Validation of Sterilizing Grade Filters

Presented by

Laura Okhio-Seaman
Sartorius Corporation

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Sterilizing Grade Filters

The definition of a sterilizing grade filter is one that will produce a sterile effluent after being challenged by microorganisms at a challenge level of greater than or equal to $1x10^7/cm^2$ of effective filtration area.

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Filter Qualification Tests

- Physical Tests
  - Flow rates, differential pressure, throughput
  - Sterilizability (SIP, Auto)
  - Integrity tests (bubble point, diffusive flow)
- Biological Tests
  - Viability
  - Bacterial challenge test
  - Bioburden studies
- Compendial Tests (USP,EP)
  - Particle release
  - Oxidizable substances
  - Biosafety
  - Endotoxin
- Other Tests
  - Non-volatile residue
  - Quantitative and qualitative extractables analyses in water and ethanol
  - Leachables testing

Validation of Sterilizing Grade Filters

- Demonstrates the filter retains microorganisms to produce a sterile filtrate
- Ensures the filter does not alter the product in an objectionable way
- Ensures the product does not adversely affect the filter – compatibility
- Ensures the physical parameters of the process do not adversely affect the filter or the product

Viability

Filter Qualification Tests

Brevundimonas diminuta (ATCC 19146)

Until the late 1960's, 0.45 µm-rated membranes were considered "sterilizing grade" filters, and were used successfully in the sterilizing filtration of parenterals. In the mid-1960's Dr. Frances Bowman observed a 0.45 µm "sterile-filtered" culture medium to be contaminated with a micro-organism, subsequently shown to penetrate 0.45 µm-rated membranes repeatedly in small numbers.

Viability Test

- Evaluation of potential bactericidal effects of the product solution
- Viability verified by direct inoculation into product and making serial dilutions
- Test exposure time should equal or exceed actual process filtration time
- If less than a one-log reduction (LRV) is observed, product considered non-bactericidal
- Greater than one-log reduction indicates product is bactericidal and alternatives should be considered

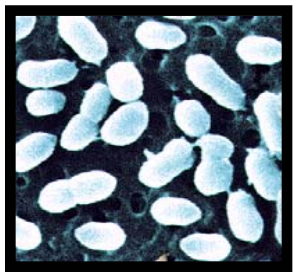
Viability Test Examples

	Test Exposure Times			
Viability Results	5 min.	10 min.	30 min.	60 min.
Standard (0.1% peptone water)	139	122	128	148
Not Bactericidal (example 1)	131	135	119	134
Low Bactericidal (example 2)	105	84	43	23
Strong Bactericidal (example 3)	0	0	0	0

Bacterial Challenge

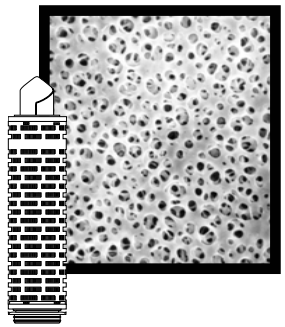
Bacterial Challenge Test

Filter Qualification by Supplier



Challenge

Stand. Cond.



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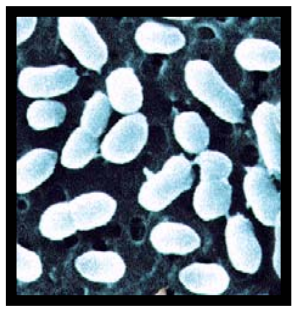
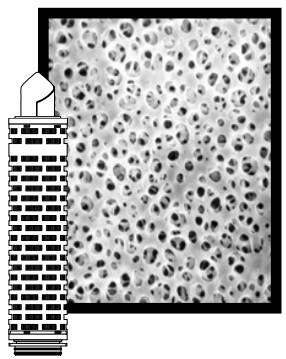
Bacteria/Water Suspension

Process-related Filter Validation by User/External Lab



Challenge

Process Cond.



Document

Bacteria/Product Suspension

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Bacterial Challenge Test

Factors potentially affecting microbial retention include

- Filter Construction (structure, membrane polymer, pore size distribution)
- Formulation components
- Formulation properties (pH, viscosity)
- Process conditions (time, temperature, pressure differential, flow-rate)

Bacterial Challenge Test

Microbial retention studies on filter devices:

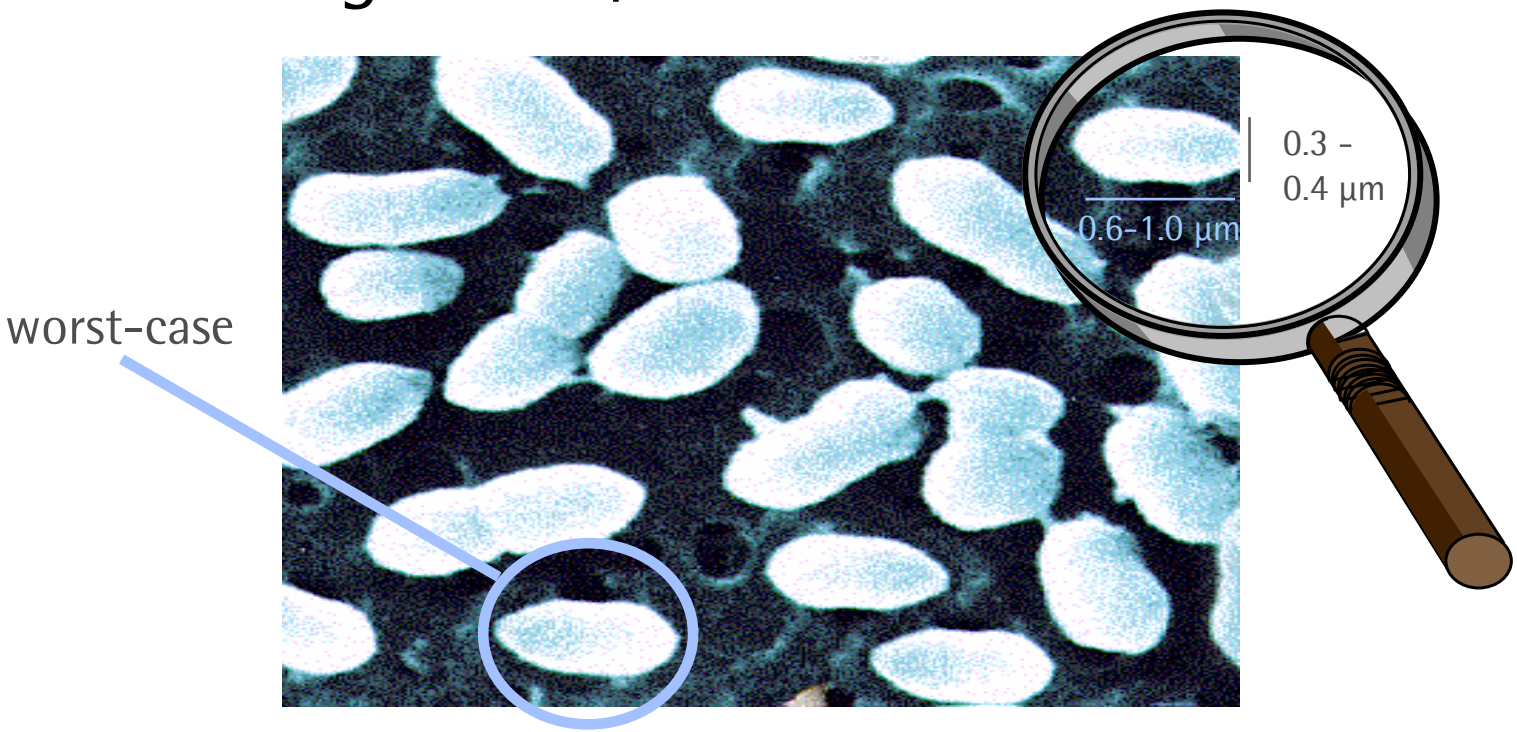
- *Brevundimonas diminuta* (ATCC 19146) has been proven to penetrate a 0.45 µm rated filter
- Spiking of the drug product with *Brevundimonas diminuta* according to ASTM 838-05
- Challenge level > 10^7 CFUs / cm^2 filtration area.
- Validation Testing should simulate *worst-case* process conditions e.g., pressure differential, flow-rate, time, temperature

Bacterial Challenge Test

- Challenge suspension should be mono-dispersed to provide 'worst-case' challenge
- Optical microscopy is used to detect aggregation and clumping of bacteria
- Ultrasonic treatment reduces aggregation
- Penetration of 0.45 µm rated membranes is indicative of single-cell conditions and this membrane is used as a positive control

Bacterial Challenge Test

Microscopic investigation
Criteria: single cells, motile cells



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Bacterial Challenge Test

- ASTM 838-05 (2005) uses *B. diminuta* as the standard challenge organism
- 2004 Aseptic Processing Guidance suggests the use of native bioburden isolate when appropriate

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Bacterial Challenge Test

Microbiological challenge tests using one lot of low Bubble Point (close to manufacturer's minimum specification) membranes should be used.*

Example:

Minimum Bubble Point Value:	46 psi
Release criteria of filter vendor:	50 psi
Low BP Range:	46 – 50.6 psi

* At or near filter manufacturers minimum integrity test value (10%), 1999 PDA / FDA Joint conference, PDA Newsletter December 1999

Filter Medium vs. Device

- The purpose of the test is to validate the retention efficacy of a particular membrane material. A small 47mm membrane disc can be used
- To more closely simulate process conditions and to determine the integrity of process filters, a small area 150 or 300 cm^2 filter device capsule can be used
- Full sized 10" filter cartridges require large volumes of product (25-30 liters) to perform the challenge testing

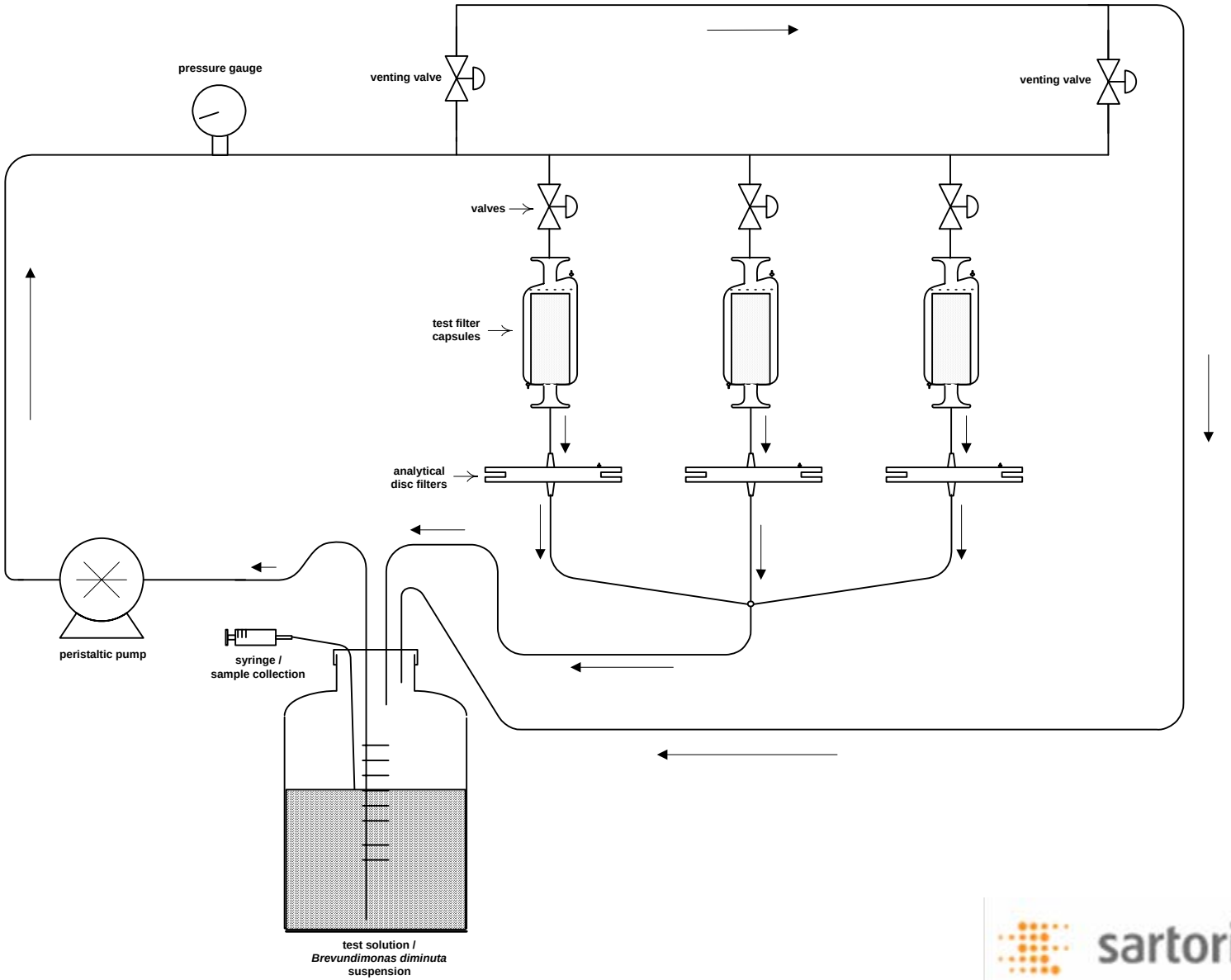
Recovery Membrane Selection

- Either 0.45 or 0.2 micron-rated filter membrane can be used for recovery membranes
- Studies indicate that 0.45 micron-rated membranes might be more efficient than 0.2 for this purpose
- Cellulose Nitrate is the preferred membrane polymer – high affinity for proteins

Pressure Differential and Flow Rate

- Maximum process pressure differentials (△P) across the filter should be used in the challenge studies
- Process flow-rate should be achieved in challenge studies
- If pressure and flow rate cannot be simultaneously achieved, the user should determine which is more relevant and develop a rationale to support the decision
- Regulators tend to prefer higher pressure data rather than flow-rate

Manual BCT Set-up



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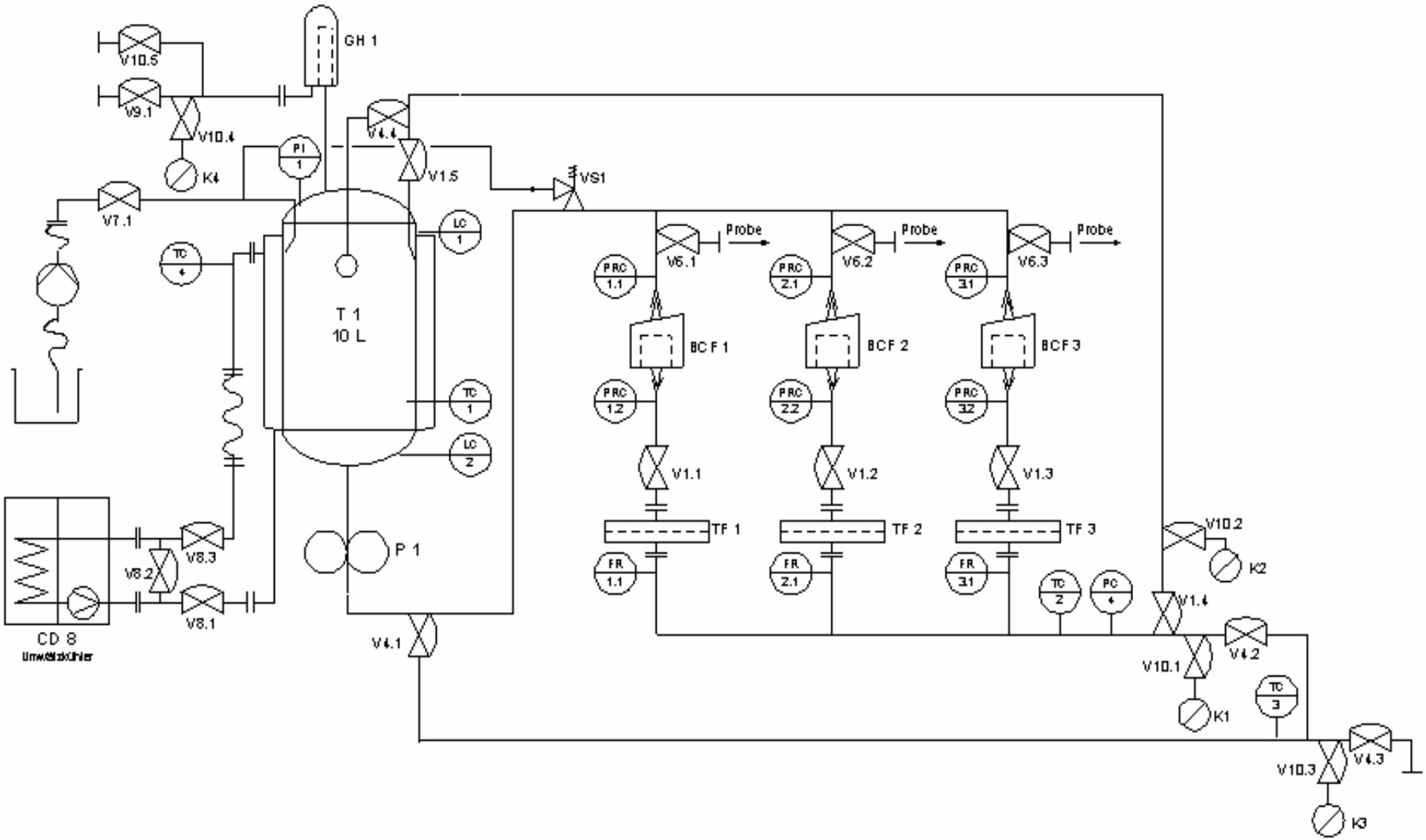
BCT Set-up for Small Scale Pleated Filters



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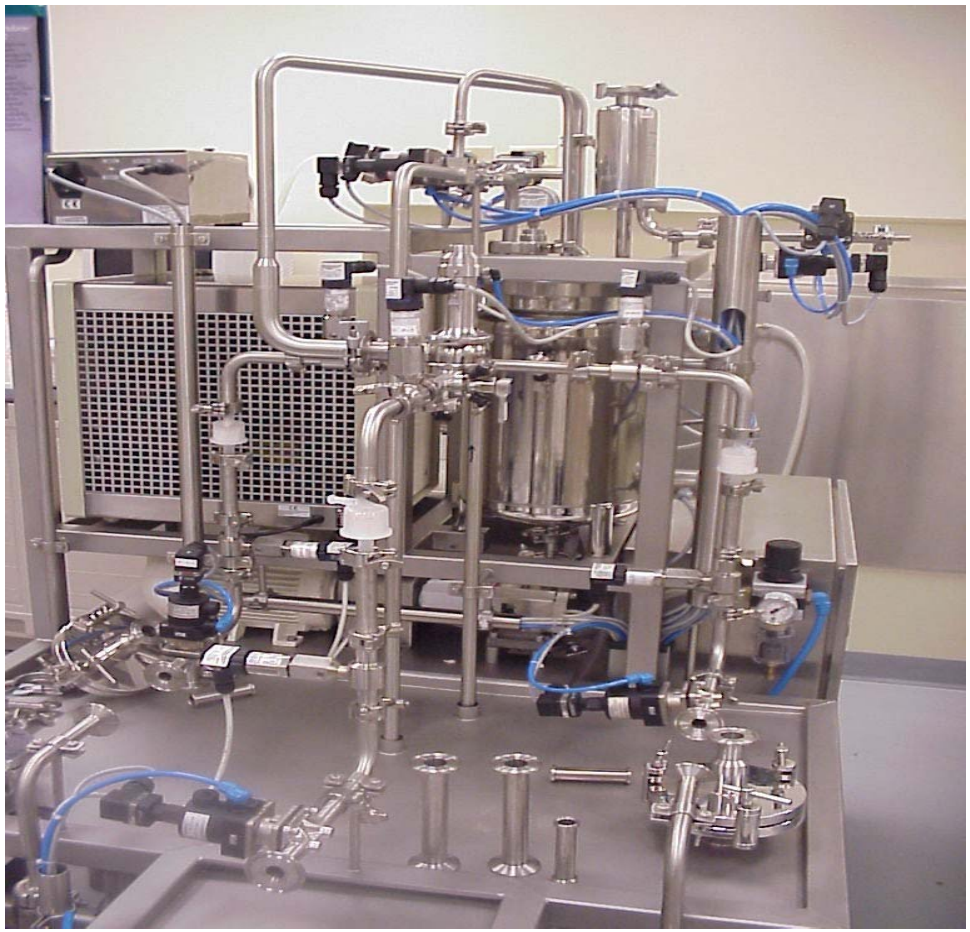

"Big Bertha" rig
Sartorius AG

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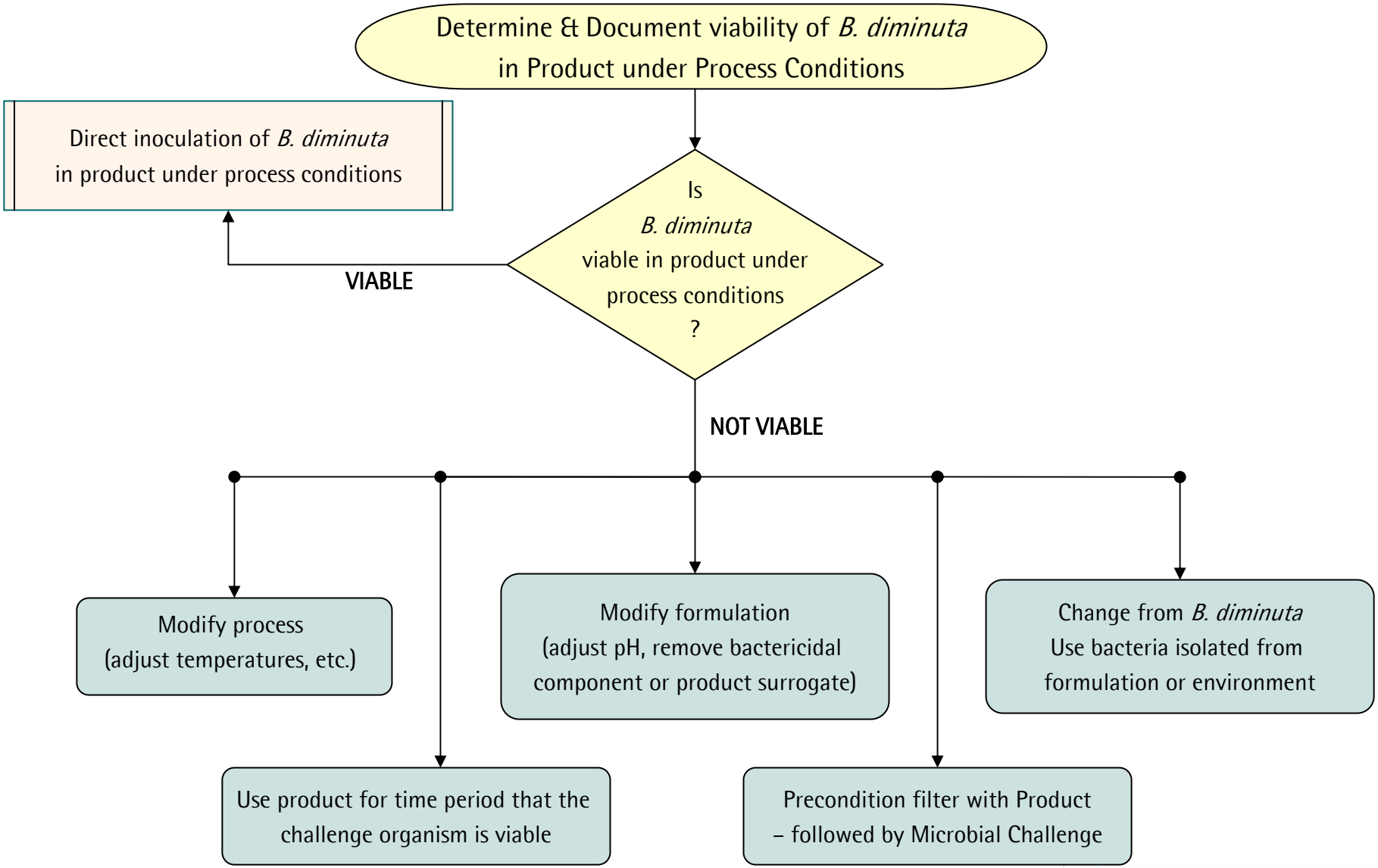
Possible BCT Strategies



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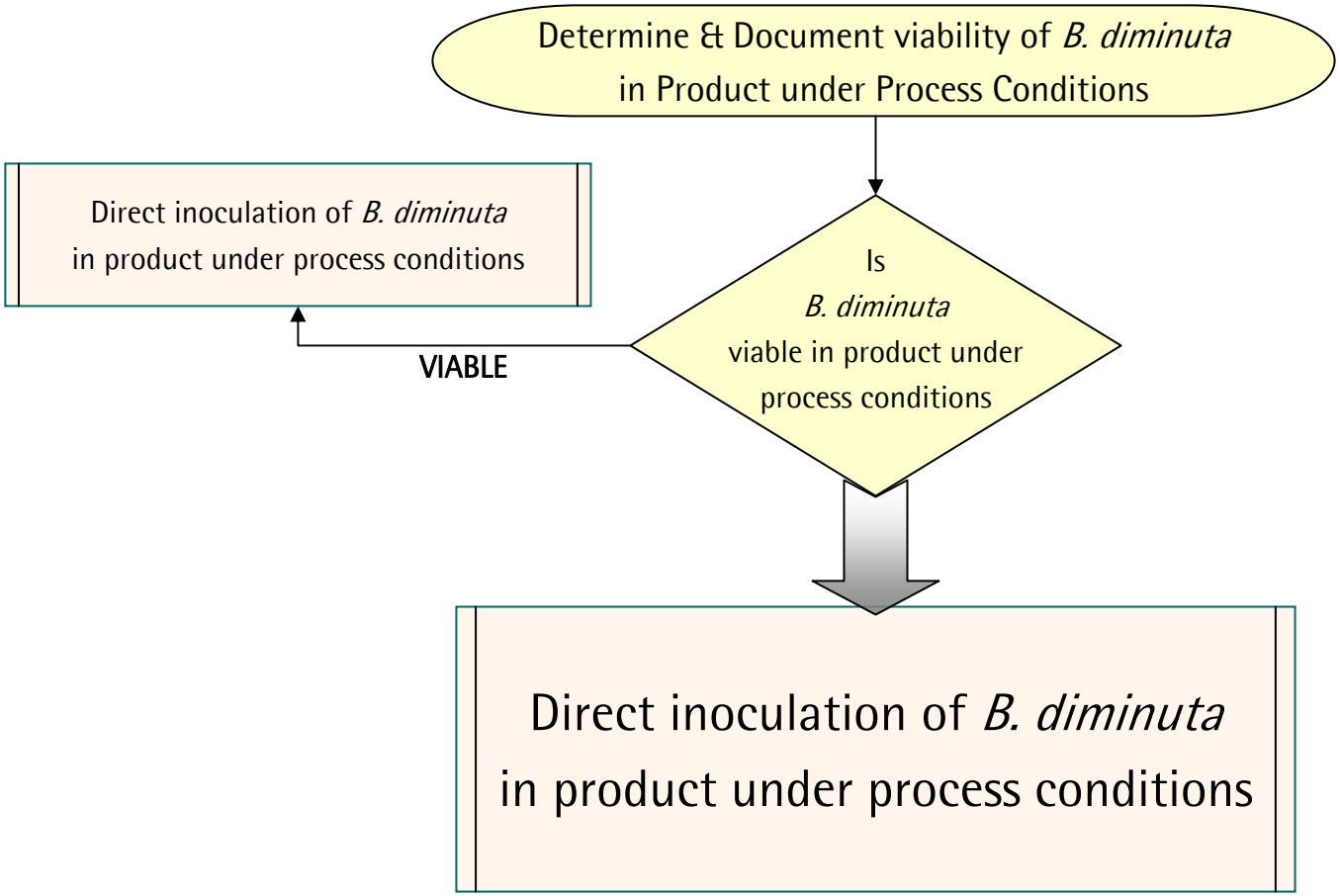
BCT Strategies – Method 1 (Direct Inoculation)



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BCT Strategies – Method 1 (Direct Inoculation)

Solutions	Test Exposure Times			
	5 min.	15 min.	30 min.	45 min.
Standard (0.1% peptone water)	129	142	119	128
Product Solution	132	142	135	130

→ BCT by direct inoculation

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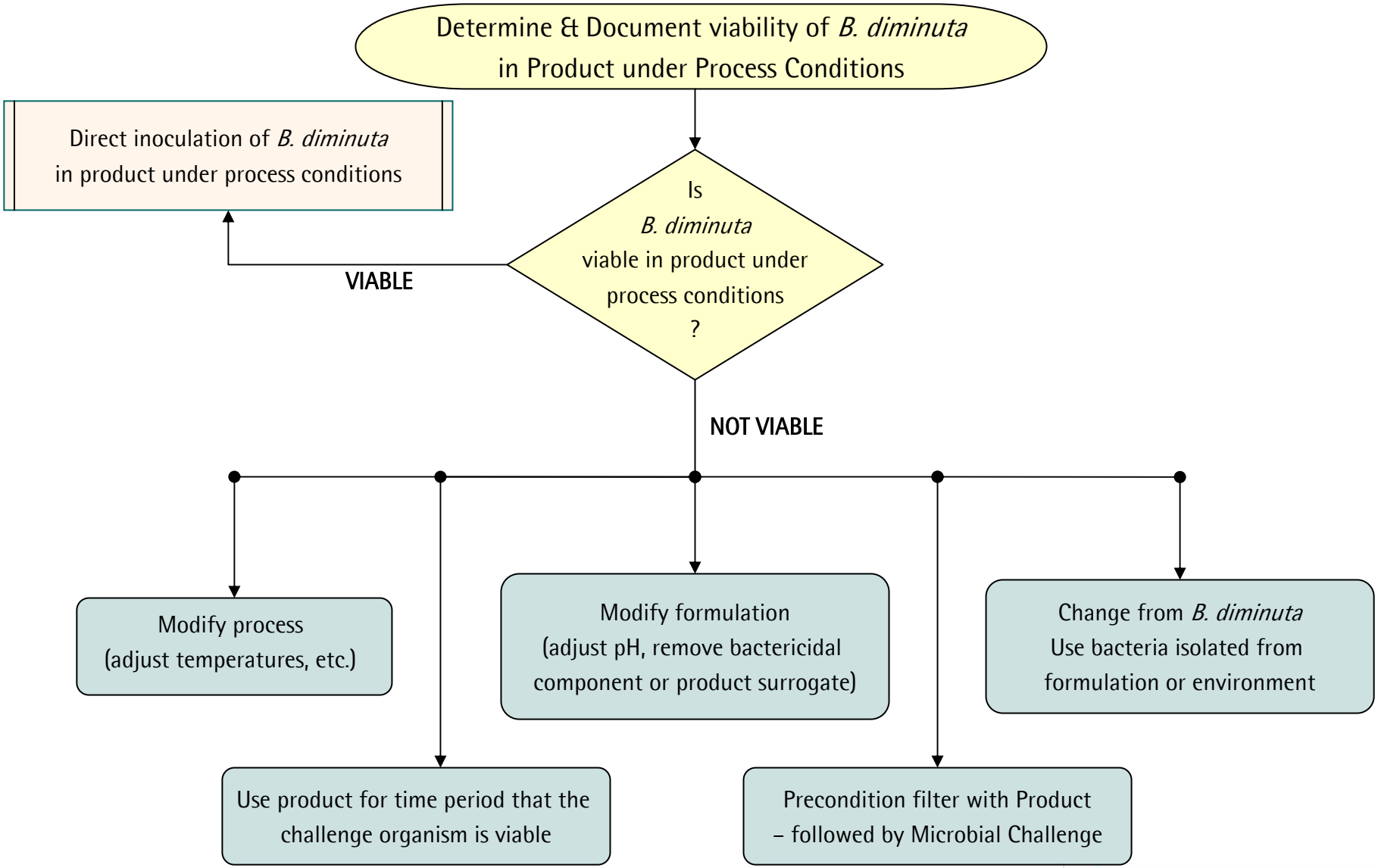
BCT Method 2 (Process Modification)



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BCT Strategies – Method 2 (Process Modification)

- Temperature of ≥ 40°C supports mortality rate of *B. diminuta*

- Check viability of test bacteria in the product solution at lower temperature

→ Direct inoculation into product solution might be possible at 35°C

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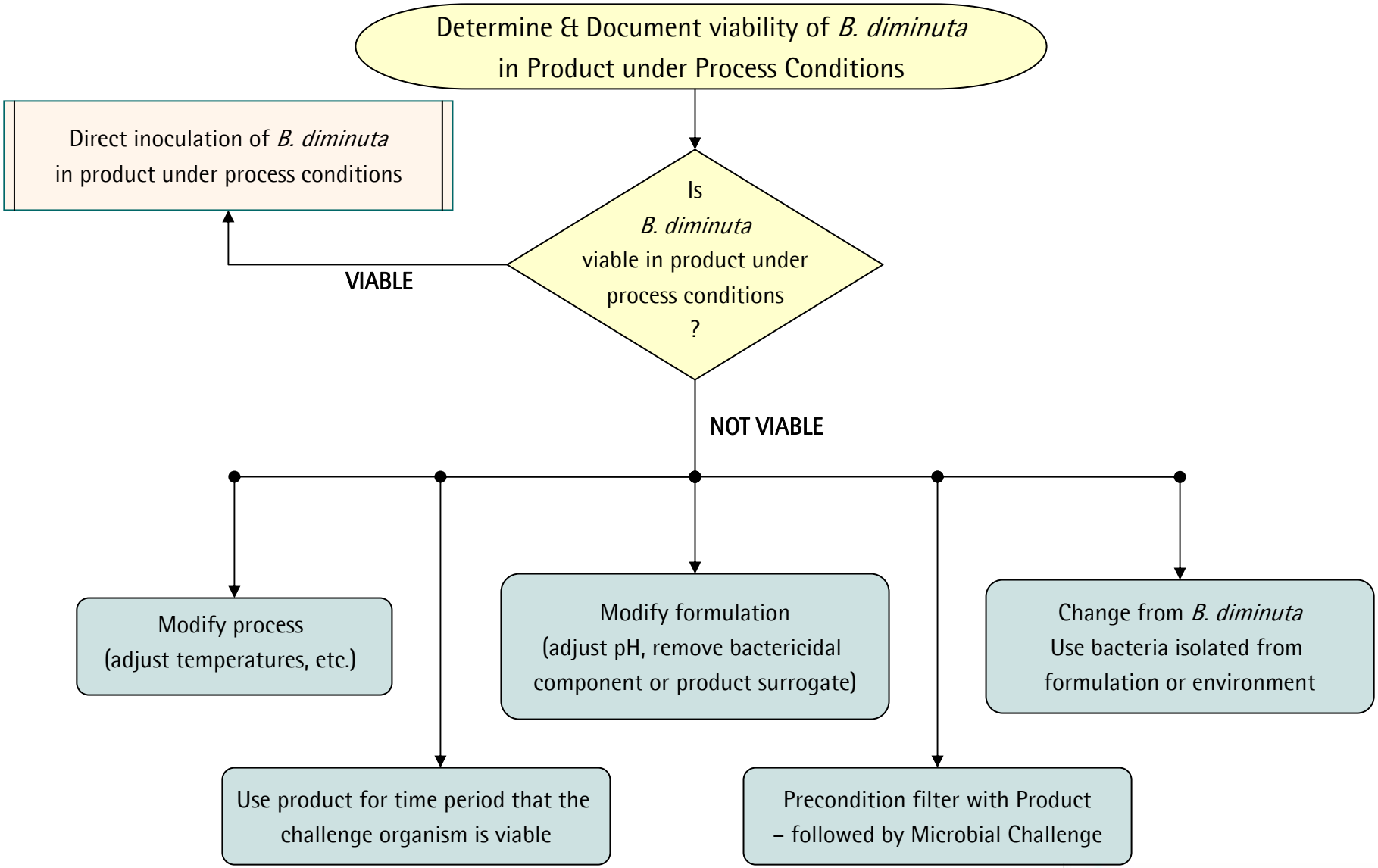
BCT Strategies Method 3 (Time Period Challenge)



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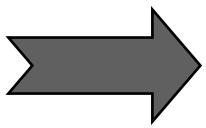
BCT Strategies – Method 3 (Time Period Challenge)

Solutions	Test Exposure Times			
	5 min.	30 min.	60 min.	180 min.
Standard (0.1% peptone water)	124	117	122	122
Product Solution	111	90	18	0



BCT by direct inoculation

Contact time bacteria / test solution max. 30 min.

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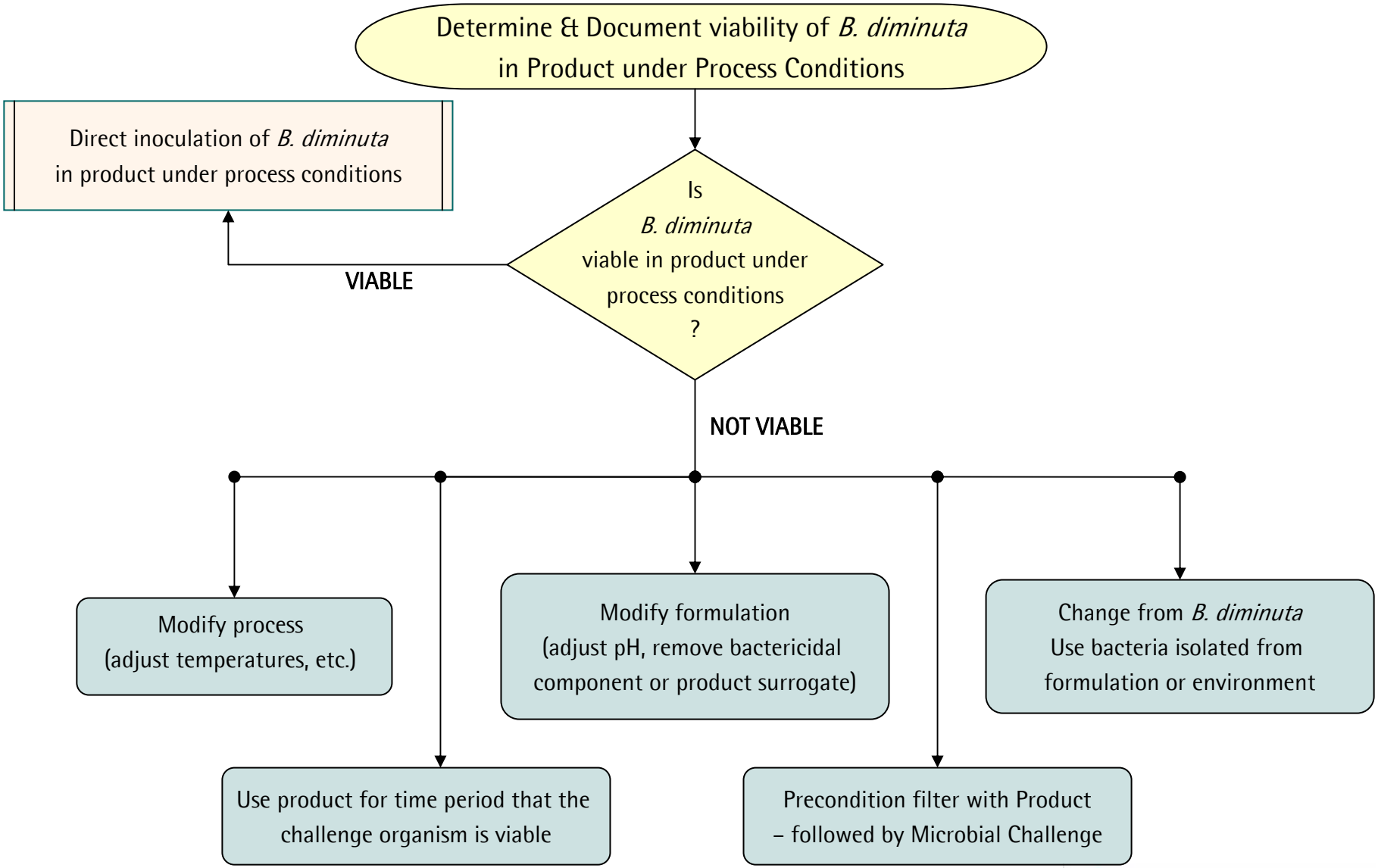
BCT Strategies –Method 4 (Formulation Modification)



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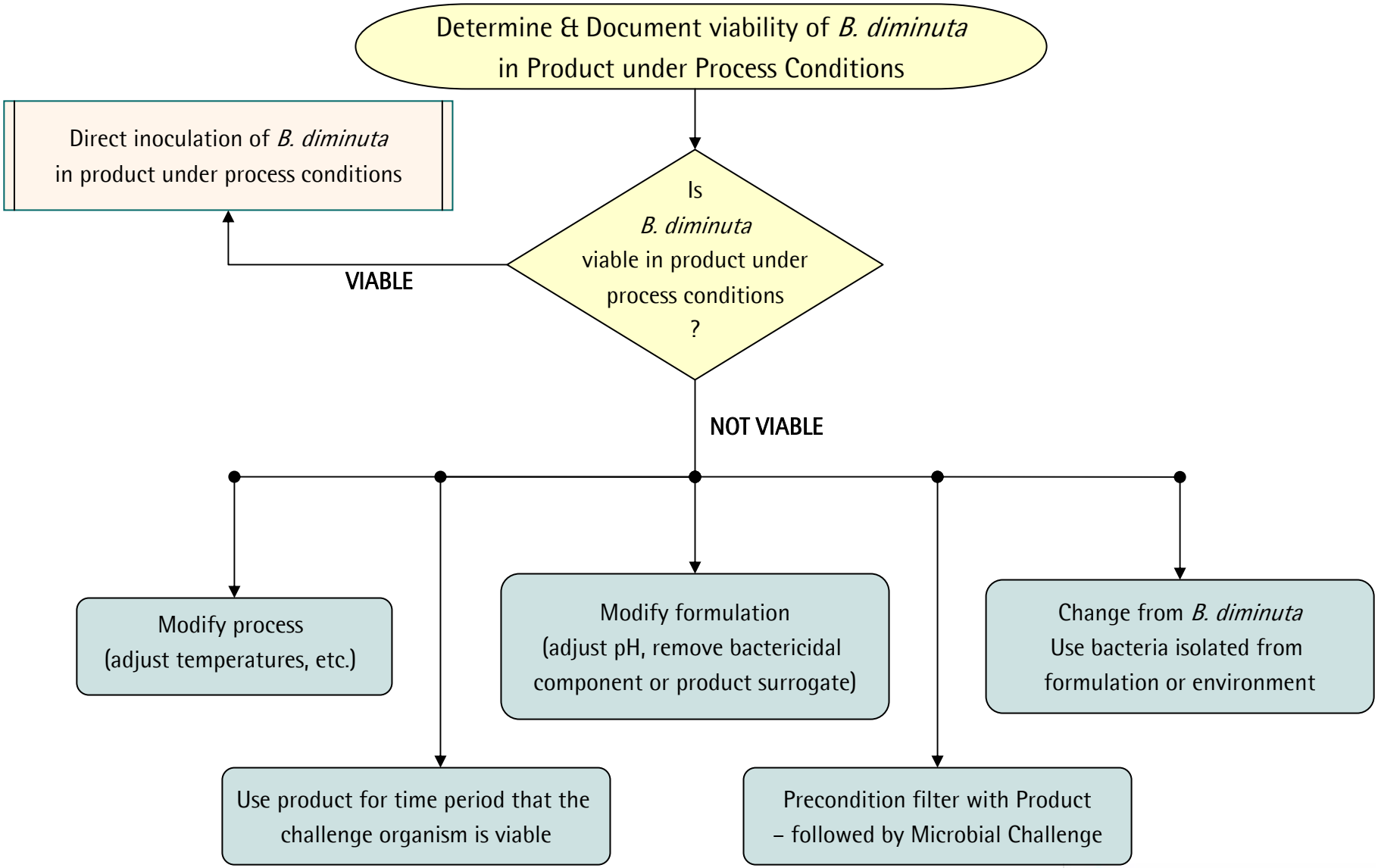
BCT Strategies –Method 5 (Preconditioning)



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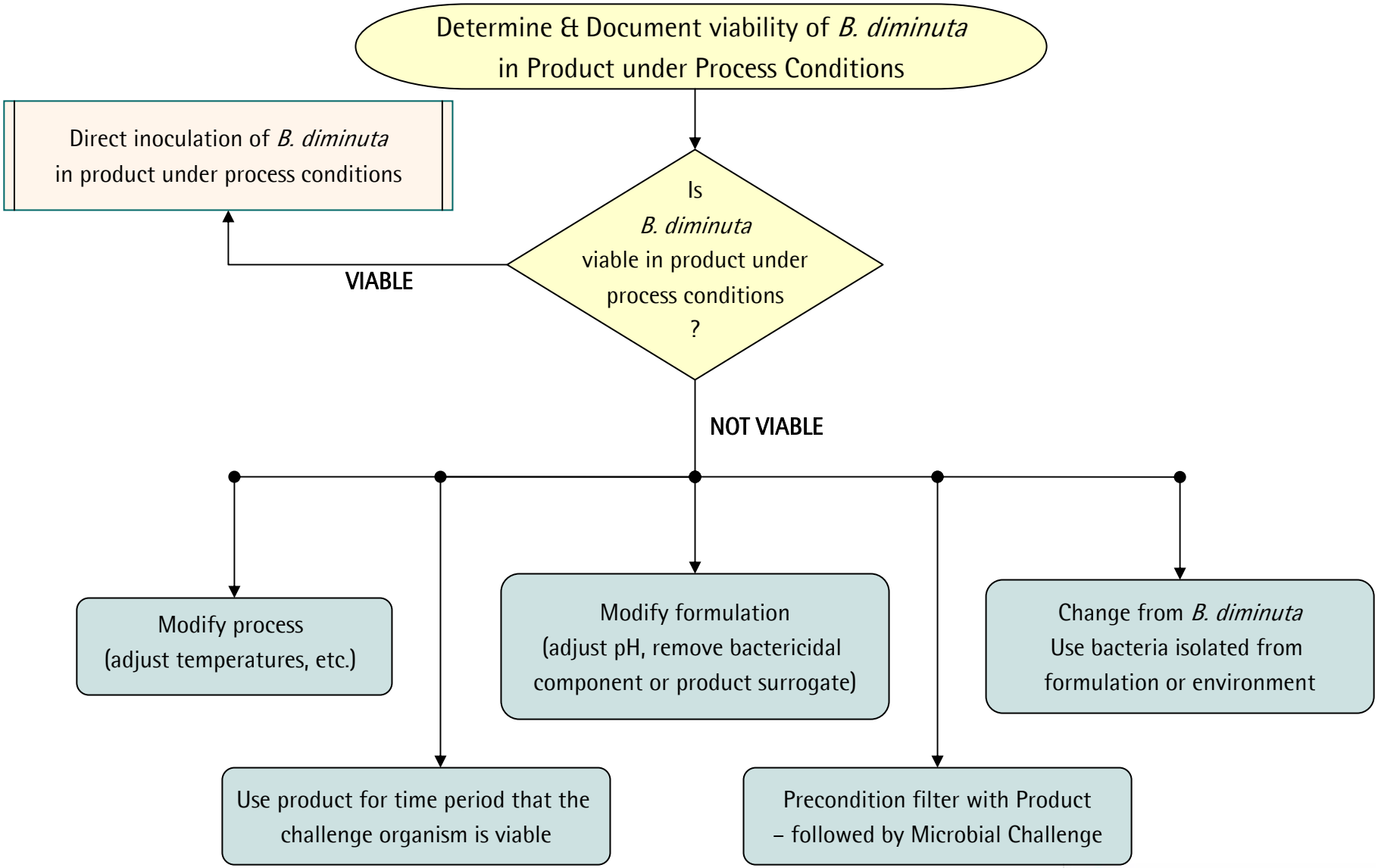
BCT Strategies – Method 5 (Preconditioning)

Solutions	Test Exposure Times			
	5 min.	15 min.	30 min.	60 min.
Standard (0.1% peptone water)	201	206	209	222
Product Solution	0	0	0	0

→ Indirect BCT by separate filtration of test solution and bacteria

BCT Strategies –Method 6 (Bioburden Isolate)



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BCT Strategies –Method 6 (Bioburden Isolate)

BCT with bioburden isolate

- Reproducible growth and size of bacteria is required
- Growth in required concentration for BCT must be possible

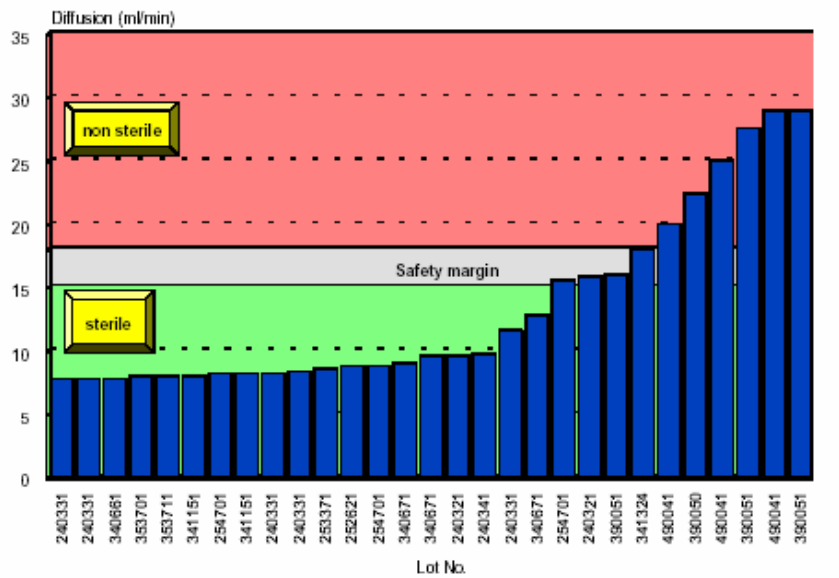
Filter Integrity

Integrity Test Correlation

Destructive Methods

For producers; applied to determined limits:

Bacteria-Challenge-Test (according to ASTM)



Non-Destructive Methods

For users; applied to every sterilizing filter *before* and after each filtration:

- Bubble Point Test
- Diffusion Test
- Multipoint Diffusion Test
- Pressure Decay Test
- Water Intrusion Test (WIT)

Direct correlation of diffusion, bubble point, and intrusion-limit values to bacteria-challenge test.

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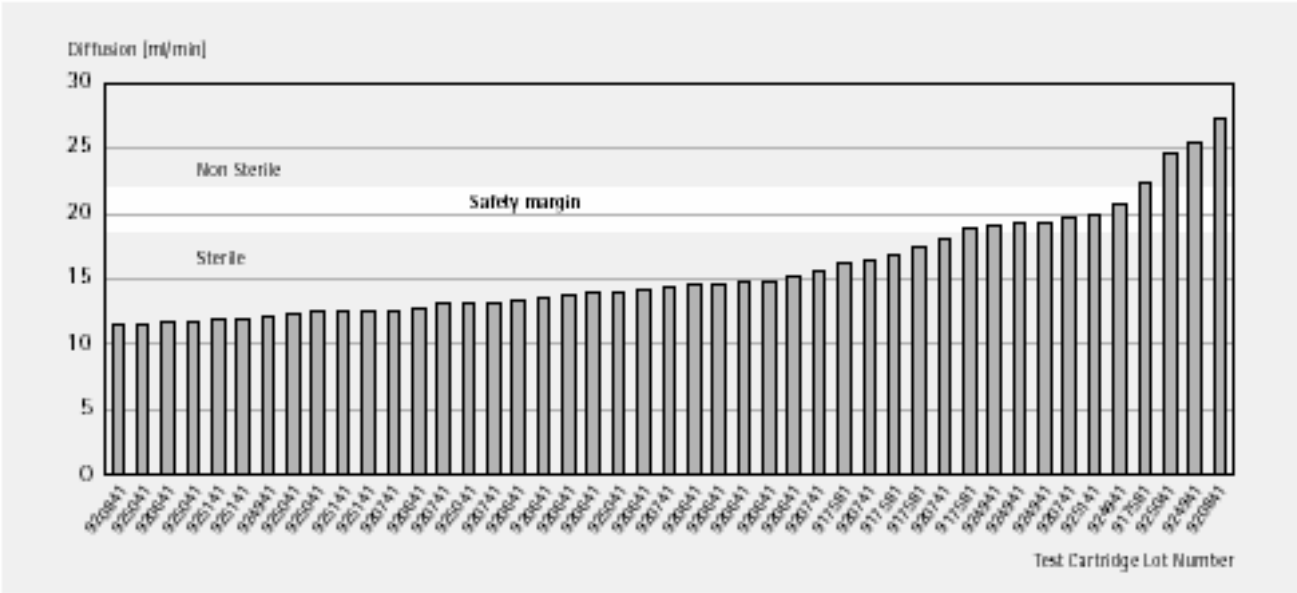
Integrity Test Correlation

5.3 **Diffusion Test Limits**

5.3.1 **Cartridges 0.2 µm (10"|250 mm)**

Note
Since most of the filters tested during the validation studies had low diffusion values and produced a sterile filtrate, the following data is a sampling from all filters tested during the validation testing indicating results near the diffusion|sterile filtrate limits.

Cartridges (10"|250 mm)

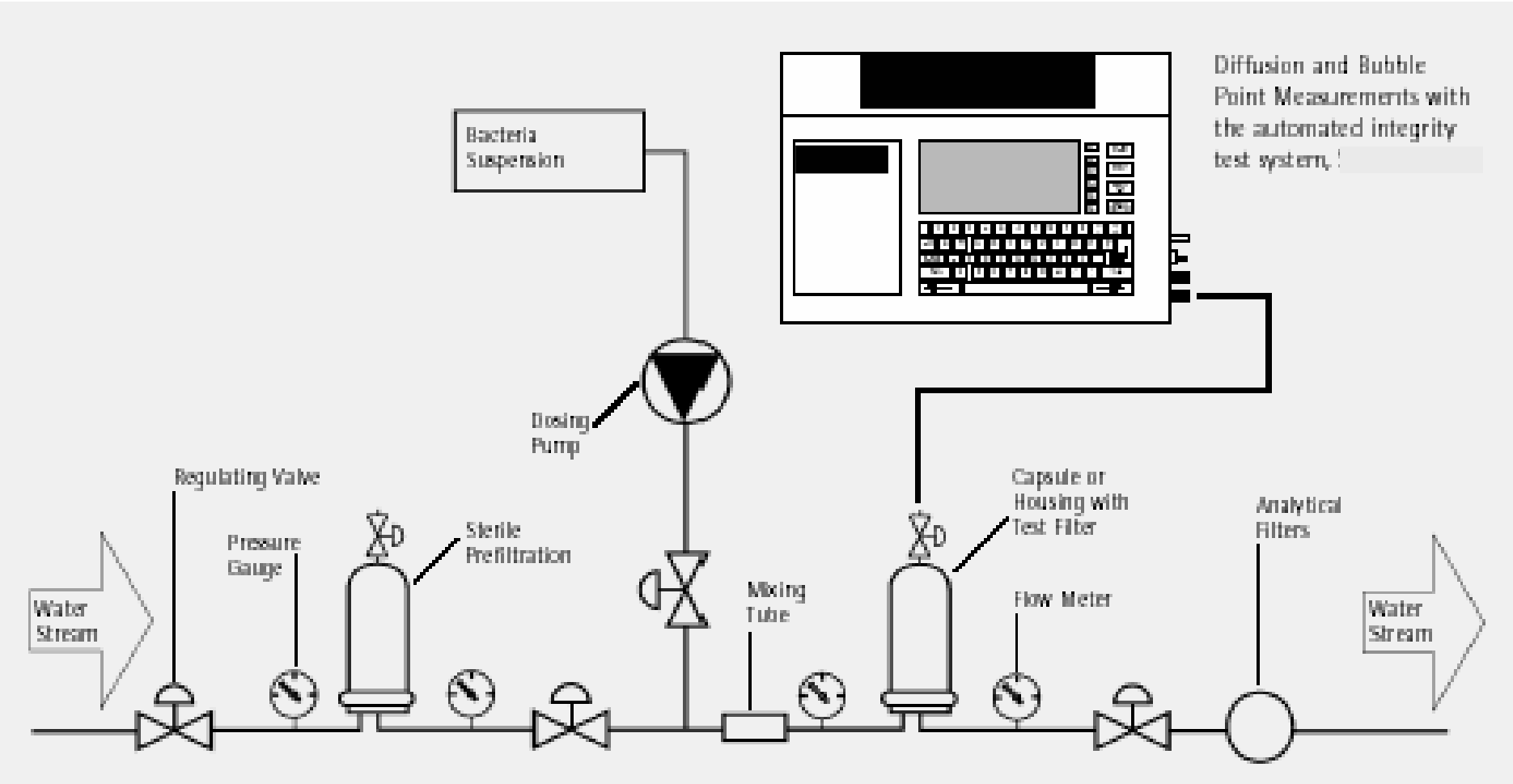


Lot Number	Diffusion [ml/min]	Bioburden [CFU]*	Filtrate Quality
920841	11.5	1.12×10^{11}	sterile
925041	11.6	1.70×10^{11}	sterile
920641	11.7	6.12×10^{10}	sterile
925041	11.8	1.70×10^{11}	sterile
925141	11.9	1.78×10^{11}	sterile
925141	12.0	1.78×10^{11}	sterile
924941	12.1	1.12×10^{11}	sterile
925041	12.3	1.70×10^{11}	sterile
925041	12.5	1.78×10^{11}	sterile
925141	12.5	1.28×10^{11}	sterile
925141	12.5	1.78×10^{11}	sterile
920741	12.6	2.63×10^{11}	sterile
920641	12.7	7.20×10^{10}	sterile
920741	13.1	2.63×10^{11}	sterile
925041	13.1	1.66×10^{11}	sterile
920741	13.2	2.63×10^{11}	sterile
920641	13.4	7.20×10^{10}	sterile
920641	13.6	6.12×10^{10}	sterile
920641	13.7	7.20×10^{10}	sterile
920641	13.9	6.12×10^{10}	sterile
920641	13.9	1.66×10^{11}	sterile
920641	14.1	7.20×10^{10}	sterile
920741	14.4	2.63×10^{11}	sterile
920641	14.5	6.12×10^{10}	sterile
920641	14.6	2.60×10^{11}	sterile
920641	14.9	6.12×10^{10}	sterile
920641	14.9	6.12×10^{10}	sterile
920641	15.3	7.20×10^{10}	sterile
920741	15.7	2.92×10^{11}	sterile
917581	16.2	1.78×10^{11}	sterile
920741	16.5	2.63×10^{11}	sterile
917581	16.8	1.78×10^{11}	sterile
917581	17.5	1.78×10^{11}	sterile
920741	18.0	1.01×10^{11}	sterile
917581	18.9	1.78×10^{11}	sterile
924941	19.1	1.12×10^{11}	sterile
924941	19.3	1.66×10^{11}	sterile
924941	19.4	1.66×10^{11}	sterile
920741	19.8	1.01×10^{11}	sterile
925141	19.9	1.28×10^{11}	sterile
924941	20.8	1.66×10^{11}	sterile
917581	22.3	1.78×10^{11}	non sterile
925041	24.6	1.66×10^{11}	non sterile
924941	25.5	1.66×10^{11}	non sterile
920841	27.3	1.12×10^{11}	non sterile

* CFU – Colony Forming Units

Bacterial Challenge Test

Test Set-up



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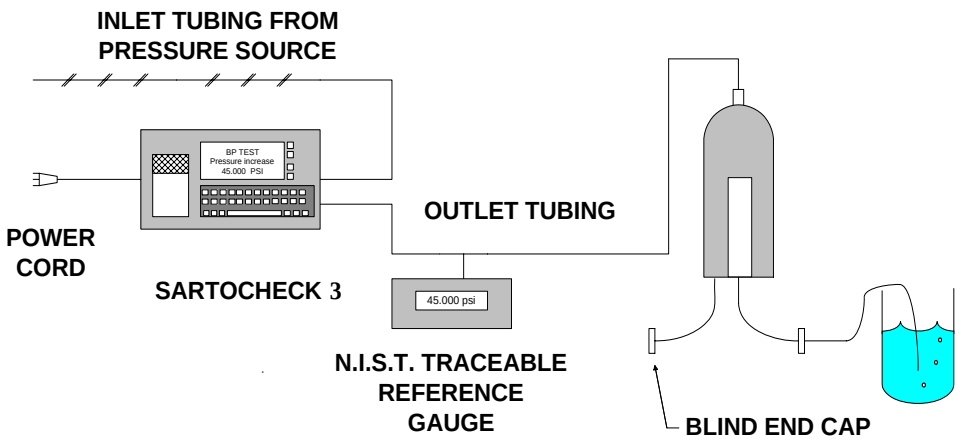
Product Wet Integrity Testing

Bubble Point

Filter membrane is wetted with the product. Pressure is applied on the upstream side of the filter. The pressure at which a stream of air bubbles is detected downstream of the filter is known as the Minimum Bubble Point of the filter.



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Product Specific Integrity Test – Bubble Point


a

b

c

Flush with Water

Test a, b, c

Calculate average, WBP_{avg}

Flush with Product

Test a, b, c

Calculate average, PBP_{avg}

PBPavg/WBPavg

e.g. 46 psi x 36 psi/49 psi

PBPmin = 46 psi x 0.73

PBPmin = 33.79 psi

PBPmin = WBPmin x Correction Factor

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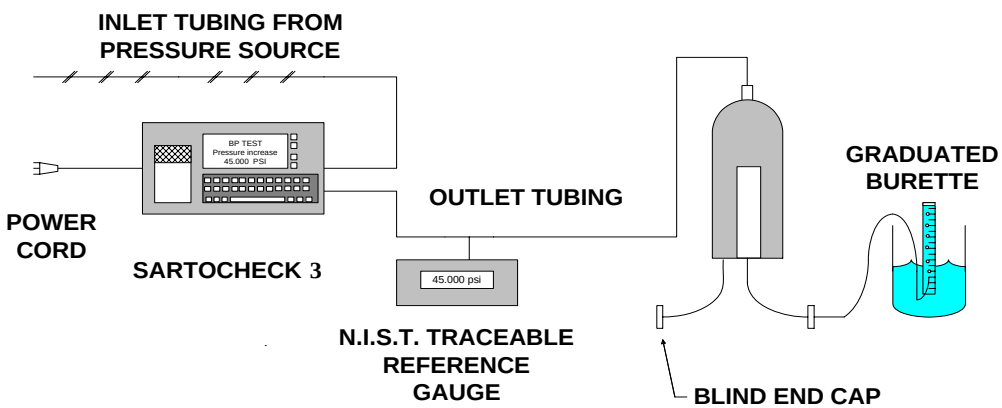
Product Wet Integrity Testing

Diffusive Flow

Depends mainly on the solubility of the test gas in the wetting fluid in addition to temperature and test pressure. The filter membrane pores are wetted with fluid and a gas pressure less than the BP is applied. Due to differential pressure, gas diffuses through the fluid in the pores and is quantified as downstream flow in mL/min.



NOTE: BEAKER AND INVERTED BURETTE MAY BE SUBSTITUTED WITH A N.I.S.T. TRACEABLE MASS FLOWMETER OR ROTAMETER.

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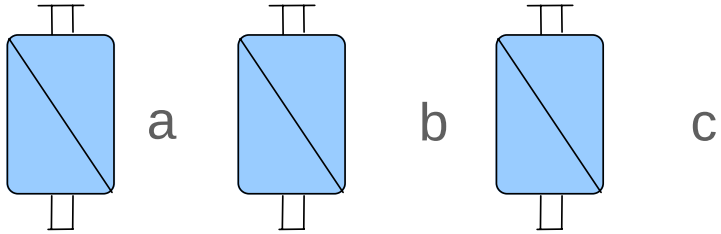
Product Specific Integrity Test – Diffusive Flow



DF_{PW}/DF_{WW}

e.g. 15 ml/min x 16 ml/min/9 ml/min

DFL_{PW} = 15 ml/min x 1.77

DFL_{PW} = 26.5 ml/min

Flush with Water

Test a, b, c with MTP_{WW}

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

Calculate average, DF_{WW}

Flush with Product

Test a, b, c with TP_{PW}

Calculate average, DF_{PW}

$DFL_{PW} = DFL_{WW} \times$ Correction Factor

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Integrity Test Failure

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

Determines when a filter has to be classified as failed

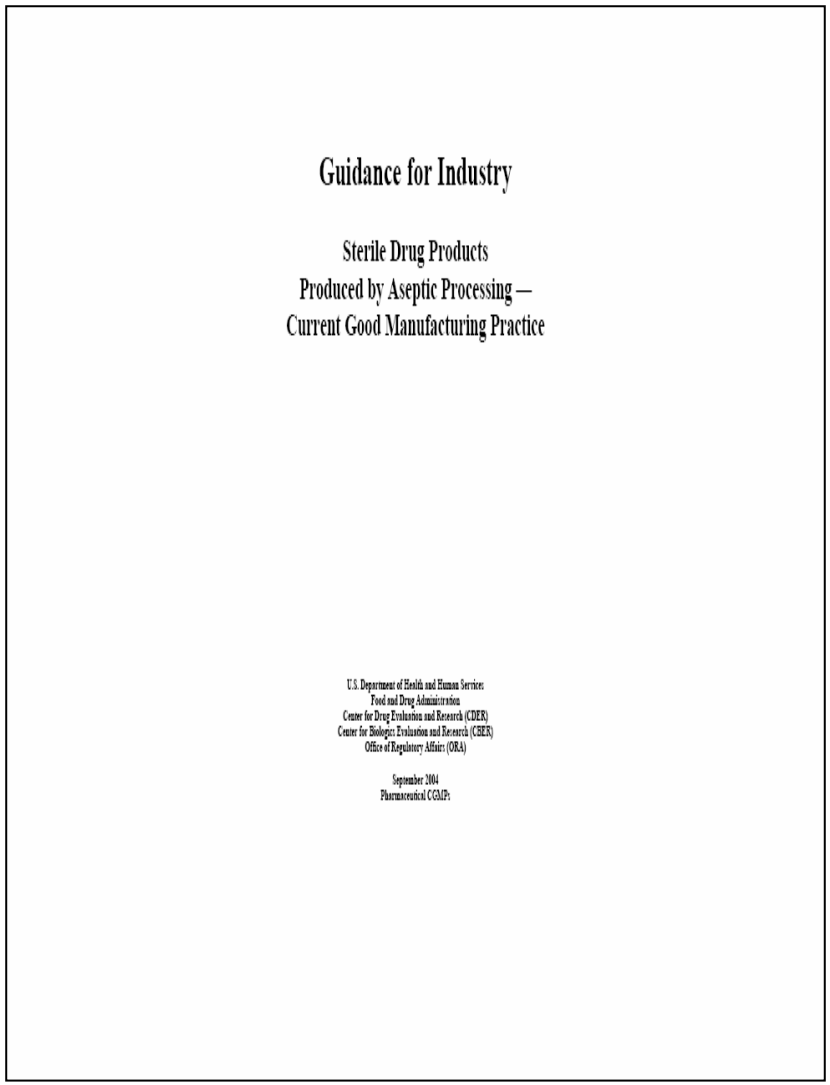
Filter fails first time → Measurements & Actions

Filter fails second time → Wetting with solvent

Filter fails third time = Filter failed

Guidance

FDA Guidance on Aseptic Processing – CGMP



Guidance for Industry

Sterile Drug Products
Produced by Aseptic Processing –
Current Good Manufacturing Practice

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Regulatory Affairs (ORA)

September 2004
Pharmaceutical CGMPs

Final Guidance released on September 29, 2004, which replaces the 1987 Guidance

Describes the integrity test requirements of liquid and air filters, as well as the validation requirements of liquid filters

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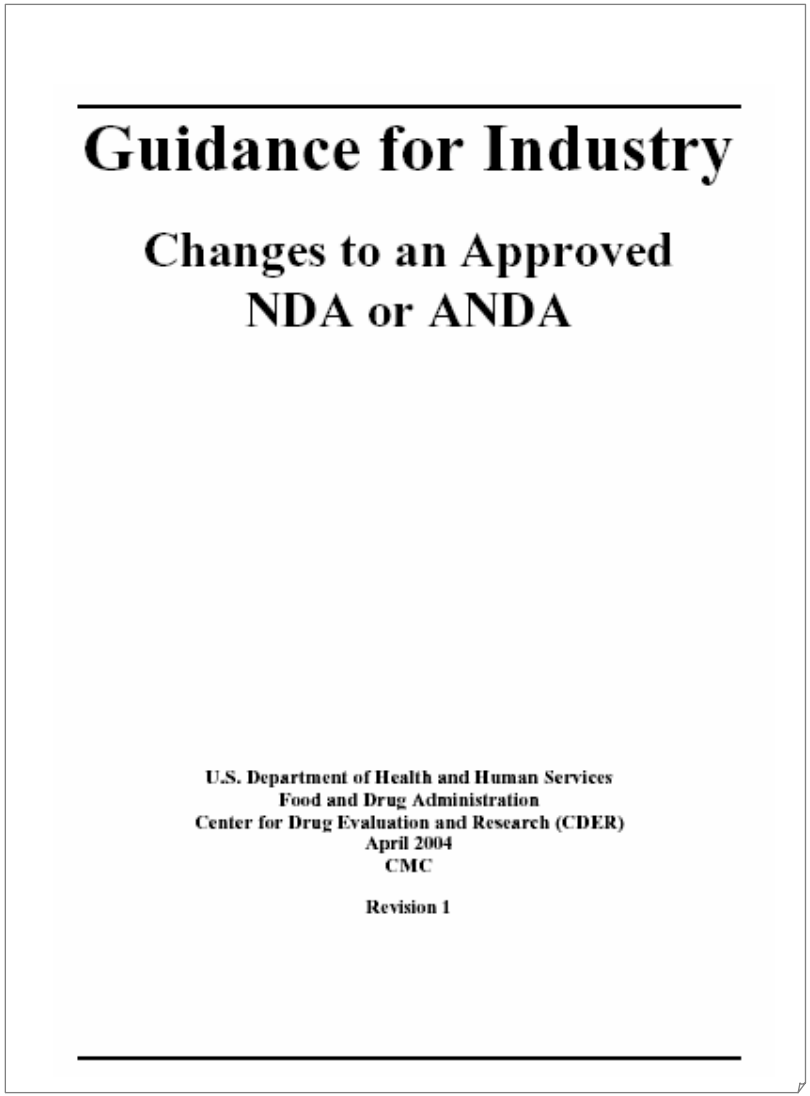
FDA



Guidance for Industry

Changes to an Approved NDA or ANDA

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 2004
CMC

Revision 1

Post approval Change Guidance for chemical entities (Revision).

Describes which changes in filtration steps are considered moderate (CBE 30) or major (Post Approval Supplement) changes.

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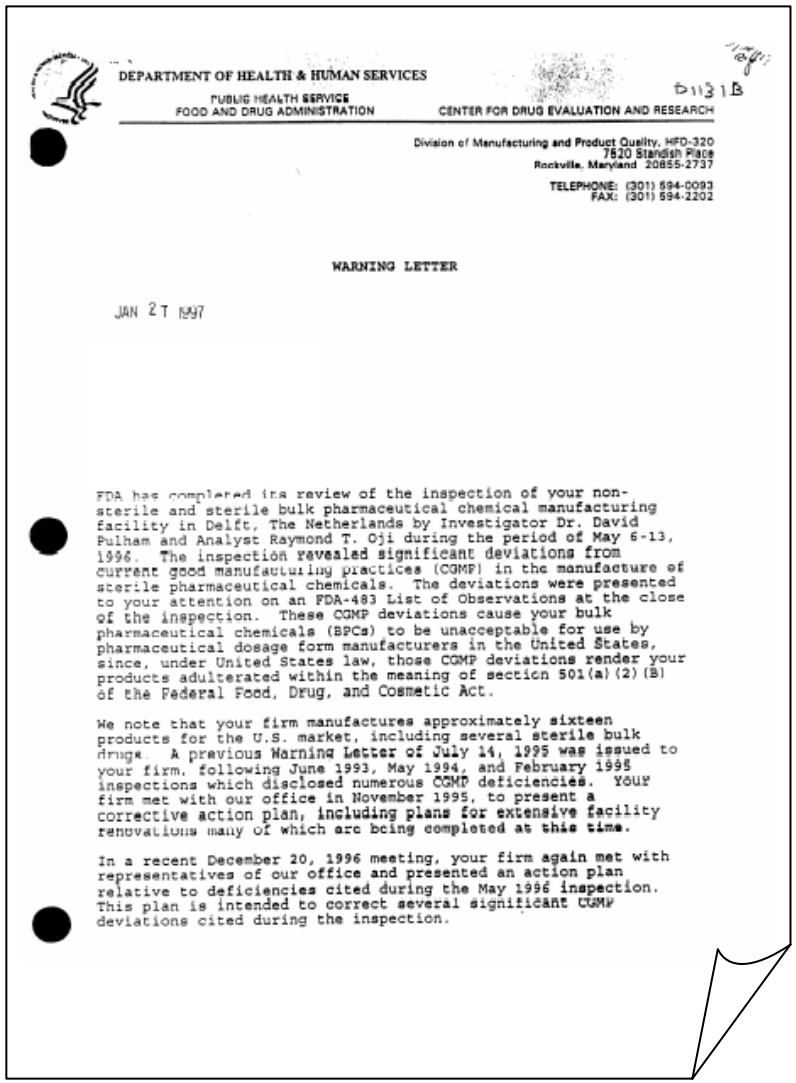
FDA



DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

D1131B

Division of Manufacturing and Product Quality, HFD-320
7520 Standish Place
Rockville, Maryland 20855-2737

TELEPHONE: (301) 594-0093
FAX: (301) 594-2202

WARNING LETTER

JAN 27 1997

FDA has completed its review of the inspection of your non-sterile and sterile bulk pharmaceutical chemical manufacturing facility in Delft, The Netherlands by Investigator Dr. David Pulham and Analyst Raymond T. Oji during the period of May 6-13, 1996. The inspection revealed significant deviations from current good manufacturing practices (CGMP) in the manufacture of sterile pharmaceutical chemicals. The deviations were presented to your attention on an FDA-483 List of Observations at the close of the inspection. These CGMP deviations cause your bulk pharmaceutical chemicals (BPCs) to be unacceptable for use by pharmaceutical dosage form manufacturers in the United States, since, under United States law, those CGMP deviations render your products adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

We note that your firm manufactures approximately sixteen products for the U.S. market, including several sterile bulk drugs. A previous Warning Letter of July 14, 1995 was issued to your firm, following June 1993, May 1994, and February 1995 inspections which disclosed numerous CGMP deficiencies. Your firm met with our office in November 1995, to present a corrective action plan, including plans for extensive facility renovations many of which are being completed at this time.

In a recent December 20, 1996 meeting, your firm again met with representatives of our office and presented an action plan relative to deficiencies cited during the May 1996 inspection. This plan is intended to correct several significant CGMP deviations cited during the inspection.

- Warning letters and inspection guides are always good to review – learn from the mistakes and from the training

- Listings are posted on FDA website as prescribed by the FOI Act.

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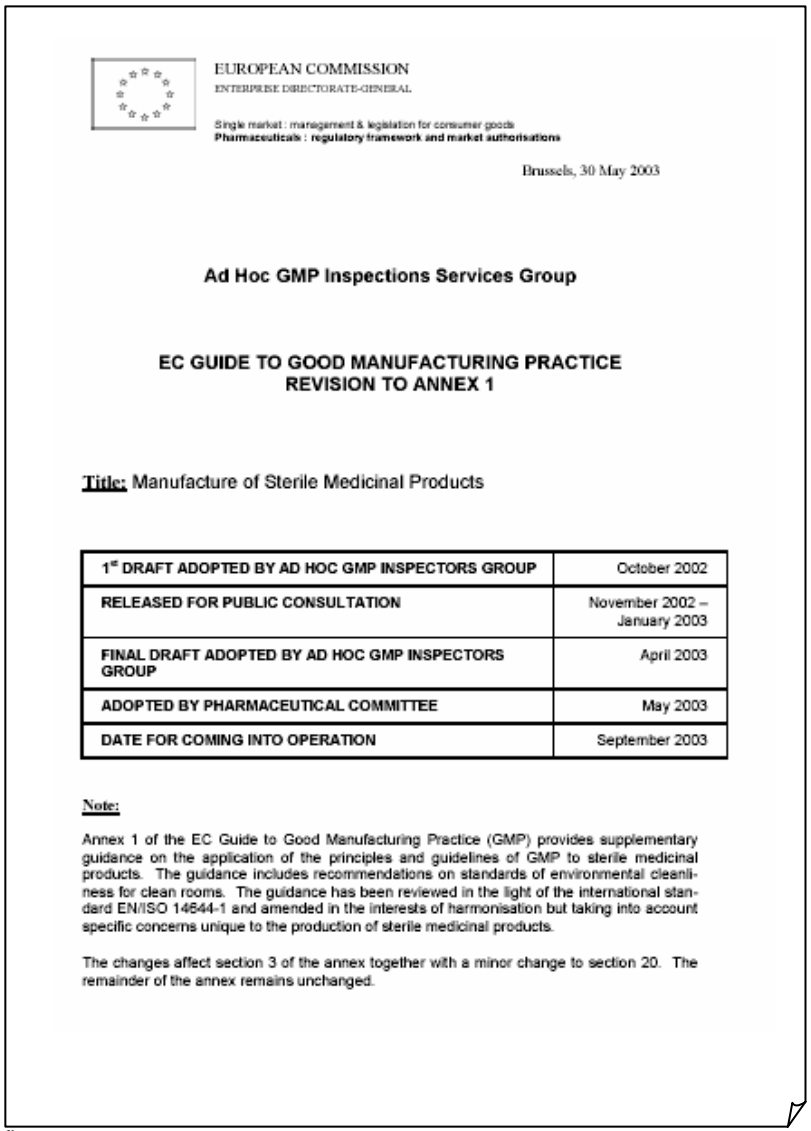
EC Guide to GMP of Sterile Medicinal Products



EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market : management & legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Brussels, 30 May 2003

Ad Hoc GMP Inspections Services Group

EC GUIDE TO GOOD MANUFACTURING PRACTICE
REVISION TO ANNEX 1

Title: Manufacture of Sterile Medicinal Products

1st DRAFT ADOPTED BY AD HOC GMP INSPECTORS GROUP	October 2002
RELEASED FOR PUBLIC CONSULTATION	November 2002 – January 2003
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ADOPTED BY PHARMACEUTICAL COMMITTEE	May 2003
DATE FOR COMING INTO OPERATION	September 2003

Note:

Annex 1 of the EC Guide to Good Manufacturing Practice (GMP) provides supplementary guidance on the application of the principles and guidelines of GMP to sterile medicinal products. The guidance includes recommendations on standards of environmental cleanliness for clean rooms. The guidance has been reviewed in the light of the international standard EN/ISO 14644-1 and amended in the interests of harmonisation but taking into account specific concerns unique to the production of sterile medicinal products.

The changes affect section 3 of the annex together with a minor change to section 20. The remainder of the annex remains unchanged.

EC cGMP Guidance,
Revision of Annex 1.

Describes sterilization by filtration, integrity test needs, some validation topics.

Important document to know for exporting.

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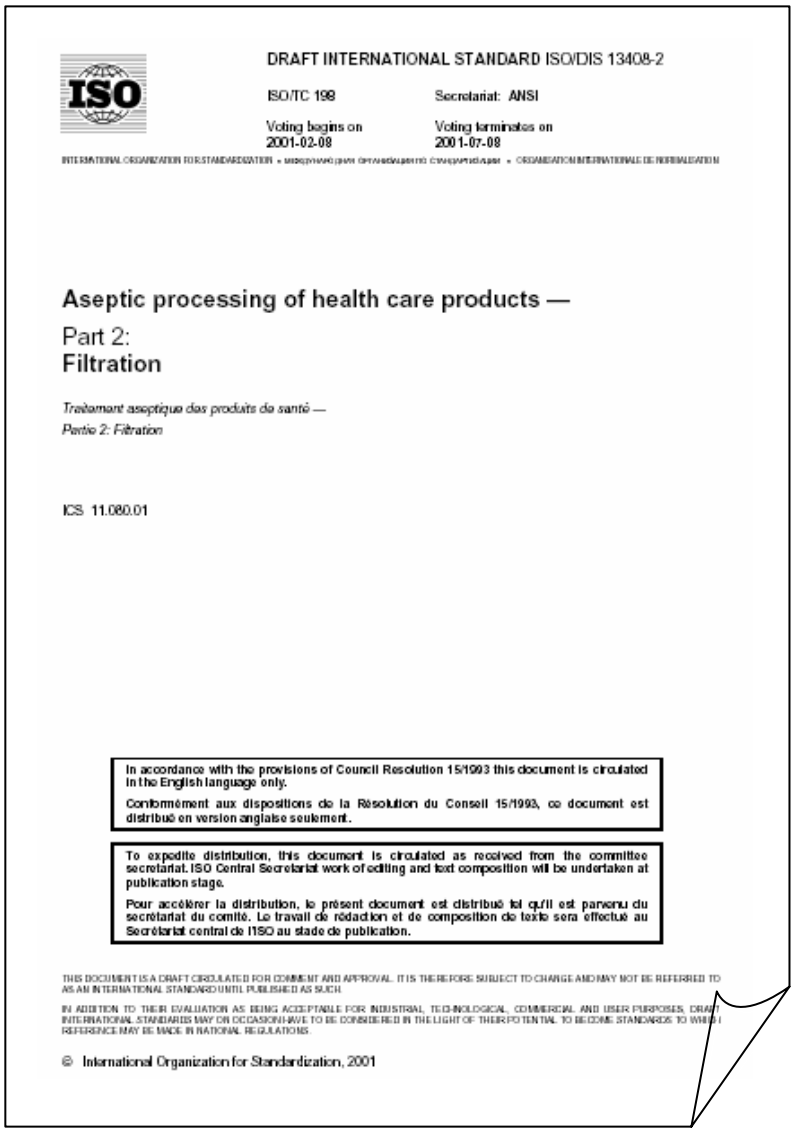
ISO: AP of Health Care Products – Filtration



DRAFT INTERNATIONAL STANDARD ISO/DIS 13408-2

ISO/TC 198 Secretariat: ANSI

Voting begins on 2001-02-08 Voting terminates on 2001-07-08

INTERNATIONAL ORGANIZATION FOR STANDARDIZATION • МЕЖДУНАРОДНАЯ ОРГАНИЗАЦИЯ ПО СТАНДАРТИЗАЦИИ • ORGANISATION INTERNATIONALE DE NORMALISATION

Aseptic processing of health care products —

Part 2:
Filtration

Traitement aseptique des produits de santé —
Partie 2: Filtration

ICS 11.080.01

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To expedite distribution, this document is circulated as received from the committee secretariat. ISO Central Secretariat work of editing and text composition will be undertaken at publication stage.

Pour accélérer la distribution, le présent document est distribué tel qu'il est parvenu du secrétariat du comité. Le travail de rédaction et de composition de texte sera effectué au Secrétariat central de l'ISO au stade de publication.

THIS DOCUMENT IS A DRAFT CIRCULATED FOR COMMENT AND APPROVAL. IT IS THEREFORE SUBJECT TO CHANGE AND MAY NOT BE REFERRED TO AS AN INTERNATIONAL STANDARD UNTIL PUBLISHED AS SUCH.

IN ADDITION TO THEIR EVALUATION AS BEING ACCEPTABLE FOR INDUSTRIAL, TECHNOLOGICAL, COMMERCIAL AND USER PURPOSES, DRAFT INTERNATIONAL STANDARDS MAY ON OCCASION HAVE TO BE CONSIDERED IN THE LIGHT OF THEIR POTENTIAL TO BECOME STANDARDS TO WHICH REFERENCE MAY BE MADE IN NATIONAL REGULATIONS.

Released ISO Guidance, part 2. on filtration.

Describes filtration requirements, validation and integrity test needs thoroughly for liquid and air filters.

A good document to have, with thorough descriptions.

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PDA

PDA Technical Report #26.

The most thorough and descriptive document on the topic of liquid sterilizing filtration.

This document is a must have, must read and must understand as it is used by QC and regulators worldwide.

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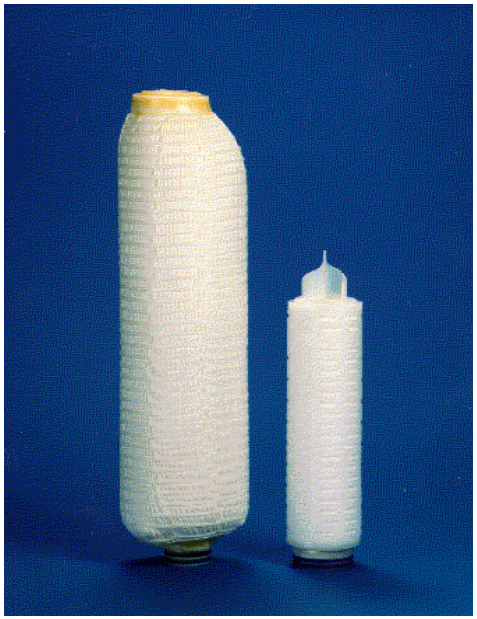
Conclusion



Regulatory Requirement

Industry Requirement

Filter Validation

- Viability Testing
- Bacterial Challenge Testing
- Chemical Compatibility
- Analysis of Extractables
- Product Integrity Testing
- Plant and Process Surveys
- Systems and Integrity Tester Validation
- Process Related Validation Studies

END