (without toxic comp.)
        - 1 or 3 product lots with 3 filter lots
      - Bacteria Challenge Test with original solution (high volume challenge)
        - 1 or 3 product lots with 3 filter lots
      - Bacteria Challenge Test after filtration (challenge of used cartridges)
        - cartridges from customers process
        - cartridges from lab filtration

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6. Bacteria Challenge Testing

microbial retention studies on filter devices

- spiking of the drug product with *Brevundimonas diminuta* according to ASTM 838-83 or actual bioburden
- challenge concentration > 10^7 /cm^2 filtration area
- testing conditions simulate the actual process conditions i.e. pleated cartridges or disc sizes, flowrate etc.

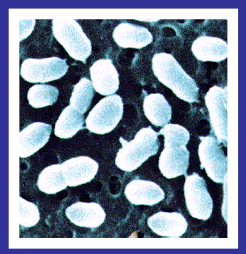
6.1 Microbial Retention

„…factors potentially affecting microbial retention include filter type (structure, base polymer…), …fluid components (formulation,…), …fluid properties (pH, viscosity, osmolarity, inonic strength), …process conditions (temperature, pressure differential,…) and the specific characteristics of the actual bioburden in the product.“

6.2.2 Microbial Retention

„... microbiological challenge tests with low bubble point (bubble point close to the specification) filter should be taken into account...“

Specific validation membranes required !



4.5 Chemical Compatibility

„...it is important to include all of the filter system components under investigation.“

„Numerous chemical interaction possibilities exist in a filter system.“

„A simple chemical compatibility chart will often not provide enough informationfor predicting filter system compatibility, thereby requiring additional testing.“

Example

	Bubble Point [bar]	Burst Pressure [bar]	NVR [mg/l]
Extraction with RO-Water	2.5 (IPA/H2O)	0.52	4
Extraction 0.1 % H_2O_2 7 days, 60°C	1.1 (IPA/H2O)	0.14	41

Incompatibility of the PP-membrane against the media:

- Bubble point decreases with disintegration of the membrane
- The chemically attacked membrane looses the physical strength (Burst pressure testing)
- The fluid is contaminated by extractables - degradation (NVR)
- Special tests required with SEM´s

Appropriate compatibility testing using multiple test methodologies is required

4.6 Adsorption Analysis

„Adsorption is the binding of formula components onto the filter (primarily onto the membrane)“

„It should be determined if adsorption is a problem; if so, it should be addressed.“

Evaluation of the adsorptive properties with the actual product contact and process conditions

4.4 Extractables

„Manufacturers can provide appropriate data on extractable levels and identities from filters...“

„Analytical techniques suitable... ...GC, HPLC, HPCE and GC-MS...“

„Most filter manufacturers test for extractables using a standard solvent (typically water). The filter user is responsible for obtaining extractable data for the drug product formulation.“

Analysis of Extractables

FDA Position

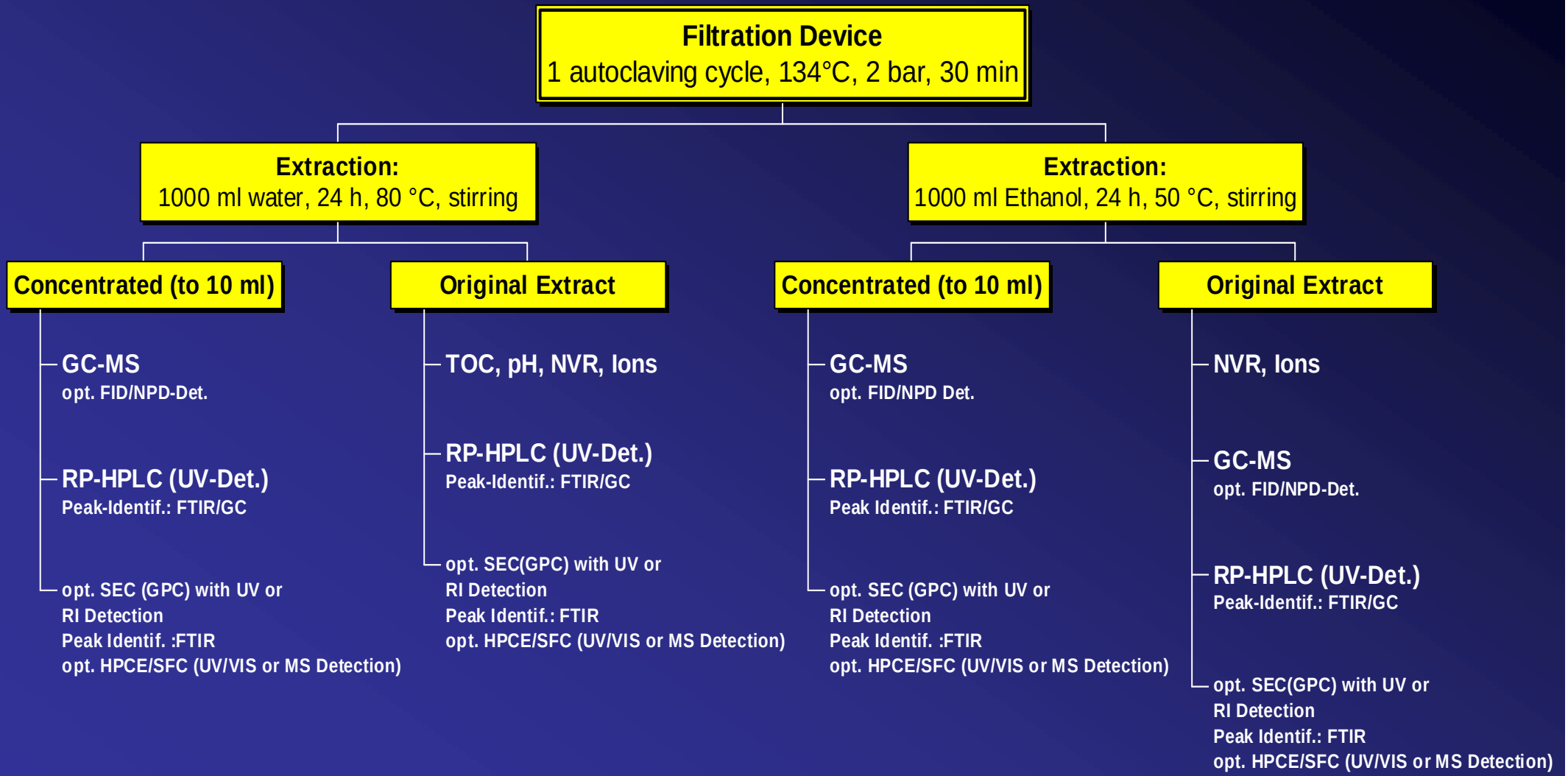
Human Drug cGMP Notes (1994):

Drug manufacturers do not have to test sterile products for filter extractables. In most cases the extractables cannot be detected because the drug product interferes with the test methods and the quantities present are very low..... *This does not mean that the drug manufacturer does not need to have information concerning filter extractables. They must have data showing the identity, quantity and toxicity of the extractables....* This information *can be supplied by the filter manufacturer.*

(Motisse, FDA, Ref. 21 CFR 211.65, Equipment Construction)

Extractable Testing

Proposed Methodology



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4.3 Particle Shedding

„Particulate contamination from the filter and process should be evaluated and considered... Tests should be conducted...“

- -use of modern analytical methods
  - -laser scattering, SEM
- -particle amount and size detection

Detection of particle retention or particle release by filter cartridges under process conditions with actual product

7. Integrity Testing

- When → pre- or/and post filtration
- What → filters in series

  redundant filtration (0.2/0.2 as a unit)
- How → exact description of the individual integrity tests product or water wetted

7.3 Product Integrity Testing

$PBP_{min} = WBP_{min} \times PBP_{avg}/WBP_{avg}$

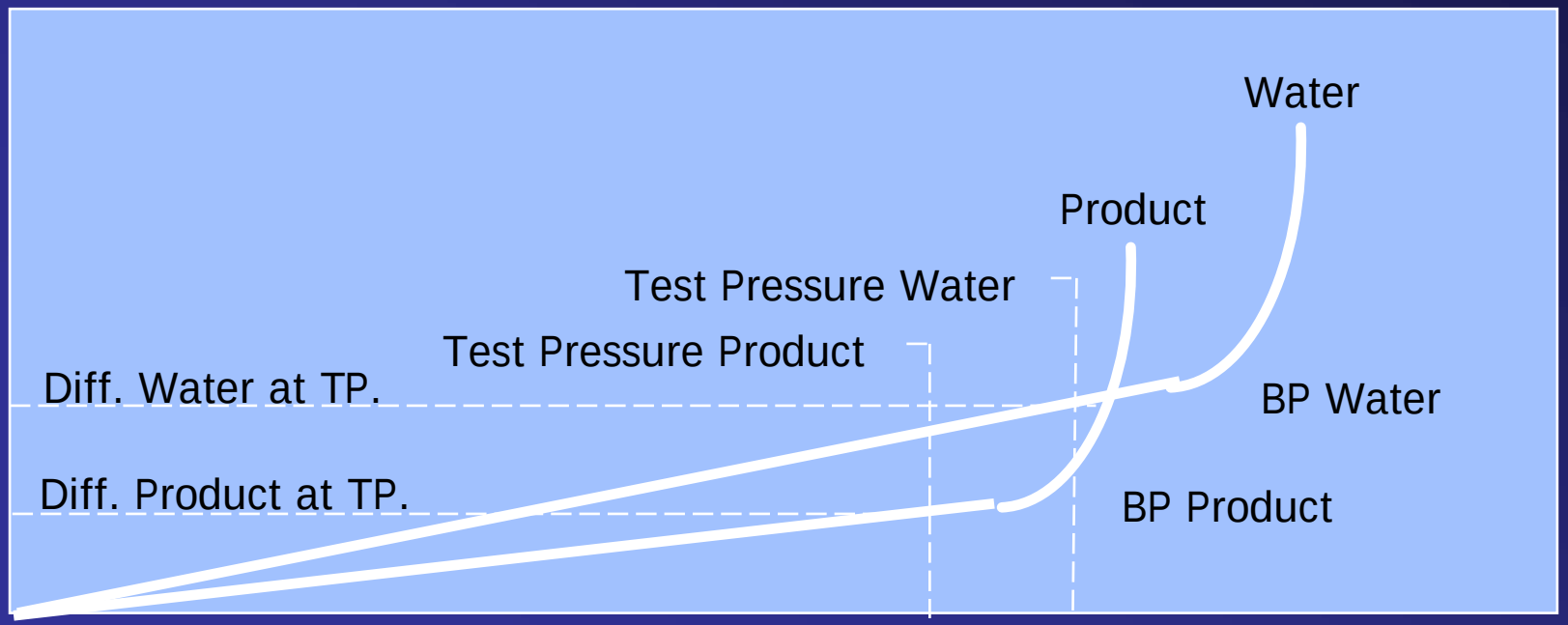
Bubble Point

$DFL_{PW} = DFL_{WW} \times DF_{PW}/DF_{WW}$

Diffusion Test

$TP_{PW} = MTP_{WW} \times PBP_{avg}/WBP_{avg}$

Test Pressure



7.6 Integrity Test Failure

TR #26 includes a Trouble Shooting Guide in case of Integrity Test Failures:

1. Steps & Actions when failing

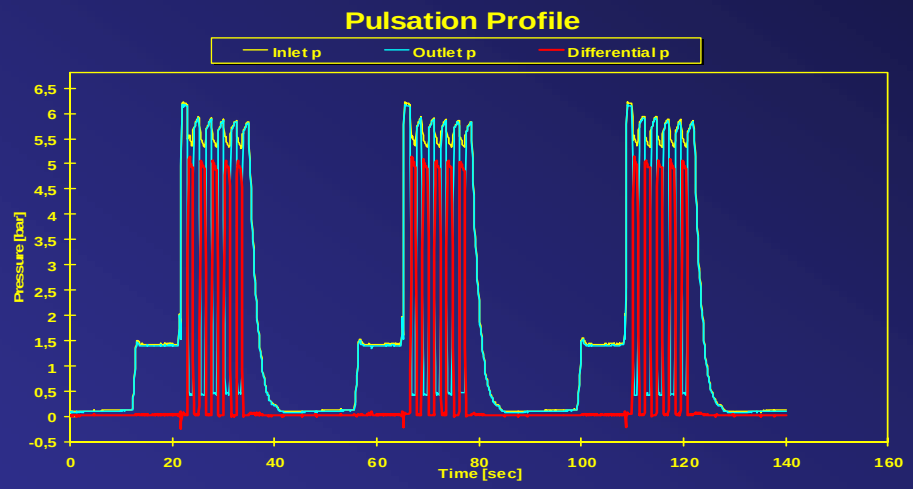
2. Definition when a filter has to be classified failed

Filter fails first time → Measurements & Actions
Filter fails second time → Wetting with solvent
Filter fails third time = Filter failed

Other Evaluations

Definitions in:

- Thermal Stress
- Sterilization
- Hydraulic Stress Resistance
- Toxicity Testing
- Filter Configuration
- Flow Rates



Conclusion

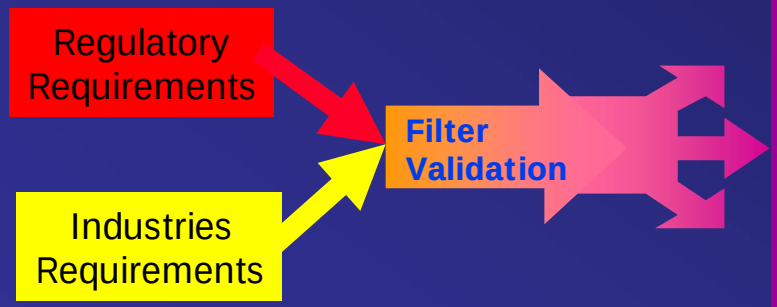
- ✓ PDA Technical Report #26 is the most detailed, comprehensive and descripitive document in respect to liquid filter validation
- ✓ It has not been meant as an industrial standard, but is often enough used as such
- ✓ Filter users have to be aware about it, because it is utilized by regulatory authorities
- ✓ Others will follow, e.g. ISO 13408-2

Conclusion, cont.

Validation support by suppliers/consultance is accepted and often required !

When doubts e.g. FDA should be contacted at the earliest stage !

Training never to be forgotten !



Viability Testing
Bacteria Challenge Testing
Chemical Compatibility
Adsorption Analysis
Analysis of Extractable
Particle Testing
Product Integrity Testing
Plant and Process Surveys
Systems and Integrity Tester Validation
Process related Validation Studies

Danke schön !

Thank you !