Sviluppo di un processo di cleaning

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WHEN YOU NEED TO BE SURE

Index

- Background
- Cleaning process
- Cleaning development
- Development of a cleaning process through QBD approach
- Cleaning process residue
- Chemical analysis
- Microbiological analysis

- Cleaning is one of the major and critical activities in Pharmaceutical operation.
- The 4 basic requirement of cGMP are:
  - Identity
  - Safety
  - Strenght
  - Purity

→ **Cleaning process**

Cleaning process

Cleaning process should be considered

NOT as the last step of a manufacturing process but as the FIRST STEP of a manufacturing process

Development of a Cleaning Process

- Understanding of a cleaning process should be documented as a part of development report
- Cleaning process understanding is to be managed according to GMP as develompment of a drug process
- Cleaning process must support expectation from Authorities (FDA, EMA)

Development of a Cleaning Process

- Cleaning process should be:
  - Robust
  - Scalable

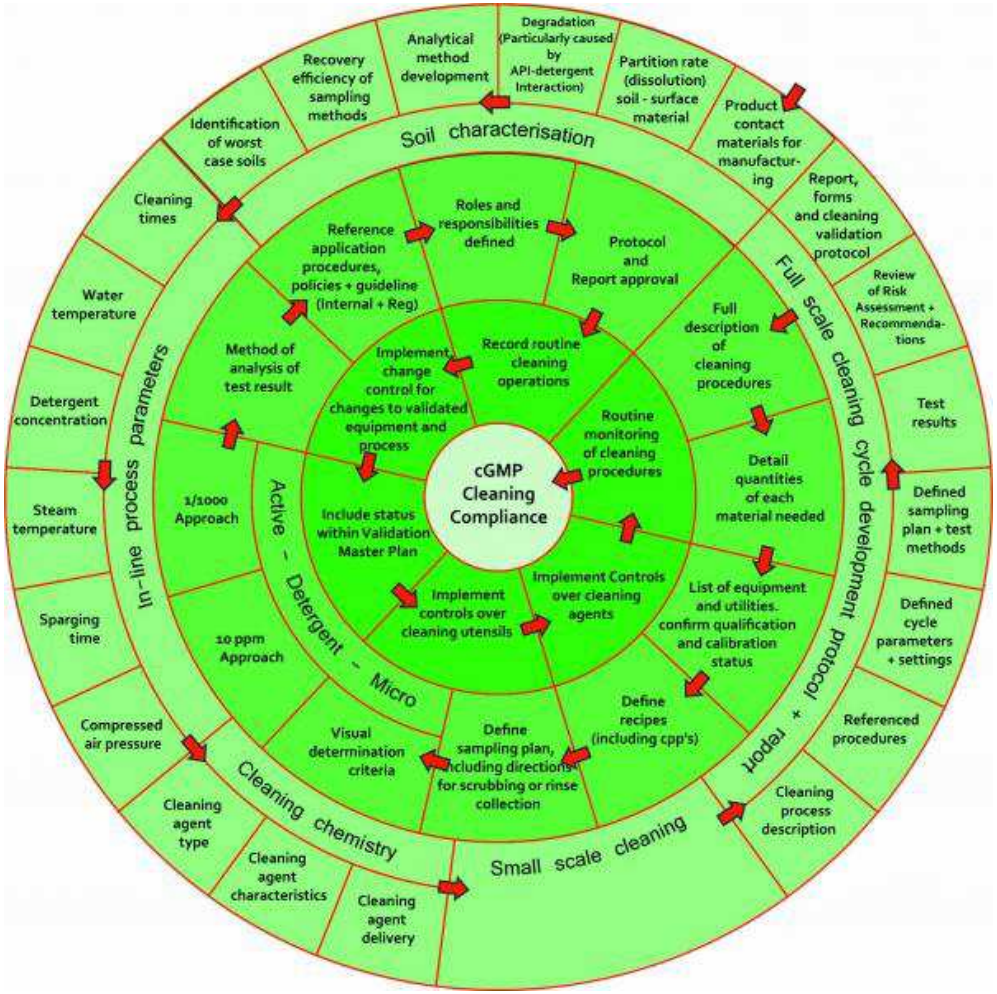
- Cycle development of the cleaning process in the manufacturing plant
- Impact on product residue and equipment surface
- Rationale of testing residue after cleaning in the manufacturing plant
- Test and analytical method validation for testing residue

Development of a Cleaning Process

Design of a cleaning method is an important task.

- What is being cleaned?
- What are the contaminants?
- What is the level of Cleanliness expected and what is the acceptance criteria?
- Which cleaning agent to be used and at what concentration?
- Who is going to do the cleaning? Who is going to supervise?
- What record will be maintened?

Development of a Cleaning Process



- Cleaning Chemistry
- Residue characterization
- In process parameters
- Small scale cleaning

Cleaning Development Risks

- Cleaning processes are often developed with a trial-and-error mindset.
- This “Quality-by-Chance” approach can lead to some adverse consequences:
  - Delay
  - Costs

New approach

- Such consequences can be prevented if we adopt a systematic approach to cleaning, and develop cleaning processes from a product life-cycle perspective.

QBD approach and process characterization at small scale

Cleaning validation:Quality By Design

- ICH Q8 “Pharmaceutical development”
- ICH Q9 “Quality Risk management”
- ICH Q10 “Pharmaceutical quality System”

- **Quality by Design**: “Design a quality product and manufacturing process to deliver in a reproducible manner”

QBD approach and process characterization at small scale

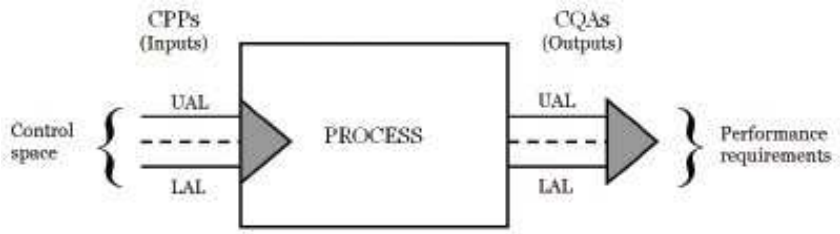


Figure 1 - Schematic representation of a typical process. Each Critical Process Parameter (CPP) or Critical Quality Attribute (CQA) can vary over a specified range defined by its lower and upper acceptable limits (LAL and UAL). The discontinuous line represents the set point

- Vantages of small scale study
- Transfer from small to large scale
- The objective of QbD is to develop robust processes through a better understanding of the relationship between operating conditions (inputs) and performance requirements (outputs)

Rizwan Sharnez, American Pharmaceutical Review - Volume 13

Cleaning development through QBD approach

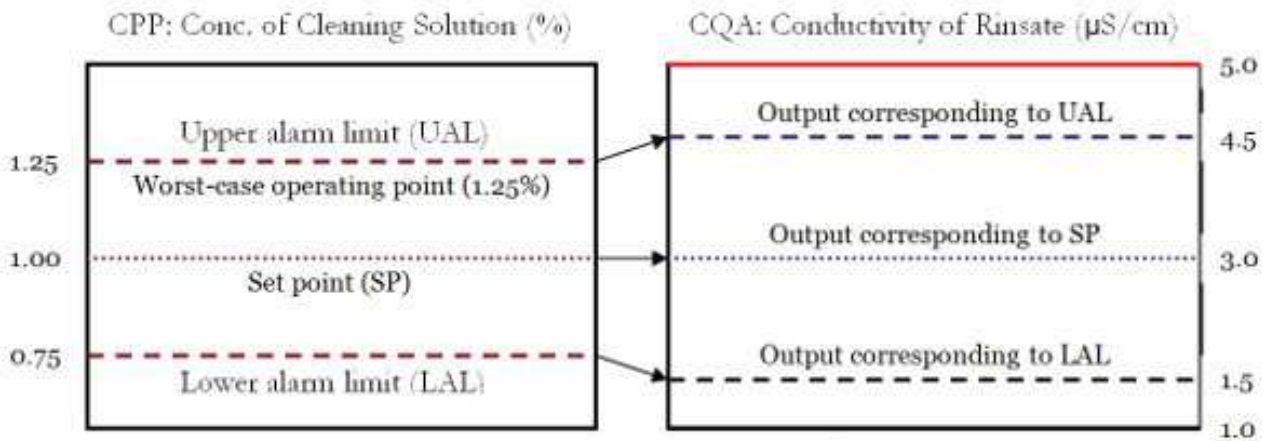


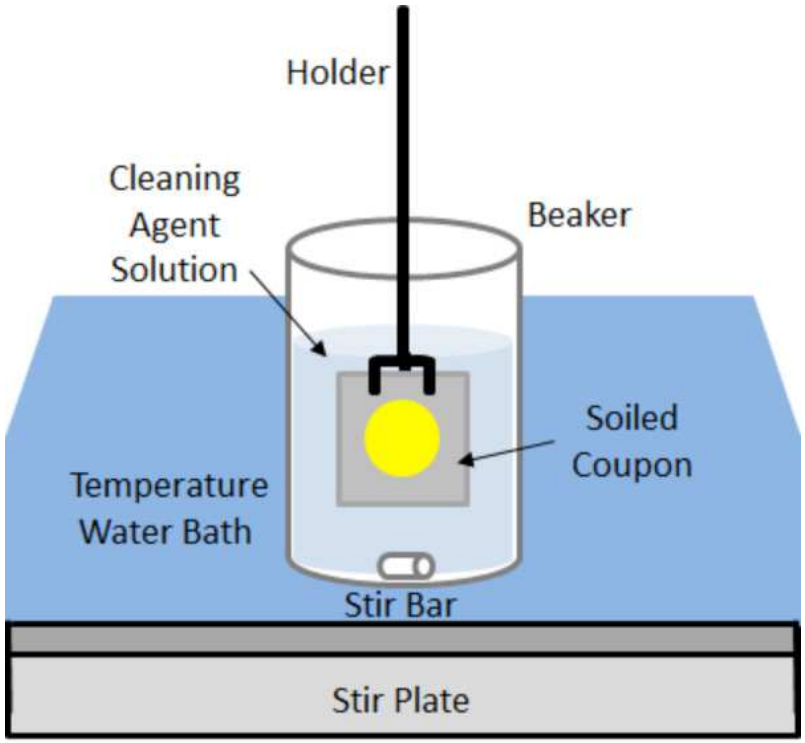
Figure 2 - Traditional versus QbD approach. With the traditional approach the process is characterized with the CPPs at their respective set points. With the QbD approach the process is characterized with the CPPs at their respective worst-case operating points (shown here to be the upper acceptable limit).

An experimental strategy for identifying the worst-case operating conditions and leveraging them to develop a **robust cleaning cycle**

- Operating conditions are defined in terms of Critical Process Parameters (CPP) and their respective operating ranges;
- Performance requirements are defined in terms of Critical Quality Attributes (CQA) and their respective acceptable limits

CCP & CQA can vary

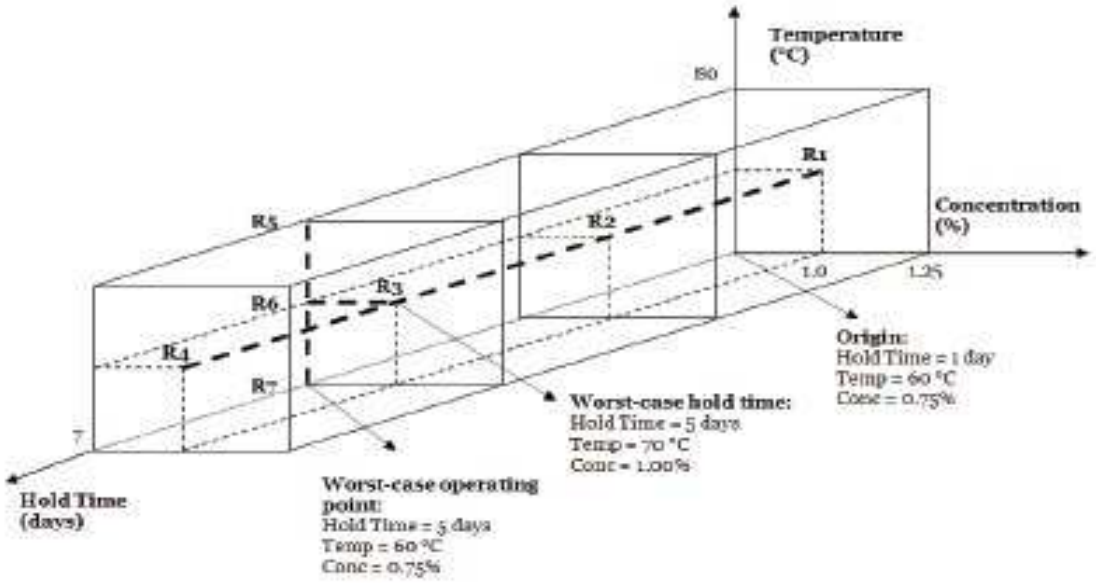
Identifying Worst-Case Operating Conditions



The worst-case operating conditions are identified through small-scale soilant characterization studies.

In these studies, the relative cleanability of the process soil is evaluated by subjecting soiled coupons to simulated cleaning conditions

Identifying Worst-Case Operating Conditions



A cleaning cycle is considered robust if it can consistently meet performance requirements under worst-case operating conditions.

The design space is delineated in rectangular coordinates for the three critical variables:

- hold time
- temperature
- concentration

Identifying Worst-Case Operating Conditions

Critical Process Parameter	Operating Range (Control Space)		Characterization Strategy	
	Lower Acceptable Limit (LAL)	Upper Acceptable Limit (UAL)	Traditional Approach: Characterize with CPPs at set point or typical operating conditions	QbD Approach: Characterize with CPPs at their respective worst-case operating points
Hold Time (days)	1	7	4	5
Concentration of cleaning solution (%)	0.75	1.25	1.0	0.75 (for wash) 1.25 (for rinse)a
Temperature of cleaning solution (°C)	60	80	70	60
Flow rate (gpm) or Pressure [b] (psig) of cleaning solution or rinse water	12 10	18 14	15 12	12 10

[a] Rinse out studies may not be required if the equipment is cleaned with process solvents (i.e. formulated cleaning agents are not used)
[b] At sprayball or other suitable location where pressure can be correlated to flow rate

The fourth critical variable, average velocity of the fluid across the surface of the coupon, is set to the worst-case operating value for the equipment (typically on the order of 10 cm/sec).

Identifying Worst-Case Holding time

Stage I:

The temperature and concentration of the cleaning solution are controlled at their respective set points (70°C and 1%).

The hold time is varied in increments of approximately 48 hours

Depending on the rate of drying and chemical degradation of the soil, shorter increments may be necessary to adequately characterize the effect of hold time.

The hold time at which the cleaning time is longest represents the worst-case hold time for cleaning.

Run	Hold Time (days)	Cleaning Time (normalized)
R_1	1	1.0
R_2	3	1.4
R_3	5	1.8
R_4	7	1.4

Wash time as a function of hold time (Stage I data). The temperature and concentration of the cleaning solution are controlled at their respective set points (70°C and 1% in this case).

Identifying Worst-Case: Temperature

Stage II:

In this stage the effect of temperature on relative cleanability is evaluated.

The hold time is set to its worst-case operating value of 5 days based on data from Stage I, and the concentration is set to the worst-case operating point of 0.75%.

The temperature at which the wash time is longest represents the worst-case temperature for cleaning.

Run	Temperature (°C)	Cleaning time
R_5	80	2.0
R_6	70	2.2
R_7	60	2.4

Identifying Worst-Case: Temperature

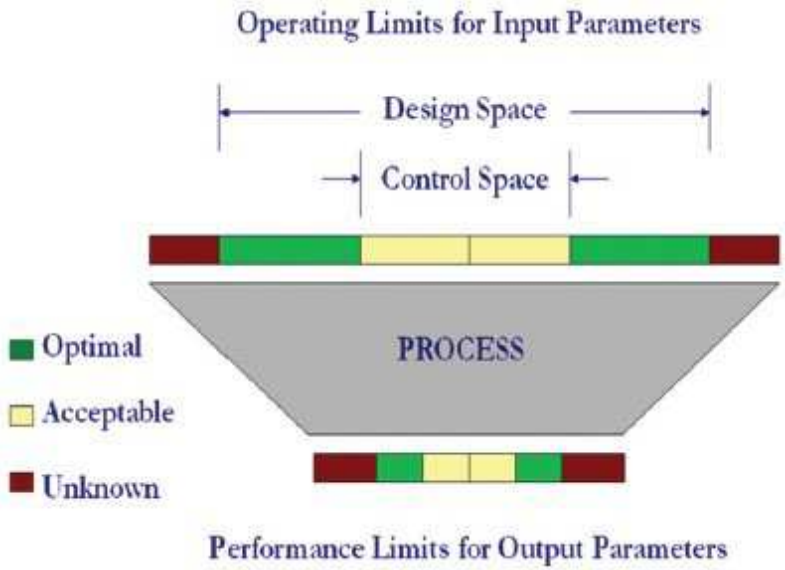
The above seven-run experimental strategy can provide a reasonable estimate of the worst-case operating point within the design space.

Additional runs could be performed to get a more precise estimate

Process step	CPPs and their worst-case operating points		
	Hold Time (days)	Temperature (°C)	Concentration (%)
Wash	~ 5	60	0.75
Rinse	NA	60	1.25

Cleaning, QbD and Design Space studies

- Quality by Design (QbD) provides a framework for implementing a systematic approach to process design, development and monitoring.
- The goal of QbD is to enhance robustness by building quality into the manufacturing process rather than testing it in. It also provides a structured framework for innovation and continuous improvement.



Cleaning process and residue determination

"…Pharmaceutical products can be contaminated by a variety of substances such as contaminants associated with microbes, previous products (both active pharmaceutical ingredients (API) and excipient residues), residues of cleaning agents, airborne matter, such as dust and particulate matter, lubricants and ancillary material, such as disinfectants, and decomposition residues which include:

- product residue breakdown occasioned by, e.g. use of strong acids and alkalis during the cleaning process; and
- breakdown products of the detergents, acids and alkalis that may be part of the cleaning process…."

WHO: Supplementary guidelines on good manufacturing practices (gmp): Validation

Cleaning process and residue determination

Know-how and process understanding of the cleaning process includes knowledge about:

- Product residue;
- Degradation products generated in the cleaning process
- Degradation products generated in time lapse to cleaning
- Detergent residue

Residue determination (analytical method)

At early step of an API manufacturing process , a high level of by-product is present and later purification steps are specifically designed to take care of these impurities. The rationale for not testing carry over from the cleaning process can be process knowledge and understanding:

- If by- products from the production process and degradation products from cleaning process are shown to be identical and purification steps are designed to remove them : no further tests are required. On the contrary, special attention and justification should be given

Residue determination (analytical method)

Contaminant:

- Chemical Residue
- Micro residue

Chemical Residue determination

The analytical method used to detect residuals or contaminant should be specific for the substance to be assayed and provide a sensitivity that reflects the level of cleanliness determined to be acceptable

Validation is required

Chemical analytical method

- Specificity
- Linearity
- Precision
  - Repeatability
  - Intermediate
- LOD/LOQ
- Accuracy (recovery)
- Range

Analytical method: specificity

The methods chosen should detect residuals or contaminants specific for the substance(s) being assayed at an appropriate level of cleanliness.

Degradation product and detergent residue should be investigated together with product that can arise from the following process:

- Moisture evaporation
- Air oxidation
- Microbial grow degradation process

→ Visual inspection

Analytical method: Accuracy- Recovery

- Swab procedure
- Surface
- Equipment

Recovery factor

- **PIC "**…the analytical methods should be challenged …contaminants can be recovered from the equipment surface and level of recovery should be known as well as the consistency of recovery"
- **PDA Technical report 29** "….The results obtained must be corrected for the incomplete recoveries due to the sampling and sampling preparation process; correction must be factored into the analytical calculation…"

Microbiological aspects of cleaning process

- Microbiological aspects of equipment cleaning should be considered. This should include preventive measures and removal of contamination where it has occurred.
- There should be documented evidence to indicate that routine cleaning and storage of equipment does not allow microbial proliferation.
- The period and conditions of storage of unclean equipment before cleaning, and the time between cleaning and equipment re-use, should form part of the validation of cleaning procedures.
- Equipment should be stored in a dry condition after cleaning. Stagnant water should not be allowed to remain in equipment after cleaning.

Cleaning procedure and microbiological aspects

- **API Contamination**

- Sterile API
- API to be used for sterile production
- API to be used for injectable (pyrogen risk)

Cleaning procedure and microbiological aspects

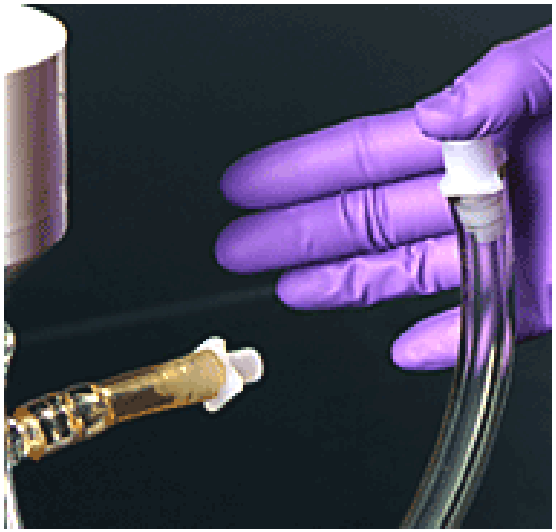
Cause of contamination

- Water residue
- Equipment not completely dried
- Holding time

- Rinse test
- Swab test

Rinse test procedure and acceptability criteria

- **Sampling**: withdraw 200 ml of last rinse water
- **Test:** bioburden test according to Eu.Ph.



- **Bioburden**≤ bioburden of cleaning water
  - Purified ≤ 100 CFU/ml
  - WFI ≤ 10 CFU/100ml
- **TOC**≤ TOC of cleaning water
  - Purified ≤ 0,5 mg/l
  - WFI ≤ 10 CFU/100ml

TOC determination on swabbed surfaces

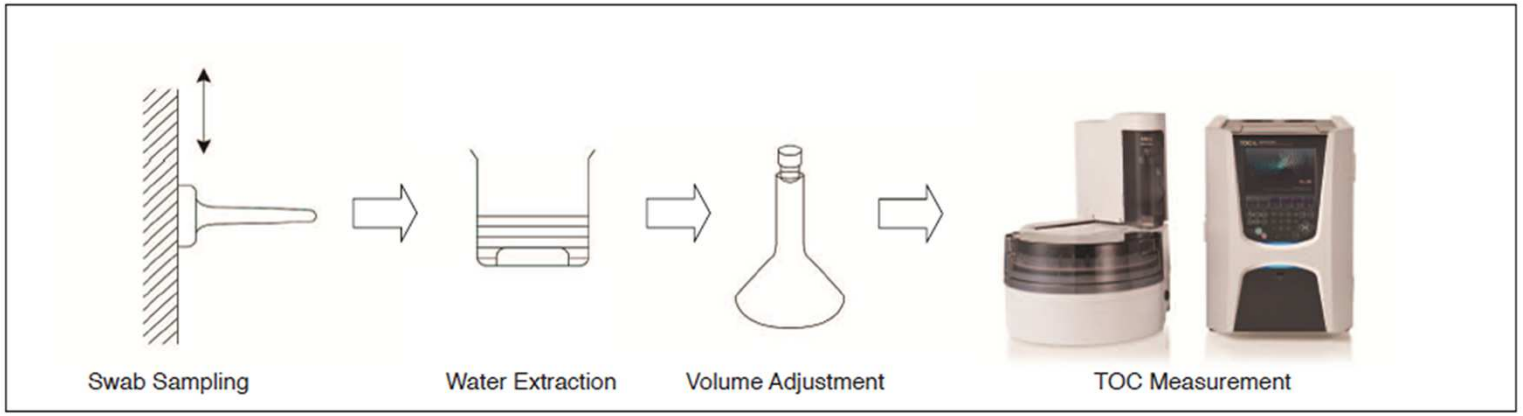


Fig. 2 Swab Sampling – Water Extraction – TOC Measurement Method

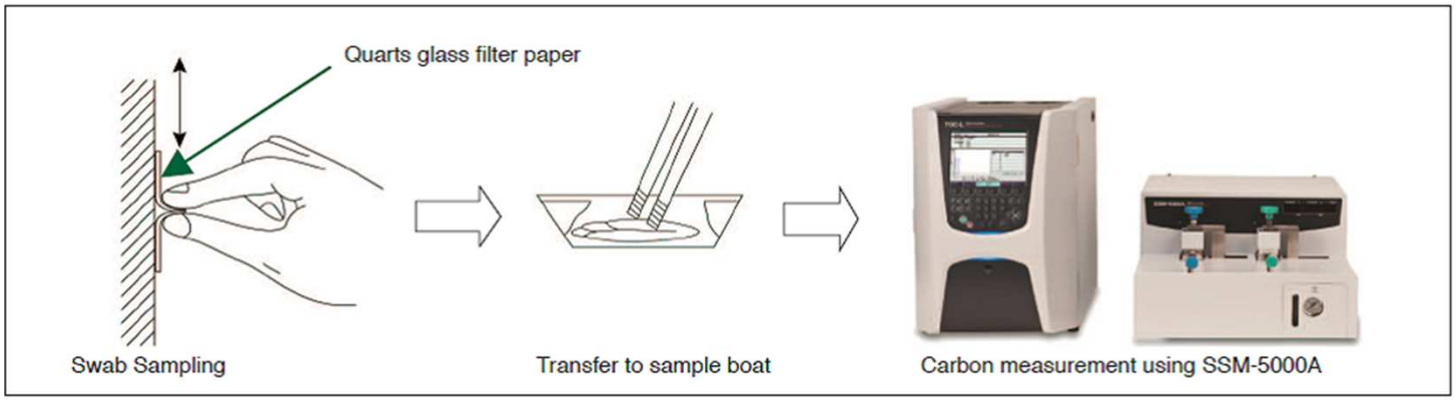


Fig. 4 Swab Sampling – Direct Combustion Method

Swab test procedure and acceptability criteria

- **Sampling**: sample 10x10 cm2 using a swab or use contact plate (55 mm – TSA)
- **Test:** bioburden test according to Eu.Ph.

- **Bioburden to be defined on:**
  - Class of environmental
  - Dimension of equipment
  - Micro Specification of API produced in the same equipment

- It is not indicated any acceptability limit for surface

Cleaning process development

Risk analysis approach

Cleaning Validation

GRAZIE PER L'ATTENZIONE !

- **EQUIPMENT VALIDATION SERVICES**
- **INSTRUMENTS CALIBRATION SERVICES**
- **INFORMATION TECHNOLOGY COMPLIANCE AND VALIDATION**
- **SAFETY AND ENVIRONMENTAL PROTECTION SUPPORT**
- **MICROBIOLOGICAL & CHEMICAL ANALYSIS**
- **PROCESS & QUALITY SUPPORT**
- **TRAINING GMP**

WHEN YOU NEED TO BE SURE