Life Sciences

PDA Technical Report No. 26 "Sterilizing Filtration of Liquids"

PDA New England Chapter
June 13, 2007

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Presentation Overview

- US FDA Issues
- PDA Tech Report Scope
- Task Force Members
- Contents Overview
- Key New Recommendations

FDA Statement

"The agency does not agree that the demonstration of the lack of holes* in the membrane, by any selected membrane integrity test, automatically implies the retention of the microorganisms which may be present in the drug product."

Peter Cooney, Ph.D., FDA CDER,
PDA/FDA Forum, 7/95

* ("defects")

FDA Published Statements on Filter Validation

- FDA Human Drug CGMP Notes, Dec., 1995
  - "Since there is a possibility that the drug product may cause reduction in the size of the micro-organism, it is best to test the microbial retentivity of the filter with the microbial challenge in the actual drug product."

FDA Published Statements on Filter Validation

- FDA CDER Perspective on Isolator Technology, ISPE Barrier Technology Conference, Dec, 1995
  - “Recently, several instances have come to the Agency’s attention, when passage of a drug product through a 0.2 µm rated filter was not sufficient to remove contaminating microorganisms.”

FDA Published Statements on Filter Validation

- FDA CDER Perspective on Isolator Technology, ISPE Barrier Technology Conference, Dec, 1995
  - Issues to be considered are….
    - How long will the filling line be operated?
    - Does the subject drug product support growth?
    - Does the drug product alter filter retentivity?
    - Does the drug product alter the size of microorganisms or other physical trait, such as deformability, that could affect filterability?”

PDA Technical Report #26
Scope Statement

- Purpose: Generate an educational monograph on sterilizing filtration technology
  - Not intended as a standard or regulatory document
- Include manufacturers, users and FDA
- Solicit PDA member and FDA review of drafts
- Publish Technical Report for industry guidance

PDA TR26 Task Force

- Drug Manufacturers
  - Pharmacia & Upjohn
  - Abbott Laboratories
  - Eli Lilly
  - Glaxo Wellcome
  - Merck
- Filter Manufacturers
  - Pall (J. Martin)
  - Millipore
  - Sartorius
  - W. L Gore & Assoc.
  - Filterite (now part of Pall)
  - Meissner
- Filtration Consultants
  - J. Wilson (ex. Abbott)
  - T. Meltzer
  - H. Schroeder
- FDA Representative
  - P. Stinavage, CDER (now at Pfizer and Chair of 2007 revision task force)

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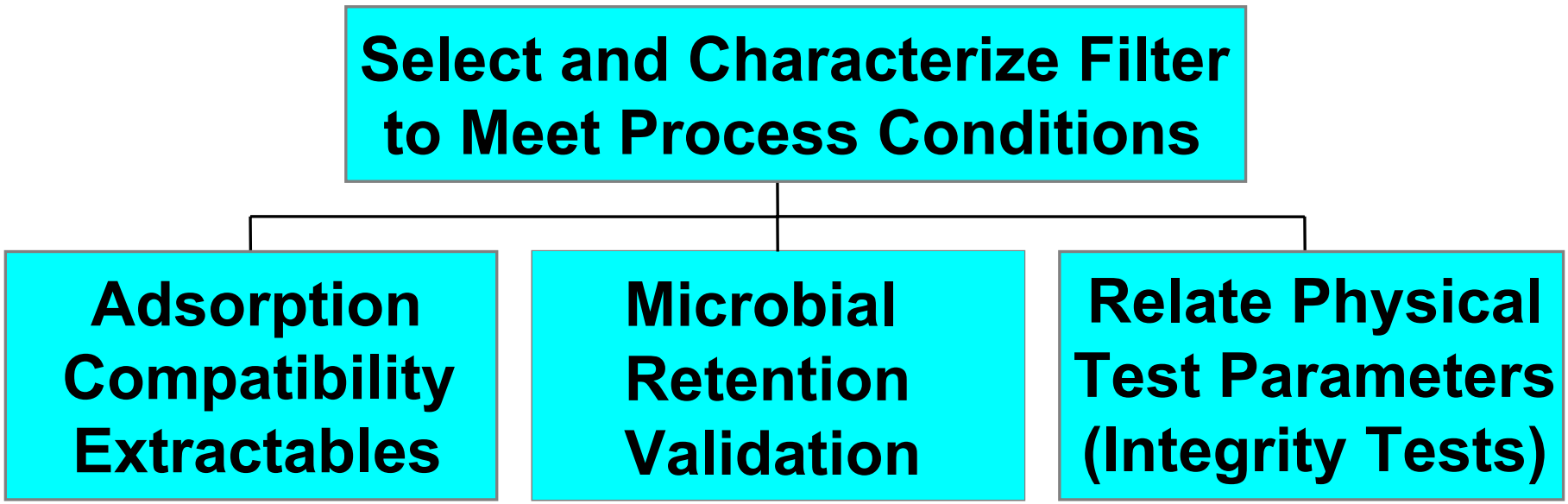
Sterilizing Filter Validation Summary Concepts



FDA Guidelines on Aseptic Processing (1987)

"A sterilizing grade filter is one which, when challenged with the microorganism *Pseudomonas diminuta* at a minimum concentration of $10^7/cm^2$ of filter surface, will produce a sterile effluent"

"Forget about it!"

Peter Cooney, Ph.D., FDA CDER

PDA Annual Meeting, Washington, DC, Nov. '98

PDA Filtration Committee Discussion Points

"A sterilizing grade filter is one that sterilizes the drug product."

Peter Cooney, Ph.D., FDA CDER

Filter claims for "sterilizing grade" will continue to be of value to drug manufacturers for selection and product-specific retention validation.

PDA Filtration Committee

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PDA TR26 Summary
Sterilization Validation

- Product sterilization may not be achieved with integral "sterilizing grade" filter cartridges
  - Filter manufacturer's integrity test limit and lot sample challenge predict *Brevundimonas diminuta* retention under standard test conditions (e.g. ASTM F838-83, now F838-05)
- Sterilization of drug product should be validated
  - Confirm that drug product, process conditions and bioburden do not affect the process filter's ability to produce sterile effluent

PDA TR26 Summary

Sterilization Validation

PDA Technical Report # 26:

"The goal of conducting bacterial retention validation studies is to generate data

demonstrating that the filtration process will consistently remove high levels of a standard bacterium, or relevant bioburden isolate,

suspended within product (or surrogate fluid), under actual process conditions"

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PDA TR26 Summary
Sterilization Validation

- Every product need not be tested
- Products can be grouped into “families”
- Family extremes can be “bracketed”
- “Worst case” product models can be selected
- Scientific rationale must be documented

PDA TR26 Summary
Sterilization Validation

- Validate filtration sterilization process under “worst case” conditions for:
  - Product - drug product formulation
  - Process - drug filtration process
  - Bioburden - drug and filling environment
  - Membrane - physical QC specifications

PDA TR26 Summary

Relating Integrity Test Values

"Validation studies should establish the relationship between the chosen integrity test method and bacterial retention…

and serve as a basis for establishing appropriate parameters for the pre- and post- use integrity testing of production filters."

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Integrity Test Correlation

- **Bubble Point**
  - **Not consistent with filter area**
    - High area cartridges may have different BP than discs cut from identical pore distribution membrane
  - **Filter mfr certifies cartridge membrane BP ≥ min. production membrane BP (prod'n BP test)**
  - **User confirms certified cartridge membrane BP > min. validated disc membrane BP (prod'n BP test)**
    - Confirms membrane in cartridge is at least as "tight" as "worst case" validated membrane
  - **User tests assembly BP to > min. allowable limit for cartridge/assembly BP**
    - Confirms cartridge is free of leaks or perforations = integral.

Integrity Test Correlation

- **Forward Flow (a.k.a. Diffusion)**
  - **Flow too low to measure on small discs**
    - Can't scale up disc flow to cartridge flow accurately
  - **Filter mfr certifies cartridge membrane BP ≥ min. production membrane BP (prod'n BP test)**
  - **User confirms certified cartridge membrane BP > min. validated disc membrane BP (prod'n BP test)**
    - Confirms membrane in cartridge is at least as "tight" as "worst case" validated membrane
  - **User tests assembly FF to < max. allowable limit for cartridge/assembly FF**
    - Confirms cartridge is free of leaks or perforations = integral.

Summary Recommendations PDA TR#26

- Parametric approach for validation of sterilizing filtration process
  - "Worst case" product/fluid or surrogate model
  - "Worst case" process conditions
  - "Worst case" bioburden model or isolate
  - "Worst case" membrane discs based on manufacturer's specification
- Relate production filter membrane/cartridge integrity to validated membrane disc retention and integrity specification

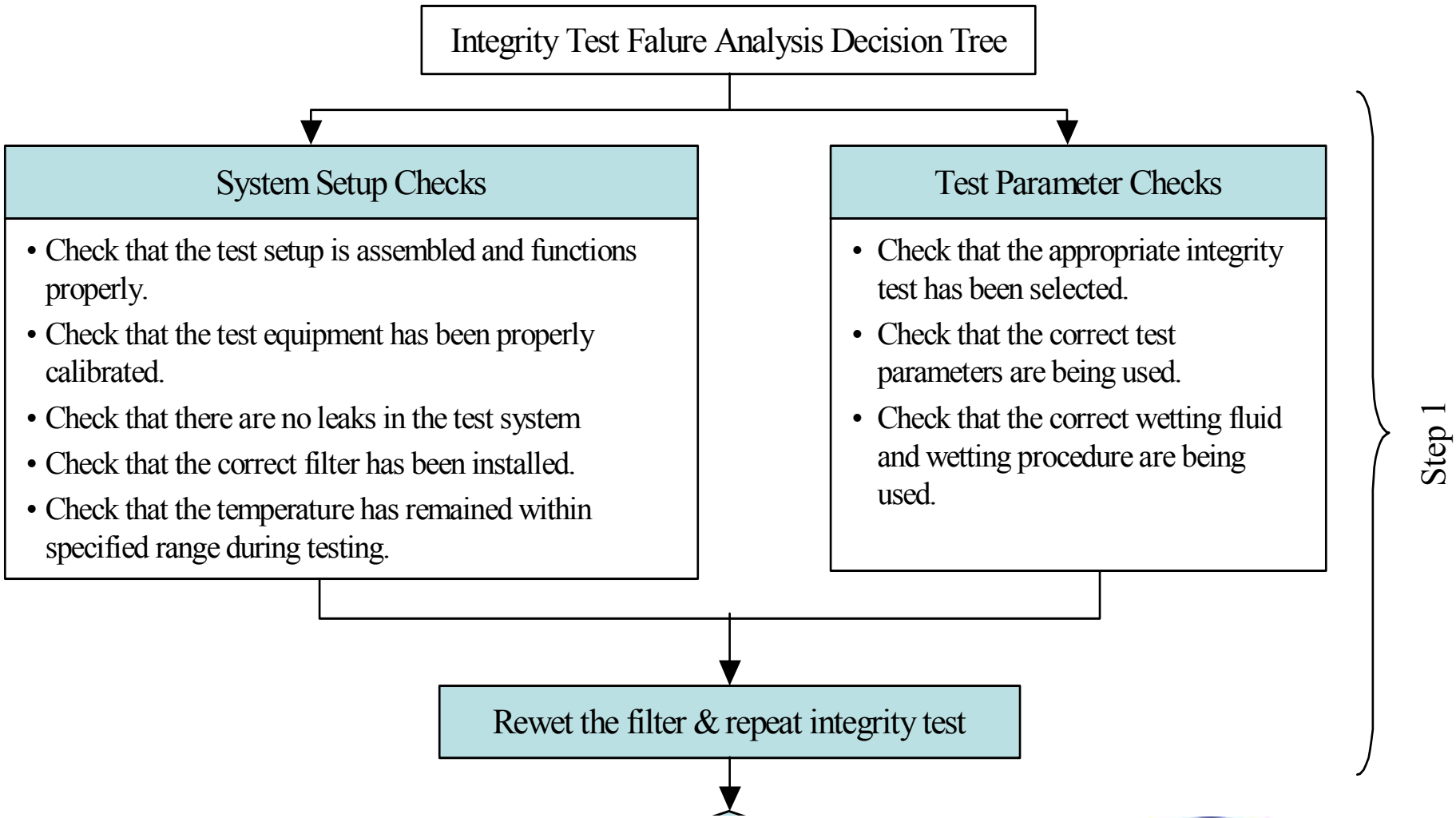
PDA TR 26 Revision 2007

- **24 Member Task Force**
  - Biotech, pharmaceutical, contract manufacturing, filter manufacturing and consultants
- **Updated for current best practices**
- **Expanded sections**
- **New sections, e.g.**
  - **Redundant filtration**
  - **Re-sterilization of filters**
  - **Integrity testing multi-cartridge systems**
  - **Disposable filtration systems**

Process Risk Assessment Factors

Higher Risk	Factor	Lower Risk
Higher levels, Diminutive organisms	Bioburden	Lower levels Large organisms
Higher	Differential pressure	Lower
Higher	Flow rate	Lower
Growth promoting	Product	Bactericidal or preserved
Ambient and higher	Temperatures	Refrigerated
Longer	Time	Shorter

Integrity Test Failure Decision Tree



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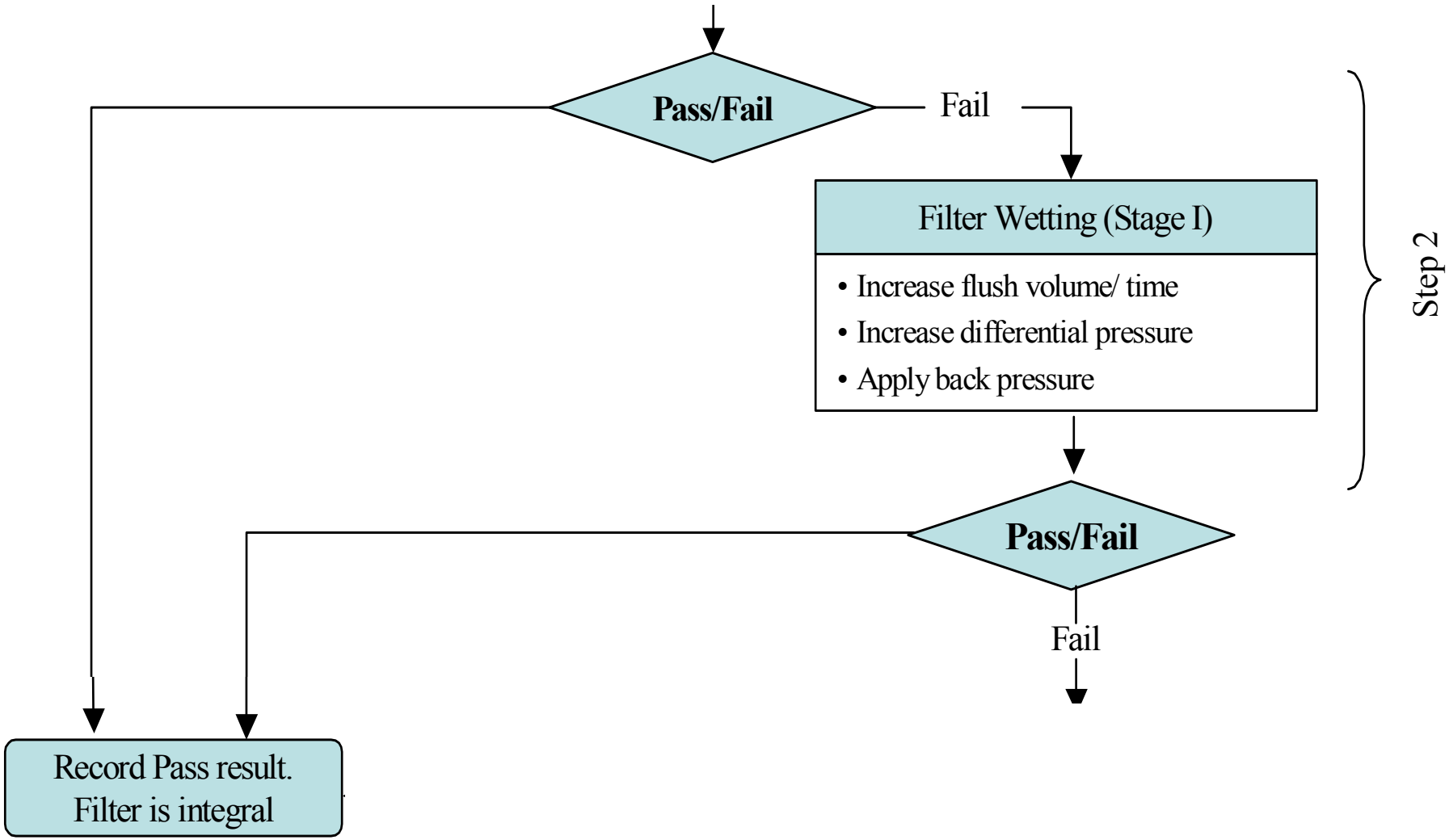
Integrity Test Failure Decision Tree



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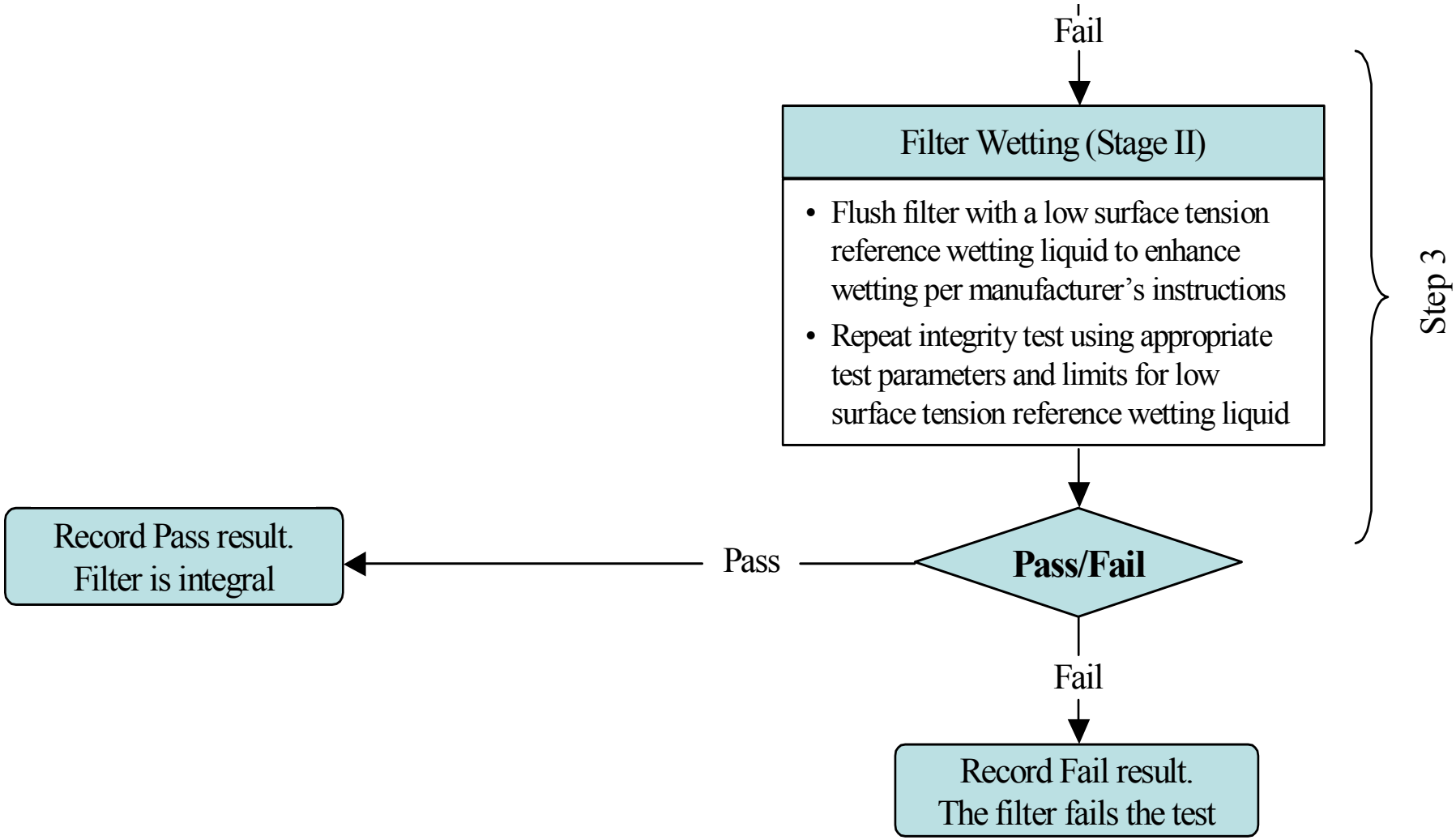

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PDA TR 26 Revision 2007

- Select Review Phase (to 8/15)
- PDA Member Review Phase (to 9/15)
  - Available to PDA members on website
- Publication (~Nov/Dec, 2007)
  - Suppl. to PDA J. Paren. Sci. & Techol.