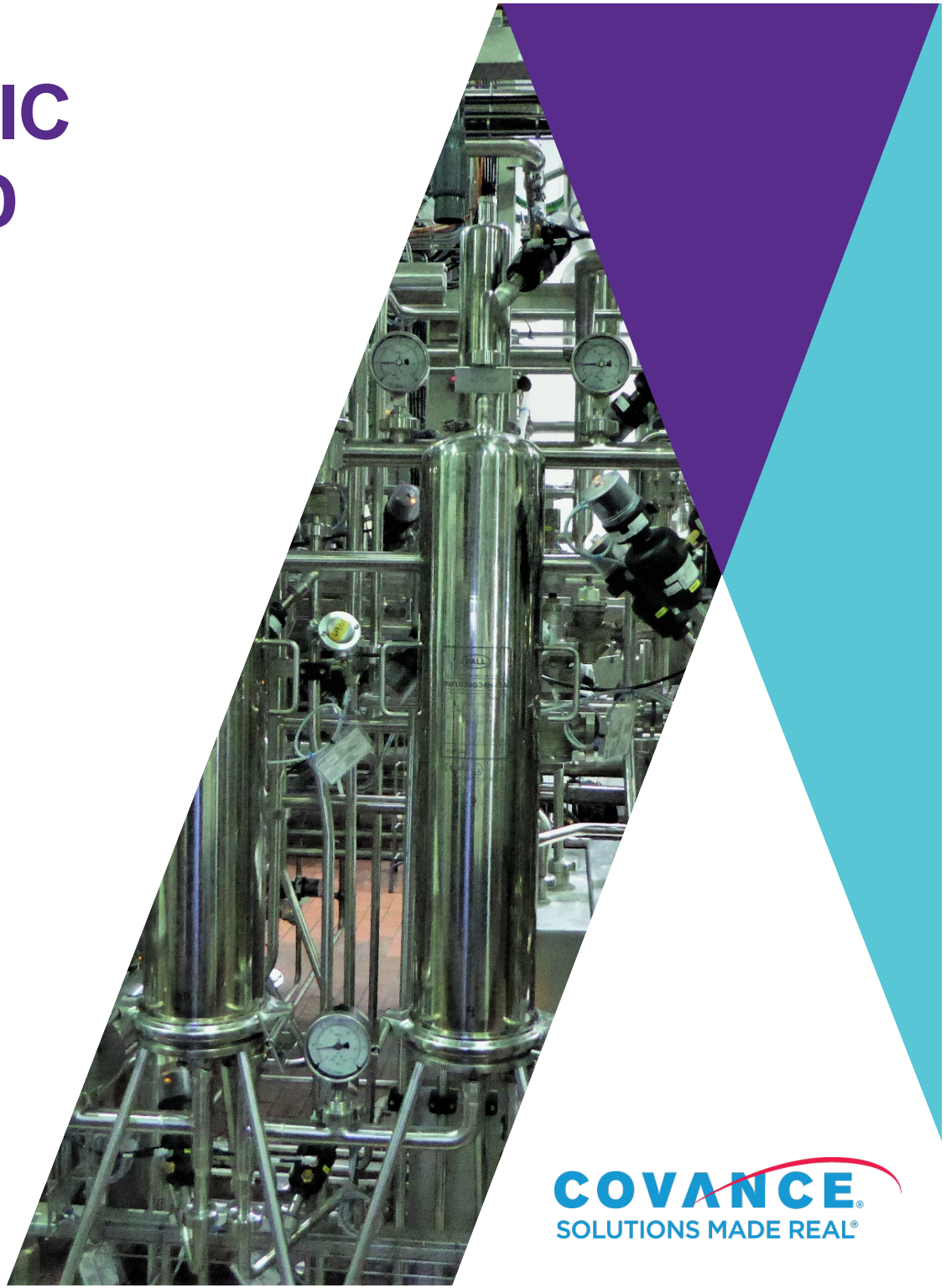
BASICS ON ASEPTIC TECHNOLOGY AND VALIDATION

IFTPS Annual Meeting 2018

San Antonio, TX



André Rehkopf

Covance Food Solutions

Madison, WI ● Anaheim, CA ● Battle Creek, MI ● Greenfield, IN ● Ithaca, NY ● Livermore, CA ● Naples, FL ● Plymouth, MN ● Harrogate, UK ● Reading, UK ● Singapore

Copyright © 2018 Covance. All Rights Reserved

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Contents

- Your product and applicable regulations
- Process design and requirements
  - Principles of thermo-bacteriology and thermal processing
- Aseptic processing and filling systems
  - Basic components
  - Regulatory requirements
- Microbiological validation of an aseptic filling process
  - Why, what, when, how?
  - FSO, control measures, performance criteria

CONFIDENTIAL

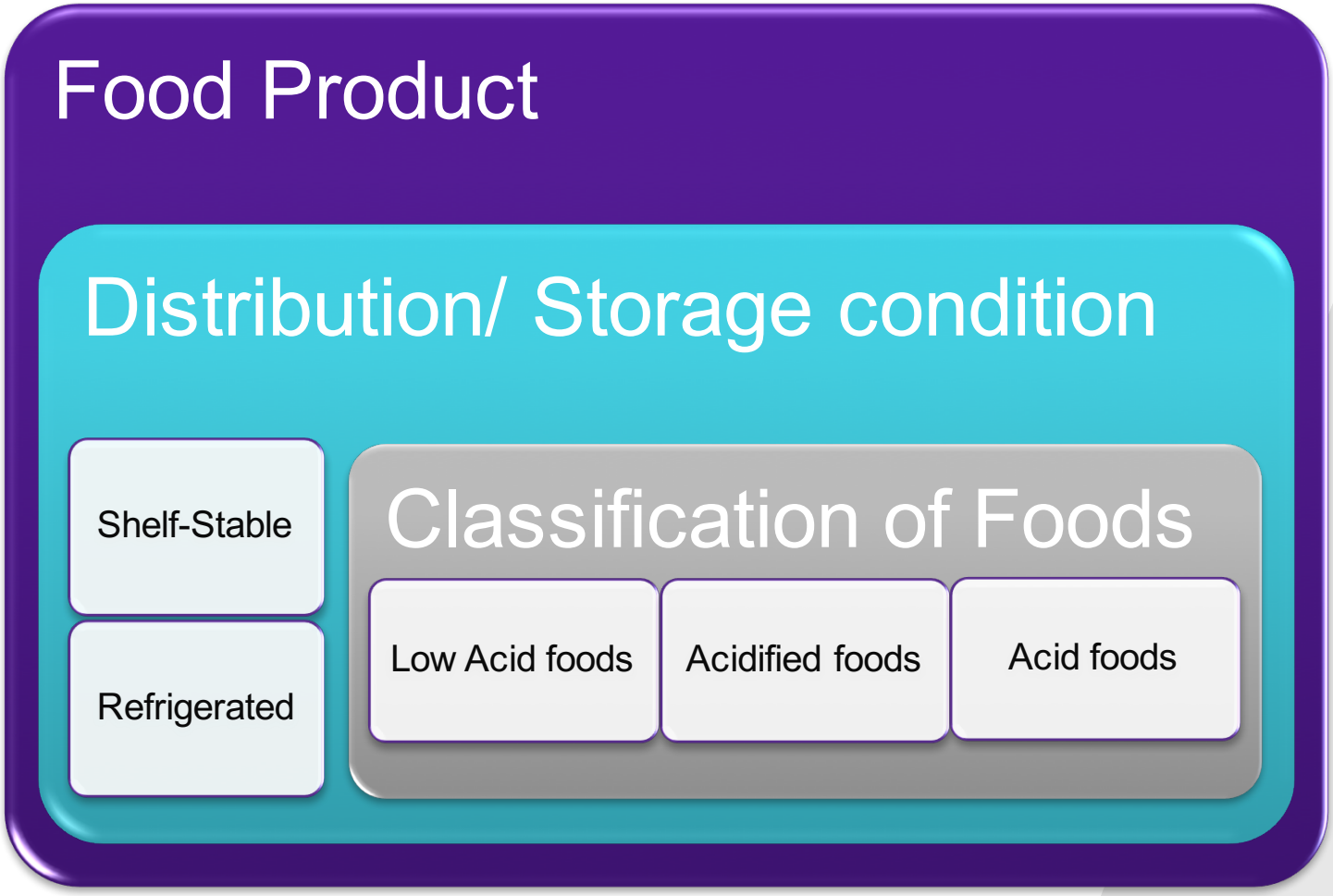
COVANCE
SOLUTIONS MADE REAL®

Applicable Regulations: Involved US Regulatory Agencies

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Applicable Regulations: FDA classification of Foods



CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Applicable Regulations: FDA classification of Foods

Low-Acid foods

Any foods, other than alcoholic beverages

pH > 4.6

a_w > 0.85

Acidified foods

Low-acid foods to which acid(s) or acid foods are added

pH ≤ 4.6

a_w > 0.85

Acid foods

Foods that have a natural

pH ≤ 4.6

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Applicable Regulations:

21 CFR

108	Emergency Permit Facility registration, process filing
110	Good Manufacturing Practices
113	Thermally Processed Low-acid Foods 113.40g – aseptic regulations
114	Acidified Foods
117	cGMP Hazard Analysis and Risk-Based Preventive Controls of Human Food
120	Juice HACCP
165/129	Bottled Water

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Process Design: Definitions

- Commercial sterility

Condition when equipment and containers are free of viable microorgansims of public health significance as well as those of non-health significance which are capable of reproducing under normal conditions of storage and distribution

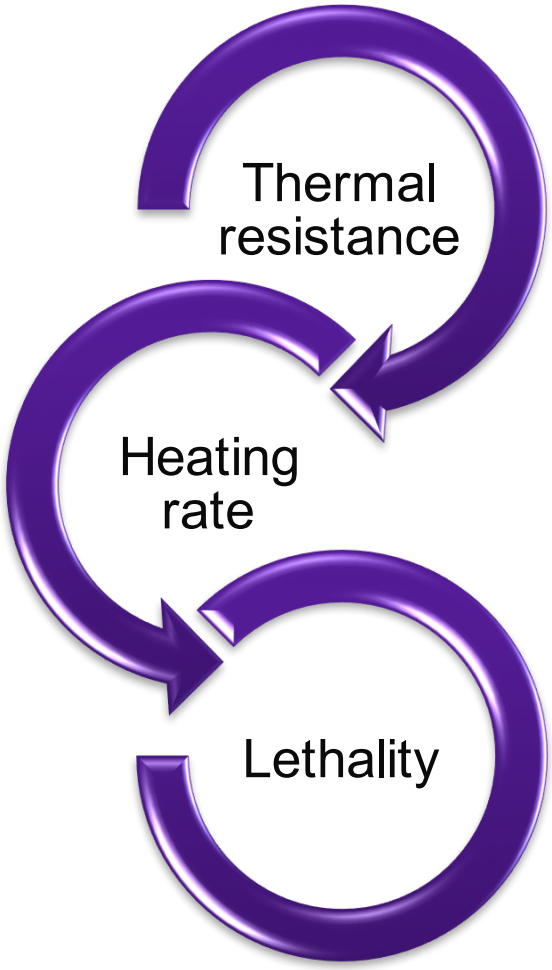
- Aseptic processing and packaging

The processing and cooling of product to a condition of commercial sterility, followed by the filling of that cooled product into pre-sterilized containers and the aseptic hermetic sealing with a pre-sterilized closure in an atmosphere free of micro-organisms.

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Process Design: Thermo-Bacteriology



- Decimal reduction time (D-value)
- z-Value

- Convection, conduction
- Heat transfer coefficient

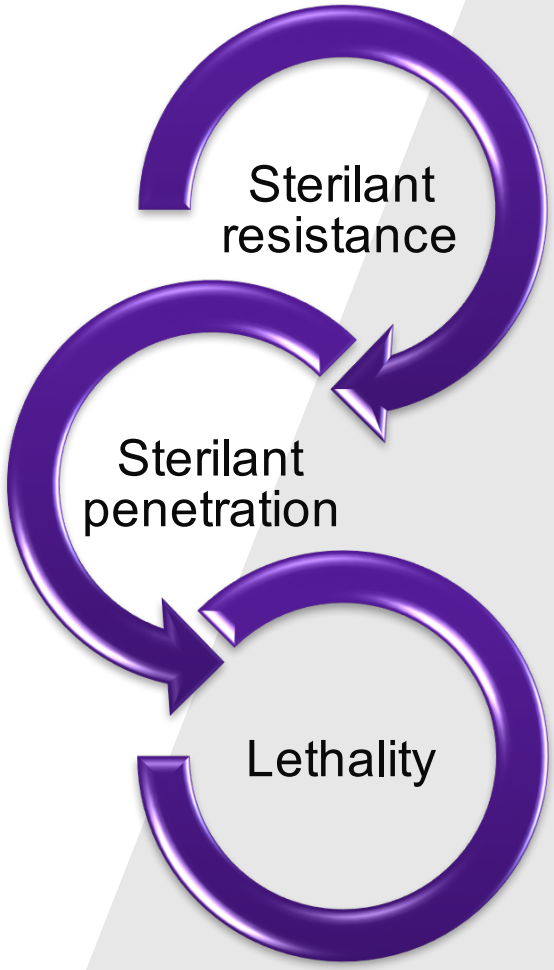
- Process lethality (F-value)

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Process Design: Thermo-Bacteriology

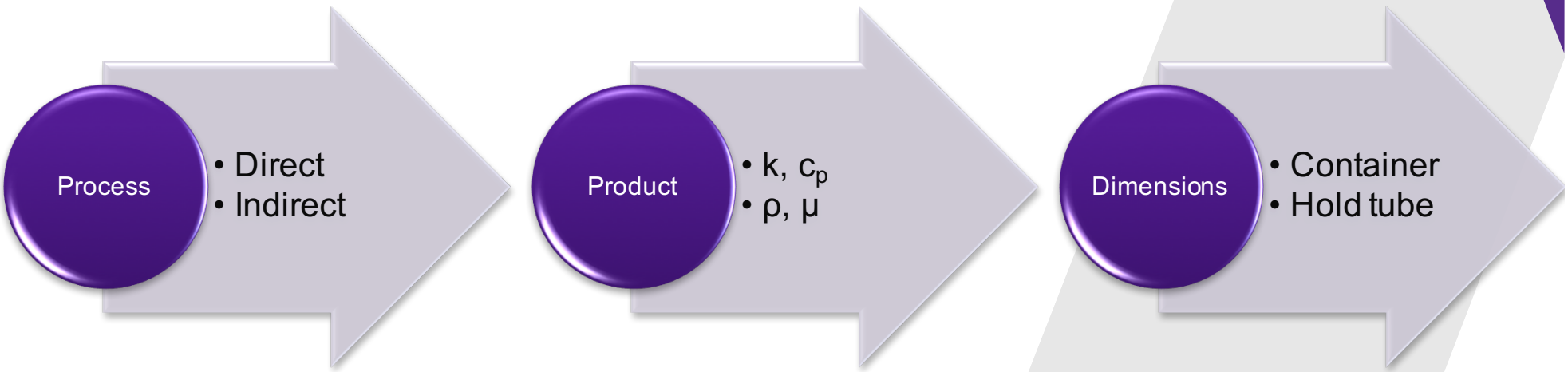
- Exposure time
- Concentration
- Temperature
- Packaging/ machine surface
- Thermal mass
- Surface tension
- Sterilization conditions



CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

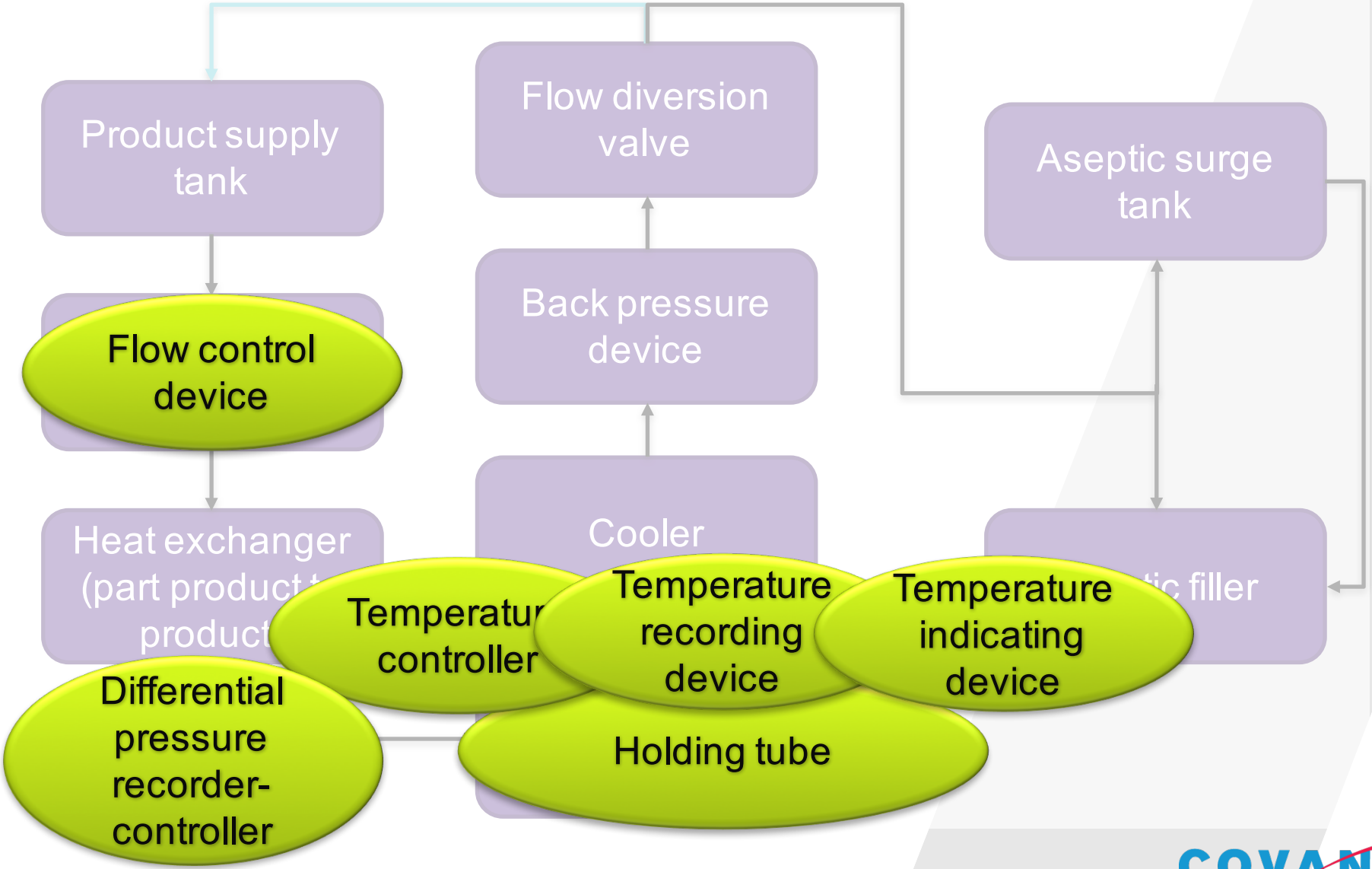
Process Design: Principles of Thermal Processing



CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Aseptic processing and filling system: Components



CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Aseptic processing and filling system: Aseptic product sterilizer requirements 21CFR113.40(g)(1)

SHALL:

- Accurate temperature-indicating device at the hold tube
- Accurate temperature-recording device at all critical locations specified in scheduled process
- Product-to-product regenerator pressure difference
- Differential pressure recorder/controller
- Flow control device upstream from hold tube
- Product holding tube (no heat, ¼ inch upward slope/ft)
- Mistreated product separation(temperature/ pressure)
- Pre-sterilization of equipment
- Record keeping

SHOULD:

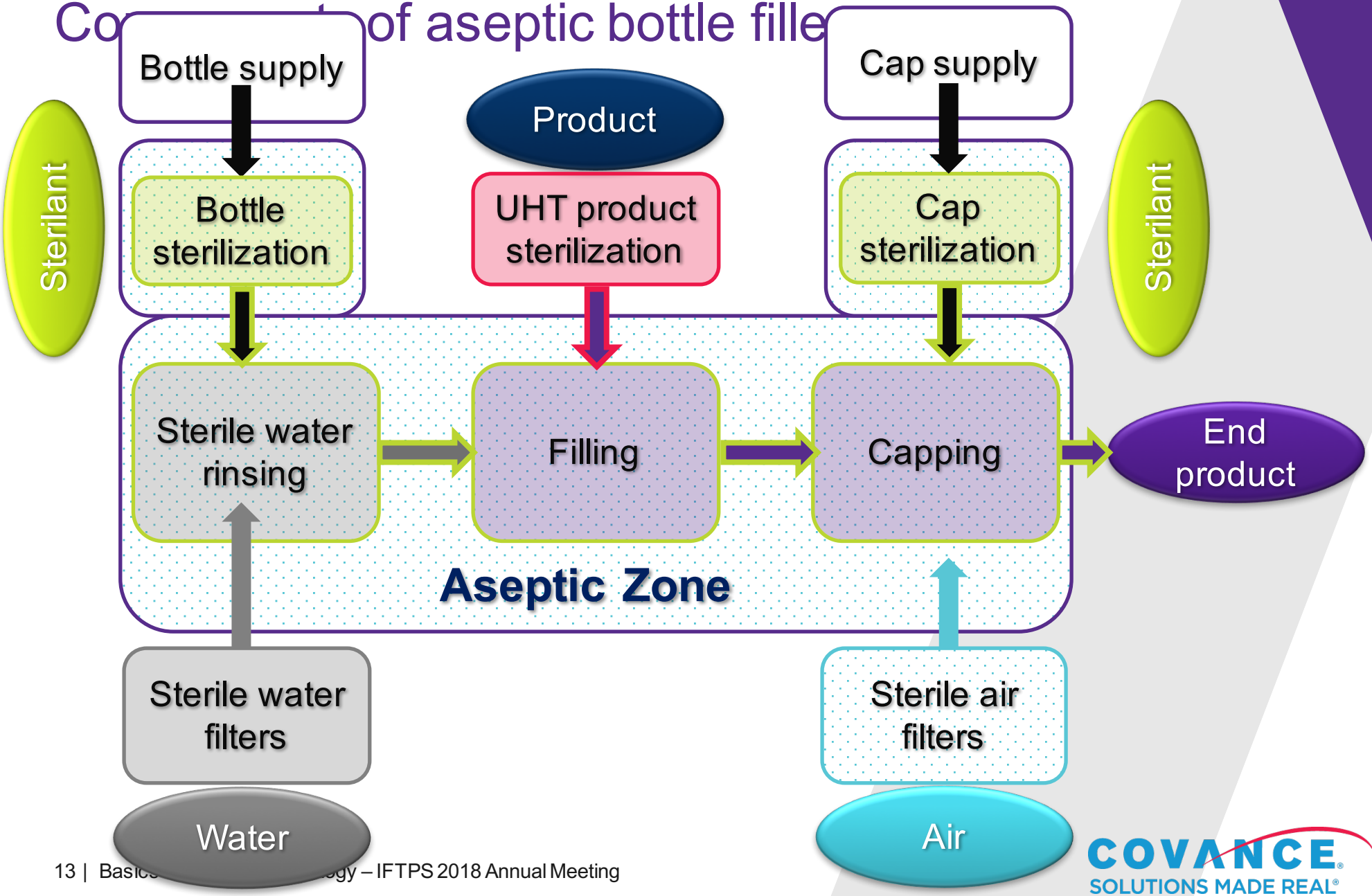
- Flow diversion device
- Effective steam barriers downstream of holding tube

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Aseptic processing and filling system:

Co[illegible]of aseptic bottle fille



CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Aseptic processing and filling system:
Aseptic filler requirements

SHALL:

- Record all critical factors
- Timing method
- Pre-sterilization of equipment and package
- In case of loss of sterility – stop and segregate
- Record keeping

  - Operator verification that data is recorded appropriately (operators log, check sheet, maintenance records)

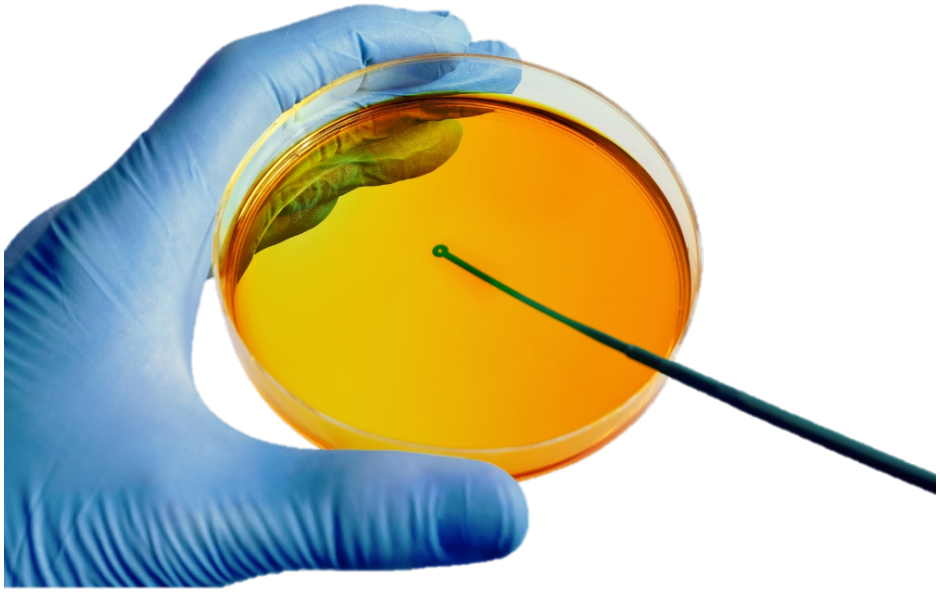
CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process

Definition

- An evaluation of collected technical and scientific information to determine that the parameters for pre-sterilization and maintenance of sterility chosen, are sufficient to provide an effective control measure.



CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: why, what, when?

Why do we need to validate?

- Demonstrating and documenting evidence to provide assurance that the determined process is sufficient to deliver a microbiologically safe and stable product.

What do we validate?

- Control measures against performance standards.

When do we need to validate?

- New installations
- Re-validation
  - System modifications
  - Changes in packaging material
  - Equipment movement and reinstallation

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: What? Control Measures and Performance Standards

- Product sterilization, aseptic zone and packaging pre-sterilization
  - Critical factors, e.g. temperature, time, concentration, pressure, speed
  - Critical limits – worst case scenario
- Target pathogen and surrogate identification
  - Pathogen of concern
  - Resistance toward control measure

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: Examples of control measures

Pre-sterilization and maintenance of sterility:

- Aseptic processor for product sterilization
- Aseptic surge tank
- Aseptic filler
- Packaging sterilization
  - Sterilization of body and lid stock
  - Internal and external bottle surface sterilization
  - Closure sterilization

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: When? Examples

- Package composition (HDPE, PET, additives)
- Package weight
- Package size
- Package shape
- Aseptic packaging system:
  - Sterilization method (e.g. chemical, ebeam, UV)
  - Sterilization application (
  - Sterilant (e.g. H_2O_2, PAA
  - Sterilization parameters (e.g. temperature, time, pressure)
  - Location of spray nozzles

1. Change management control program!

2. Confer with your Process Authority if you made a change!

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: How? Teamwork

Microbiology

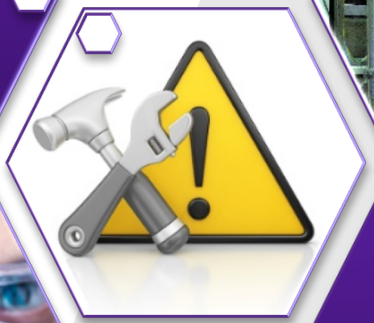
Chemistry

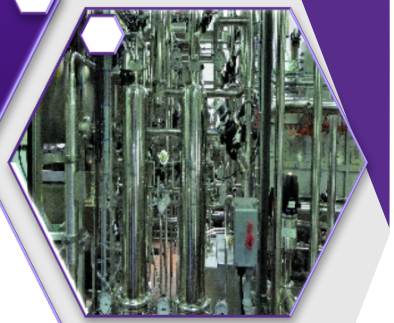
Process Authority

Engineering

Maintenance

Equipment manufacturer



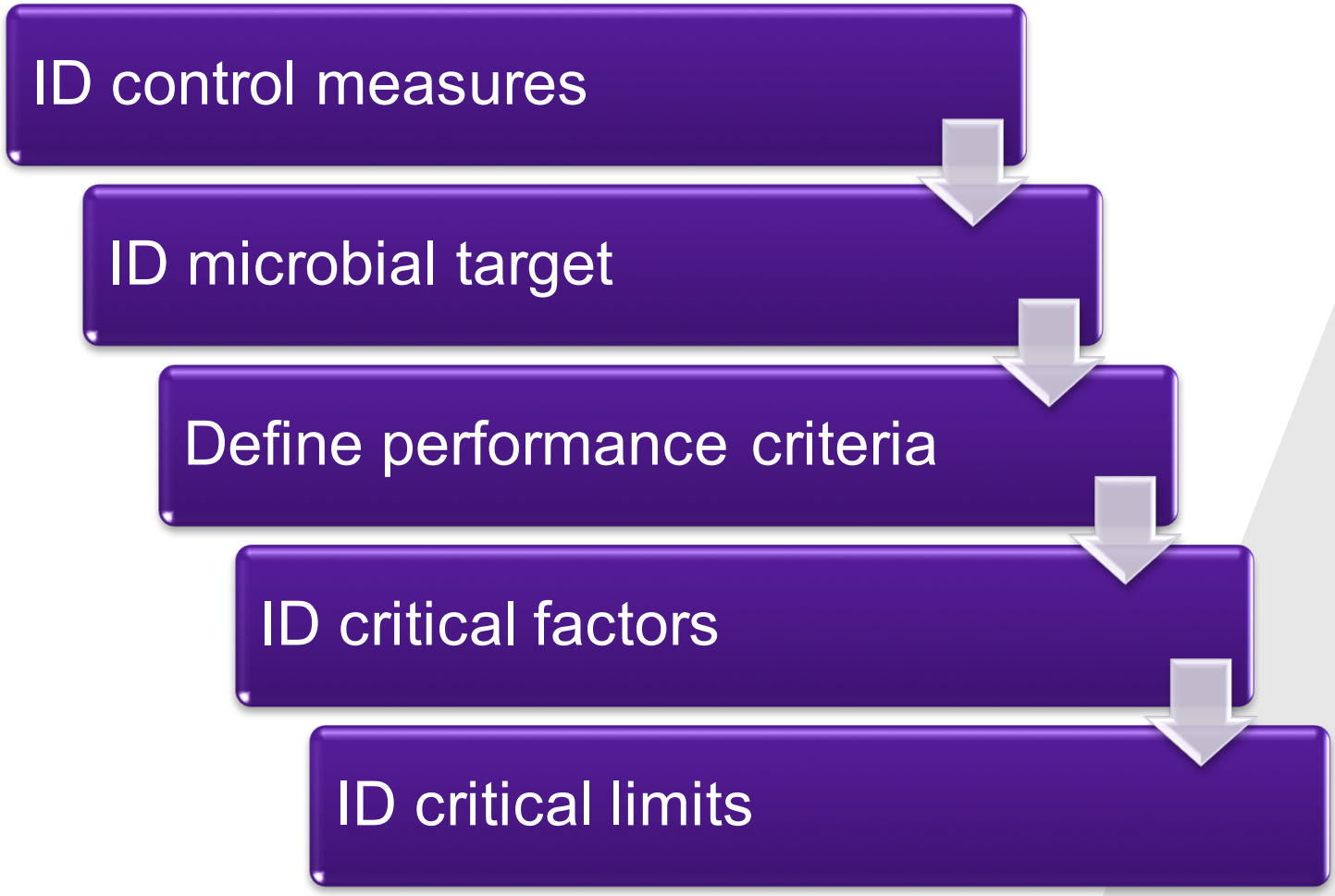


Operations

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

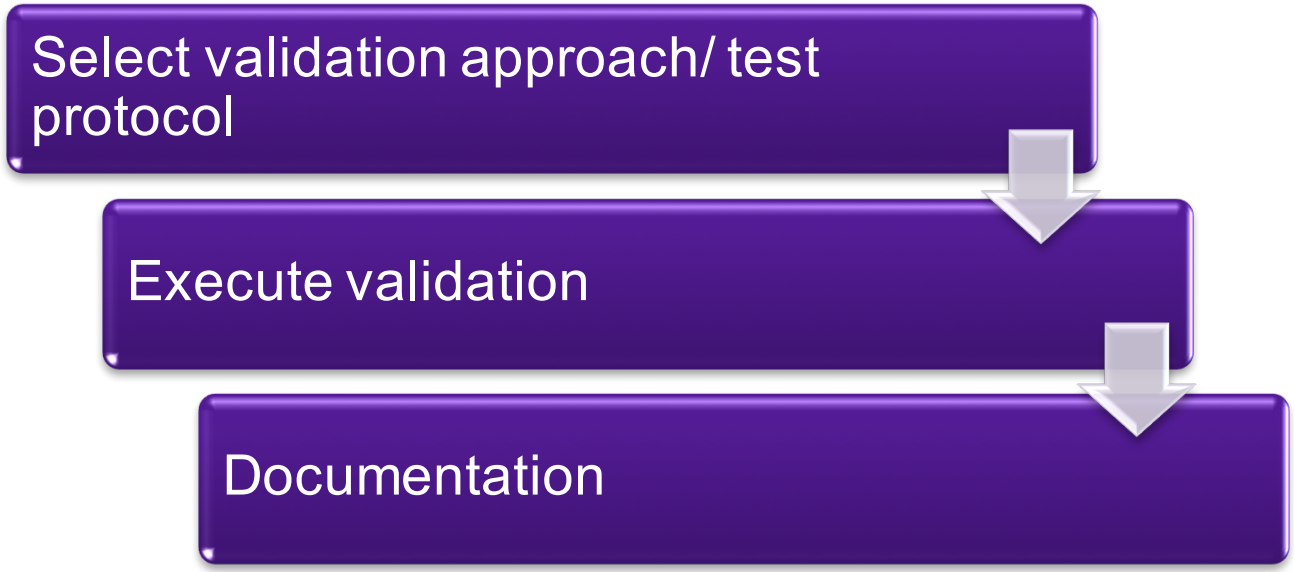
Microbiological Validation of an Aseptic Filling Process: How? Identification



CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: How? Execution



CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: Pre-Requisites

- Equiment must be of good hygienic design
- Process and control logic is defined (steps, sequence, critical factors, critical limits, etc.)
- Equipment is design and fabricated to meet intended task (i.e. packages commercially sterile, aseptic product)
- Equipment is capable of operating within required parameters (IQ and OQ are completed)
- Alarm verification completed for all critical functions
- Management of change control program is in place
- All instruments used to measure critical factors are calibrated

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

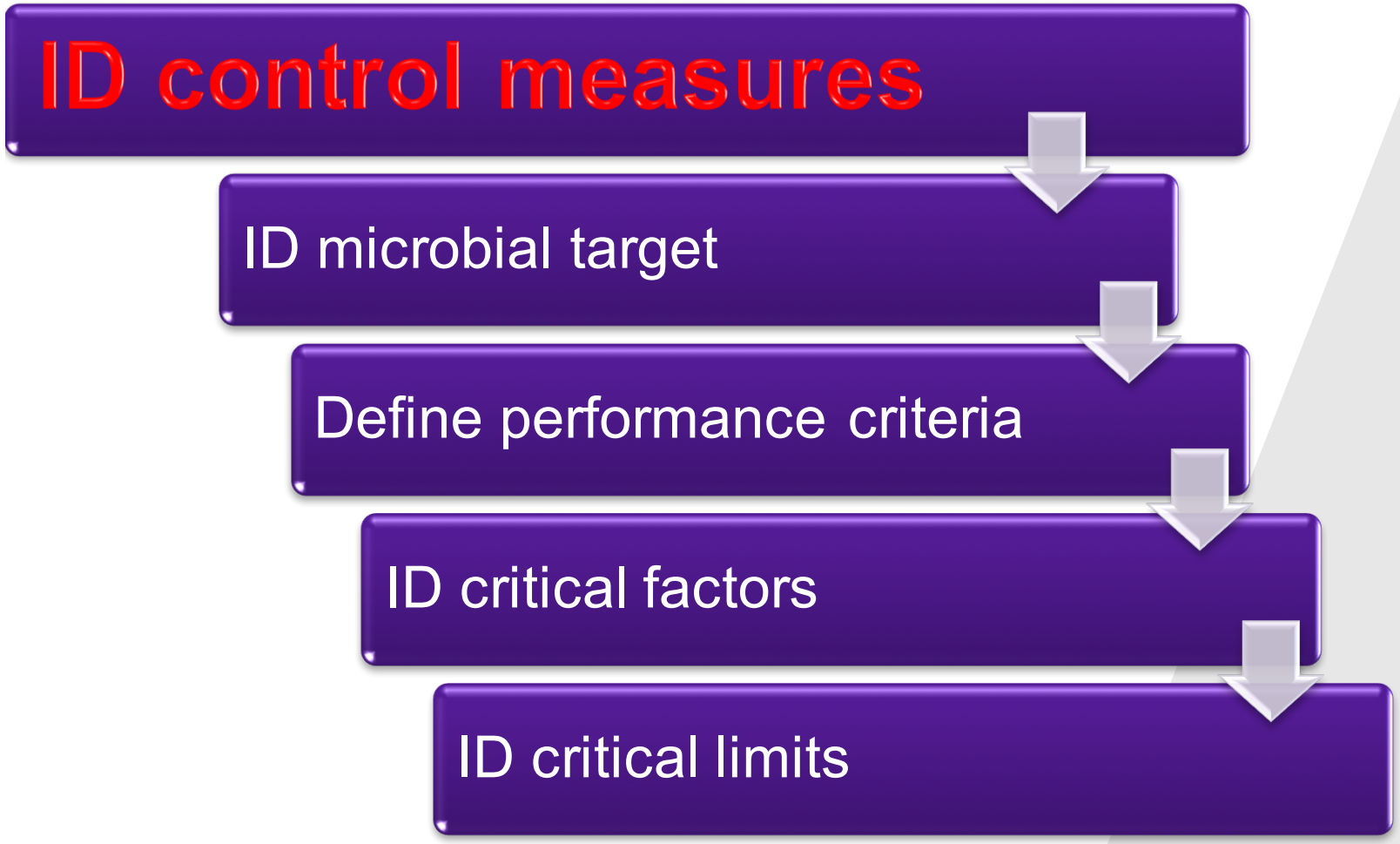
Microbiological Validation of an Aseptic Filling Process: Pre-Requisites

- Microbiological validation is NOT a process development effort to determine limits of critical factors!
- Most failures of microbiological validations are a result of a lack of understanding of the efficacy of the critical factors prior to starting the validation efforts.

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: Identification



CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

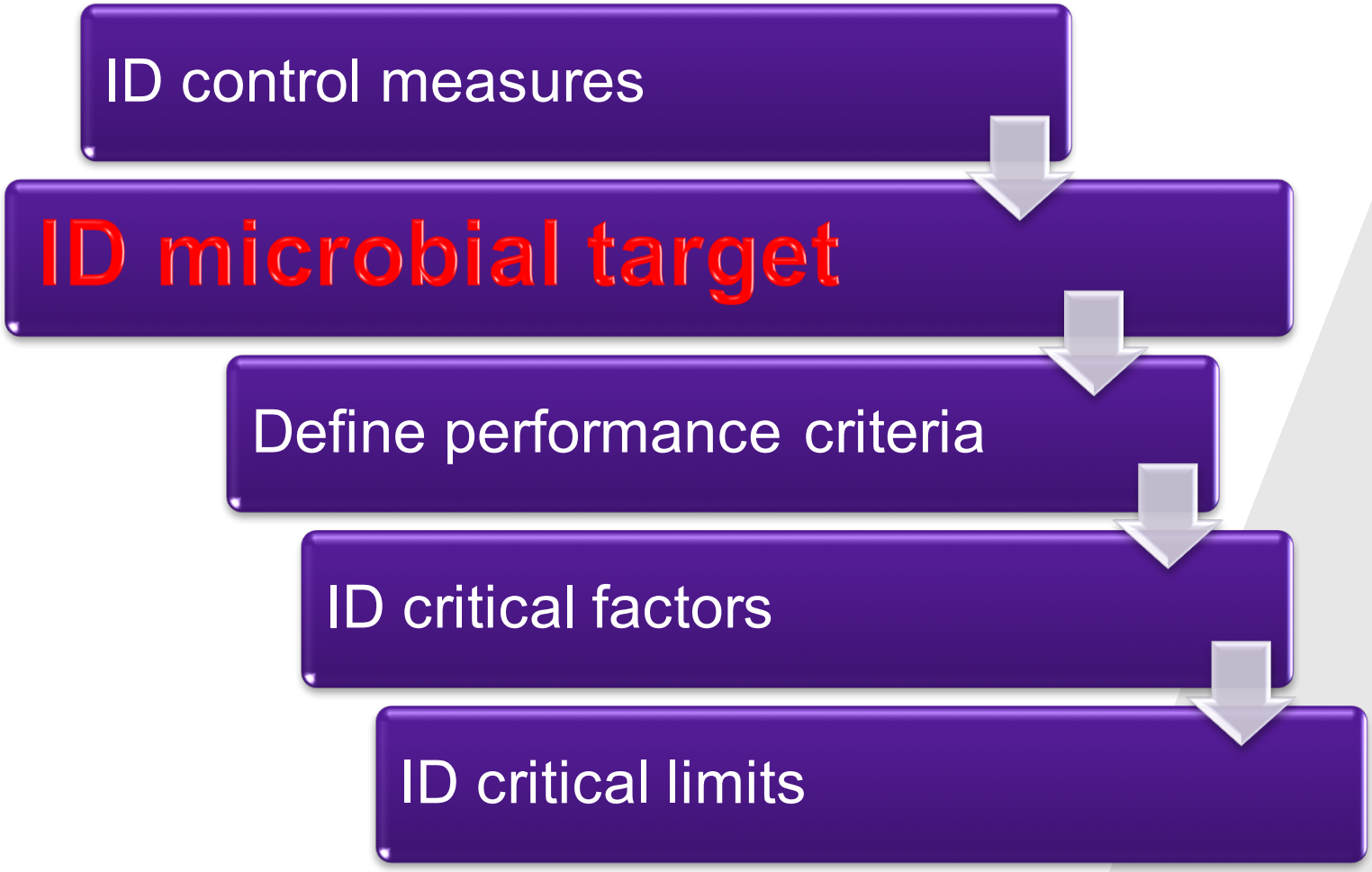
Microbiological Validation of an Aseptic Filling Process: ID Control measures

1. Package sterilization
   - Bottle exterior and interior
   - Closure exterior and interior
2. Aseptic filler sterilization cycles
   - ► Filler pre-sterilization – aseptic zone, non-food contact surfaces (chemical)
   - ► Product contact surfaces – filler bowl, filler nozzles (steam)
   - ► Sterile air and water filters
3. Product sterilization
4. Aseptic surge tank sterilization
5. Maintaining sterility in aseptic zone – sterile air overpressure (smoke test)
6. Hermetic seal application

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: How?



CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: ID microbial target

MICROORGANISM OF CONCERN BASED ON PRODUCT

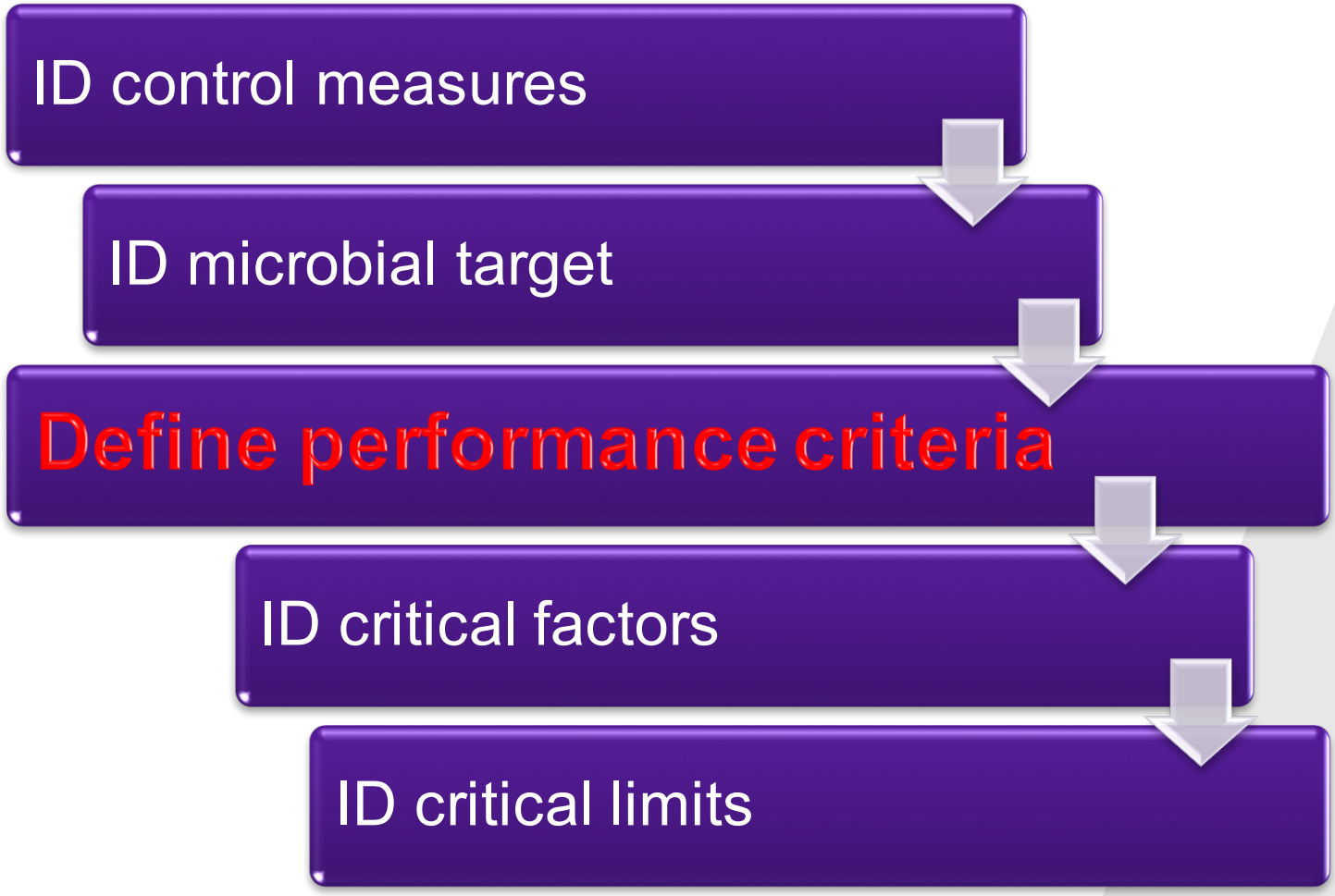
Most resistant pertinent microorganism for product (storage condition) and applied process:

- Food Safety:
  - *Clostridium botulinum* (low-acid, shelf stable)
  - *Salmonella*, *E. coli* O157:H7, *Listeria monocytogenes* (high-acid, acidified)
- Quality (spoilage):
  - *Clostridium sporogenes*, *Bacillus* spp. (low-acid, shelf-stable)
  - *Alicyclusbacillus*, *Lactics* (high-acid)

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: How?



CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: Define PC

PERFORMANCE CRITERIA

Goal for shelf-stable foods is to achieve commercial sterility (statistical approach)

1. Determine the expected initial load

2. Define the Food Safety Objective (FSO)

Probability of a non-sterile unit of 1×10^{-9} or 1 in a 1 billion units (for LACF) for target microorganism

3. Calculate the performance criteria for the process to achieve the defined FSO.

log reduction of target microorganism

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: Define PC

CALCULATING PROCESS TARGET LOG COUNT REDUCTION (LCR)

Target MO: *C. botulinum*

$$LCR = logN_0 - logN$$

N_0 = *expected initial spore load* = 10^3

N = *FSO* = 10^{-9}

$$LCR = log10^3 - log10^{-9}$$

$$LCR = 12$$

12 log reduction of C. botulinum is an industry standard for Performance Criteria in the processing of LACF

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: Define PC

CALCULATING PACKAGING/ MACHINE LCR

Target MO: *C. botulinum*

$$LCR = logN_0 - logN$$

N_0 = *expected initial spore load* = 10^{-3}

N = *FSO* = 10^{-9}

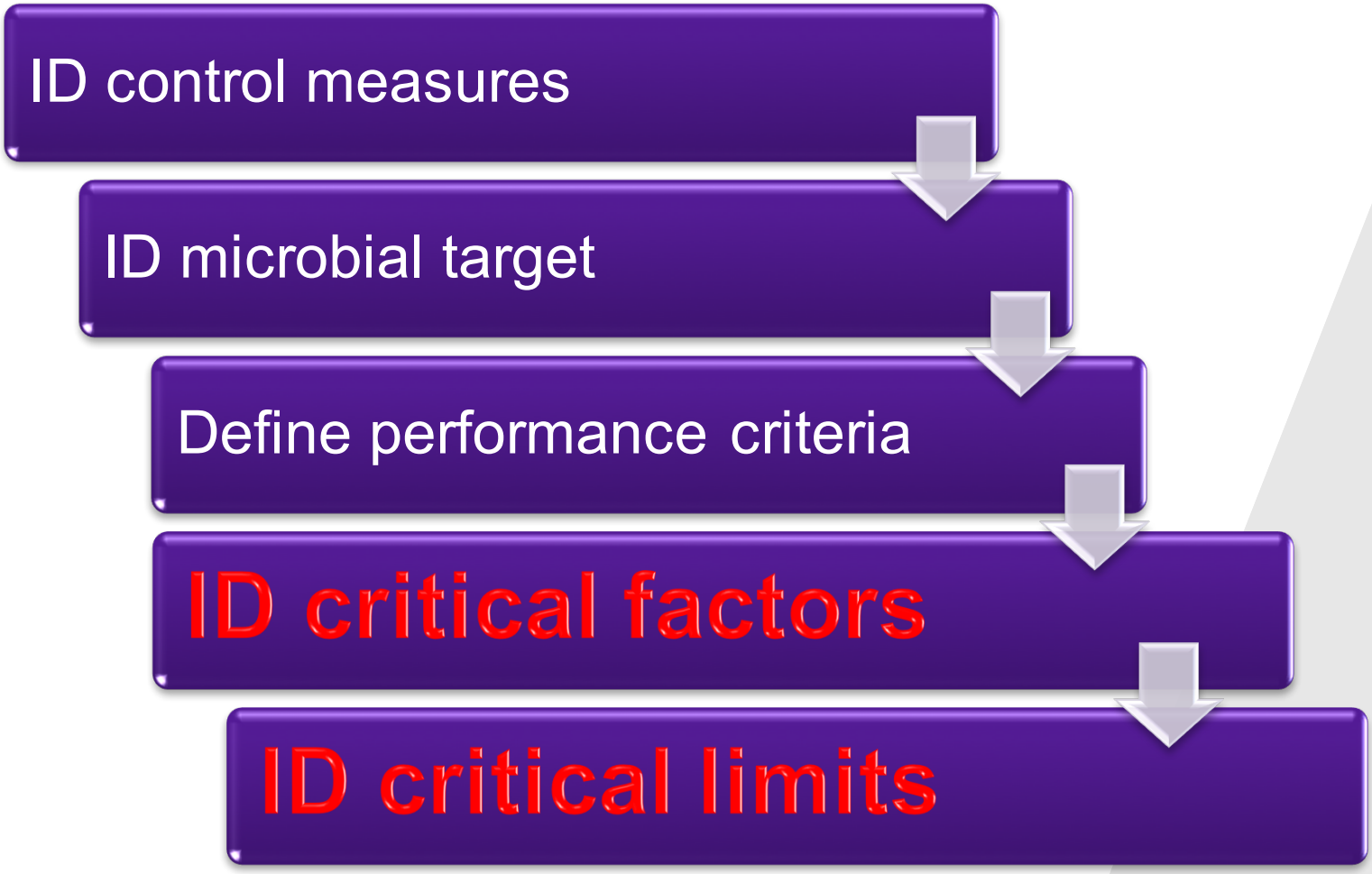
$$LCR = log10^{-3} - log10^{-9}$$

$$LCR = 6$$

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: How?



CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: ID CF

CRITICAL FACTORS

- All critical factors affecting the control measure must be carefully identified – PRIOR to start of validation
- Differentiation between critical and control – e.g. UHT:
  - Product temperature at ENTRY of holding tube is an important control point but NOT a critical factor
  - Product temperature at the EXIT of holding tube IS a critical factor
- Extremely important for large sophisticated machines, e.g rotary bottle filler that can have several hundred controlled parameters but only about ¼ of them are critical
- CF, frequency, monitoring and recording have to be agreed upon by OEM, validation team and processor

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: ID CL

CRITICAL LIMITS

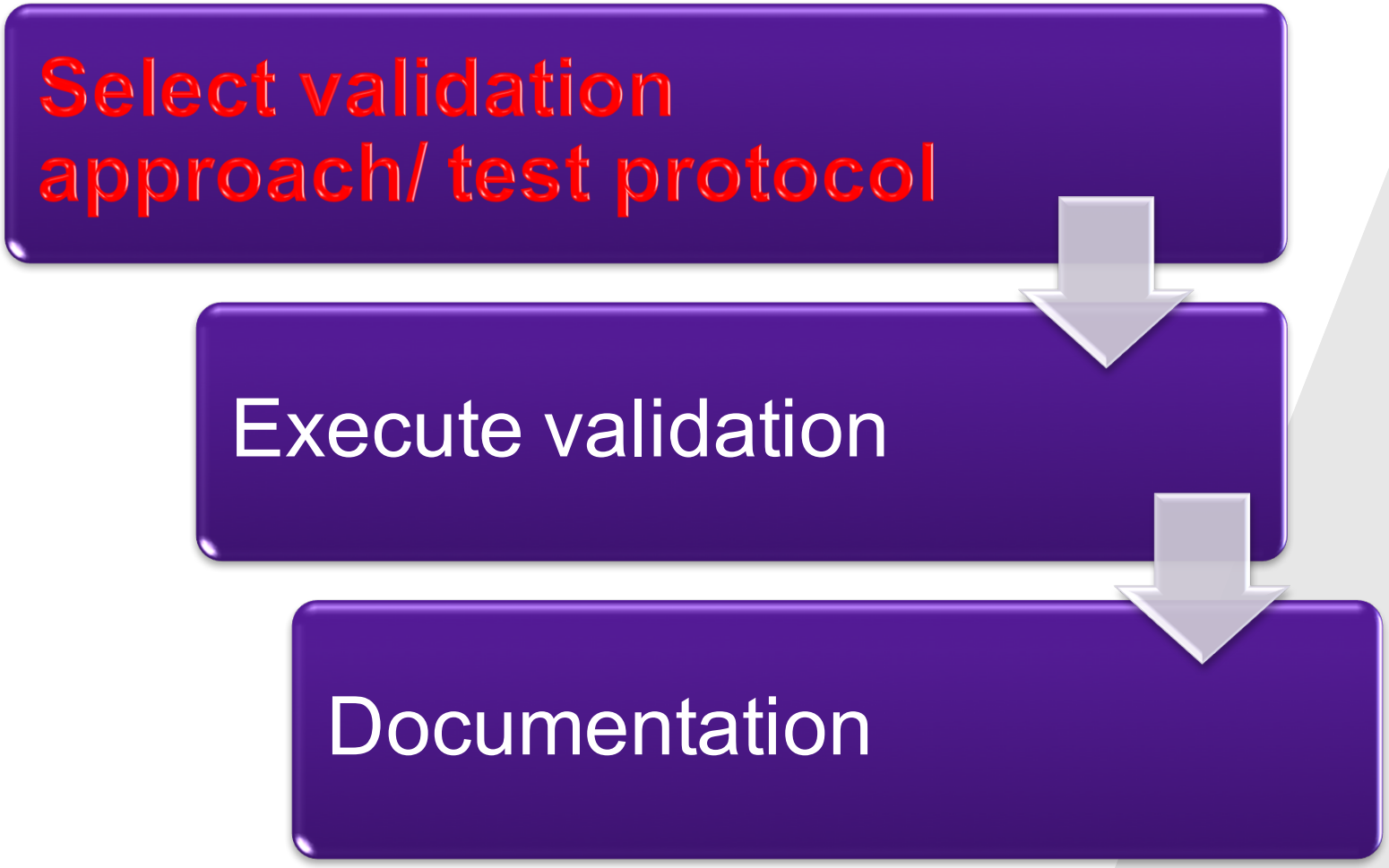
- Identify the operational limits or processing envelop for the critical factors (worst case scenario) = critical limit
- Examples
  - Speed, CL = 600BPM, validation set point 604BPM
  - Conc. CL = 34%H2O2, validation set point 33%
- Alarms may have to be disabled during validation

Alarms and operational parameters need to be re-set after validation is completed!!

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: How?



CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: Select approach

VALIDATION APPROACH

- Develop a protocol to collect scientific on-site experimental data that the FSO is achieved
- Reminder: FSO 6 / 12 log reduction of C. botulinum

Experimental Approach:

- Use a surrogate that has similar sterilant resistance as *C. botulinum* but is NOT pathogenic to conduct the microbiological challenge tests of the various sterilization and pre-sterilization cycles.

CONFIDENTIAL

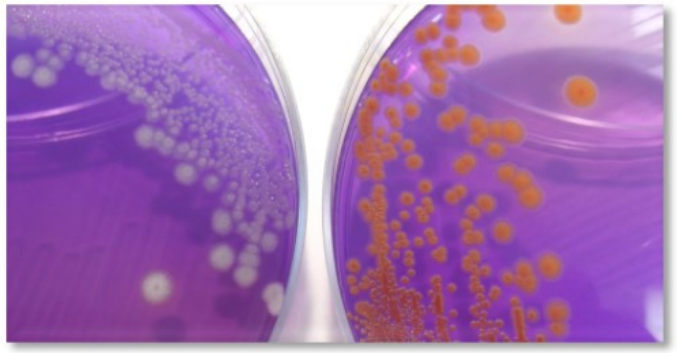
COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: Select approach

SURROGATE

Characteristics:

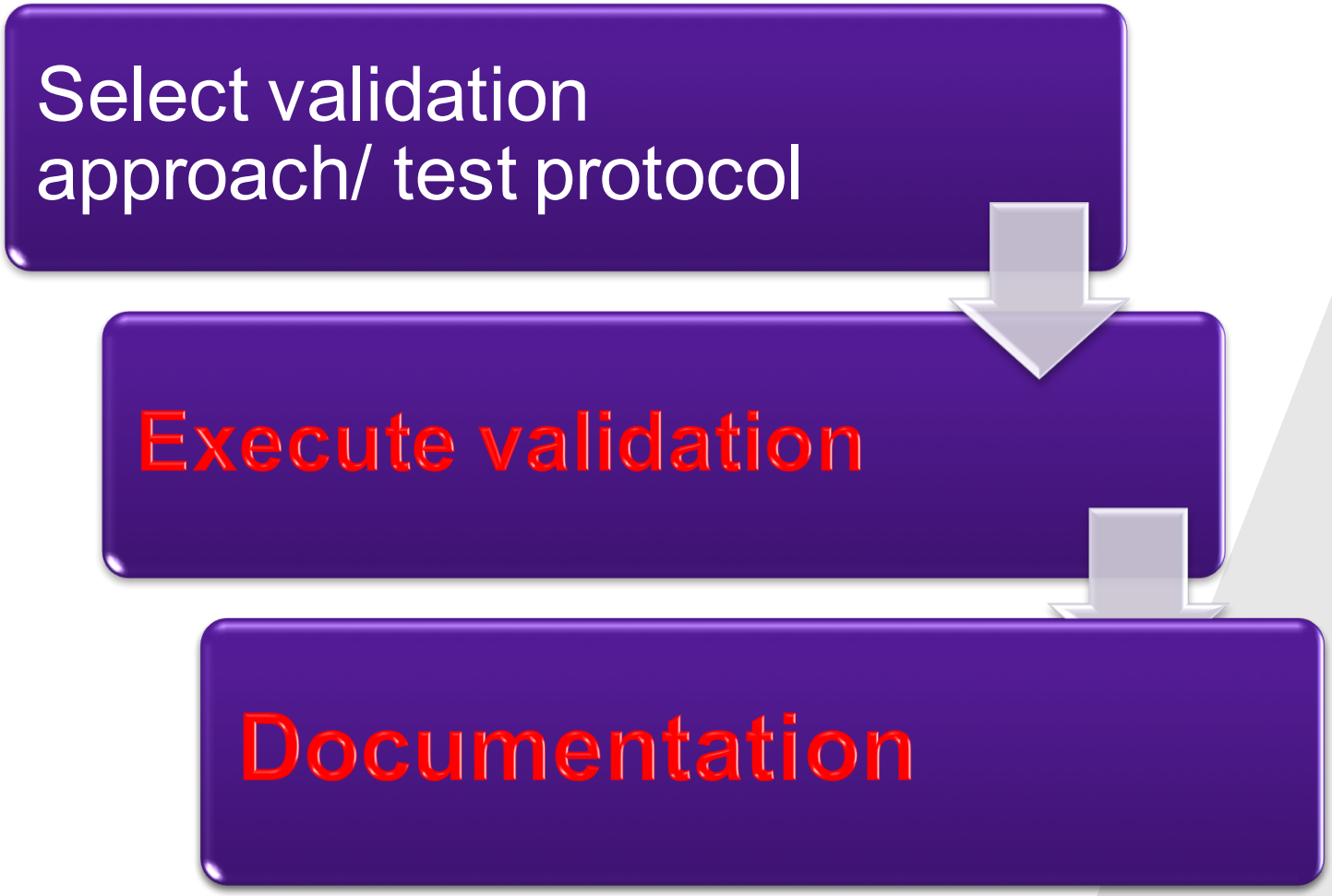
- Non-pathogenic
- Resistance is quantitatively correlated to *C. bot* (D and z values)
- Correlation must be
  - established for each sterilant
  - valid over the range of the sterilization process (concentration, temperature)
  - re-established for each crop (calibration)
- Must result in a stable suspension
- Must possess distinct metabolic or morphological characteristics



CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: How?



CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

André Rehkopf

andre.rehkopf@Covance.com

o: +1.925.551.4285

m: +1.925.315.2586

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®

Microbiological Validation of an Aseptic Filling Process: ID microbial target

MICROORGANISM OF CONCERN BASED ON STERILANT

Sterilant	Microbial Target : Food Safety/Quality
Liquid H_2O_2	*C. botulinum*
Vapor H_2O_2	*C. botulinum*
Steam	*C. botulinum* / *C. sporogenes*
Dry heat	*C. botulinum* / *G. stearothermophilus*
Peracetic Acid (PAA)	*Bacillus cereus*
Electron Beam	*C. botulinum*
Gamma radiation	*C. Botulinum*

CONFIDENTIAL

COVANCE
SOLUTIONS MADE REAL®