Annex 1- Contamination Control Strategies: How to Achieve Faster, Easier Process Monitoring

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EP/USP Harmonized Water Requirements

Sievers Pharma Water Analytics Focus History and Future

✓ **1998- Total Organic Carbon (TOC)**
TOC limit = 500 ppb

400

900 Series

500 RL

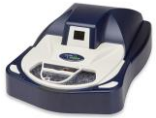
IONICS
IONICS, INCORPORATED

✓ **2014- Simultaneous TOC**
✓ **& Conductivity EP/USP Stage 1 testing**

M9

500 RL

✓ **2019- Rapid Endotoxin testing**
limit = 0.25 IU/mL with compliant 3-point standard curve
✓ **TOC**
✓ **Conductivity**



Eclipse

M500

M9 2.0

SUEZ

✓ **2023- Rapid Bioburden CFU equivalent**
✓ **Rapid Endotoxin testing**
✓ **TOC**
✓ **Conductivity**

VEOLIA

✓ **DataShare Elite helps handling your Data&Metadata**
✓ **We care about our Customers with State of the Art 21 CFR Part 11 and ALCOÁ+ Compliant Systems and Software**

Agenda

- What is a Contamination Control Strategy (CCS)?
- Mitigating Risk
- Process Monitoring
- Real Time Release/Monitoring
- Cleaning Validation

What is a Contamination Control Strategy?

- A **Contamination Control Strategy (CCS)** considers microbiological and chemical monitoring of assessed points to **manage risks**
- Testing for **contamination** involves different methods; a few which are critical release tests to **mitigate risks** to the entire manufacturing process.
- A CCS should be monitored over time for its **effectiveness** and **contamination prevention**
- Every CCS starts with a **Culture of Quality**
- New **innovative** technologies now allow companies to easily monitor their production processes and be proactive
    - *Bacterial Endotoxin Testing (BET), Rapid Bioburden, Total Organic Carbon (TOC), and Conductivity*

Three Stage Approach

1) Development
2) Compilation of CCS documents
3) Evaluation of CCS

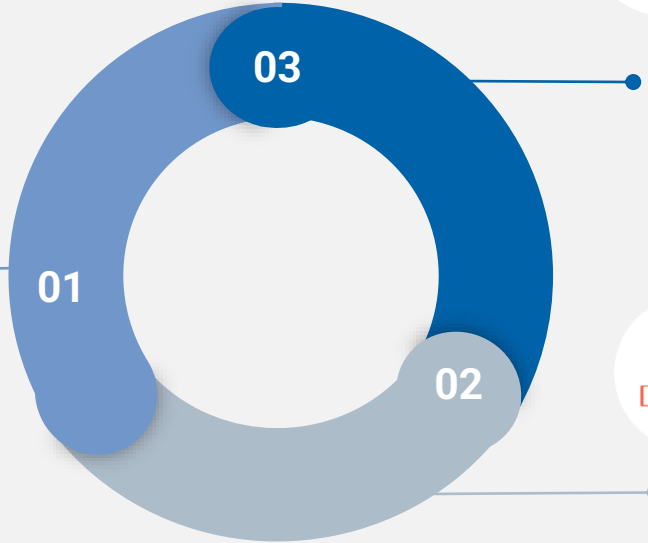
Reference: "How to develop and Document a Contamination Control Strategy" - Guidance Document by the ECA Foundation Version 2.0, December 2022

What is a Contamination Control Strategy?

Stage 1: Develop (or review and refine/improve) the CCS

Identify the risk of contamination and the measures (including procedures, controls, rationale, QRM, etc.) that should be implemented to minimize contamination (Chapter 4.2) as follows:

1. Level A: Explicit Annex 1 Requirements- expressed in figure and numbers
2. Level B: explicit Annex 1 Requirements- written expectations
3. Level C: Implicit or not clearly written requirements for a specific process, situations, or condition



Stage 2: Compile the CCS Documentation

Document all the measures (including procedures, controls, rationale, QRM, etc.) to prove that CCS is implemented (Chapter 4.3).

Stage 3: Evaluate the CCS

Provide evidence that the measures are working to prevent contamination by ongoing and periodic review, resulting in appropriate quality system updates (Chapter 4.4).

Reference: "How to develop and Document a Contamination Control Strategy" - Guidance Document by the ECA Foundation Version 2.0, December 2022

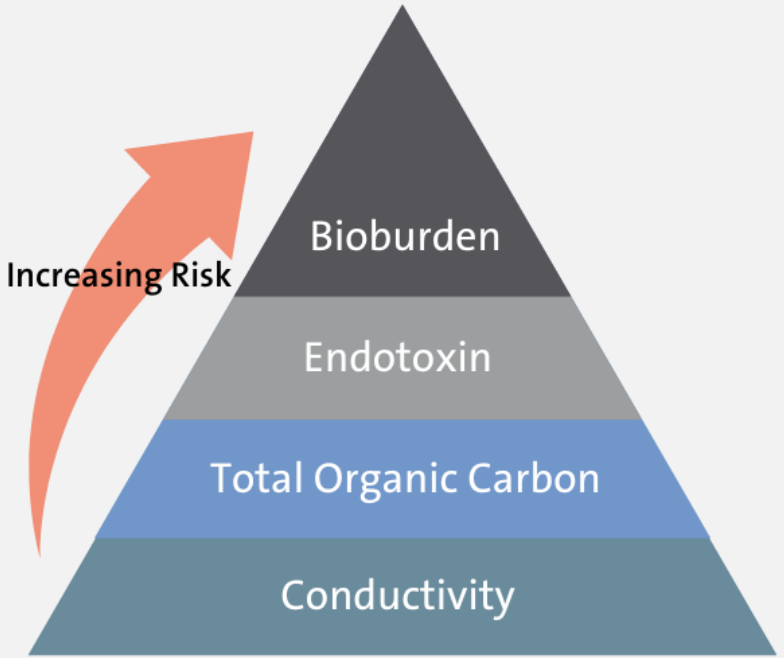
Mitigating Risk through Process Control and Understanding

Types of Risk:

- Time
- Business
- Process
- Patient

To improve **process control** and understanding, process analytical technologies (PAT) should be used:

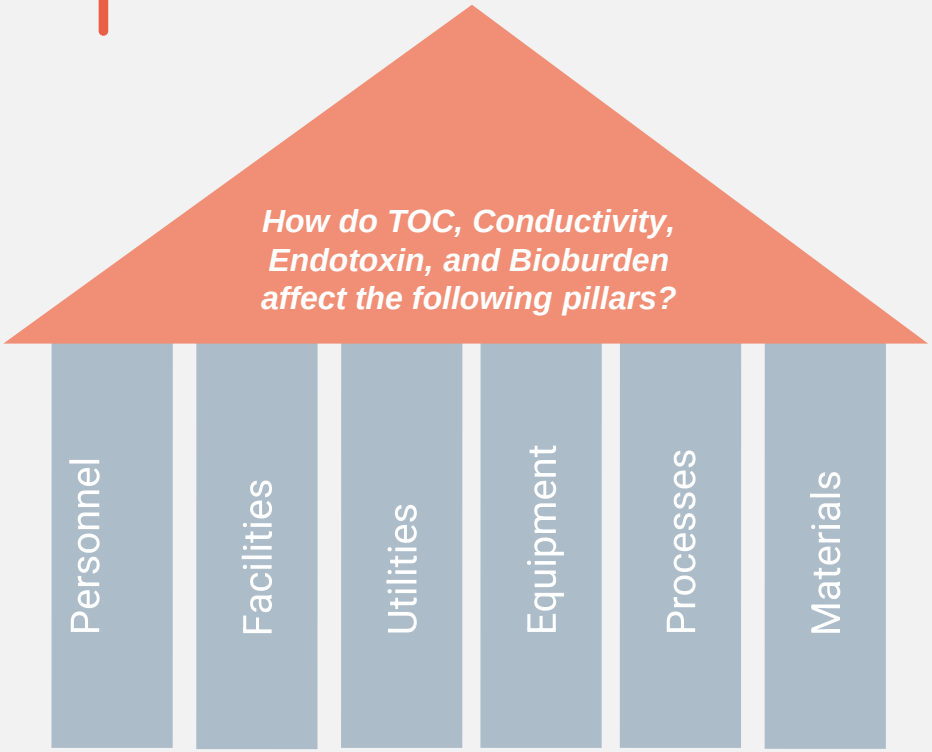
- Track and trend
- Real-time decision making
- Optimize up-time
- Fewer out-of-specification (OOS) investigations



Faster, Easier Process Monitoring

Raw materials, intermediates, and final sterilisation

Annex 1: TOC, Conductivity, Endotoxin, and Bioburden



Released August 22, 2022.

This Annex provides general guidance that should be used in the design and control of facilities, equipment, systems and procedures used for the manufacture of all sterile products applying the principles of Quality Risk Management (QRM), to ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product.

"Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources includes a series of interrelated events and measures. These are typically assessed, controlled and **monitored individually but their collective effectiveness should be considered together."**

Reference: EU GMP Annex 1, Manufacture of Sterile Medicinal Products. Finalized August of 2022 by the European Commission.

Utilities

Water Systems and Production

Risks: Contaminated water systems can lead to microbial in final products, raw materials, and intermediate samples

- TOC and conductivity contamination inherent to organic matter and atmosphere when manually sampling

Solutions:

- **Implement** microfluidic technology for endotoxin testing -> fast and early detection
- **Test** several loops at once, at line or in lab for actionable results
- Microfluidic technology can be used for cleaning **validation** to ensure reduction in endotoxins/biofilms
- **Reduce Time to Results**

"6.15 WFI systems should include continuous monitoring systems such as Total Organic Carbon (TOC) and conductivity, as these may give a better indication of overall system performance than discrete sampling. Sensor locations should be based on risk."

Reference: EU GMP Annex 1, Manufacture of Sterile Medicinal Products. Finalized August of 2022 by the European Commission.

Equipment

- **Cleaning validation:**
  - **TOC** and **conductivity** can indicate residual contamination from product carry-over
  - Sanitization for reduced risk of microbial contamination
  - Rapid micro methods can detect bacteria within turnaround time of equipment.
- Gram-negative bacteria can still be present on equipment even after cleaning
- **Ease of access** and use is important
- **Preventative** maintenance plans
- Equipment that does not have a routine scheduled cleaning can increase the risk of biofilm
  - Rapid micro methods can detect biofilm contamination

“Rapid/alternative methods and continuous monitoring systems should be considered to [protect] the product from potential extraneous sources of… microbial contamination and [for] rapid detection of potential contaminants in the environment and the product.”

Reference: EU GMP Annex 1, Manufacture of Sterile Medicinal Products. Finalized August of 2022 by the European Commission.

Quality Control

“For products with short shelf life, the environmental data for the time of manufacture may not be available; in these cases, the compliance should include a review of the most recent available data.”

Manufacturers of these products should consider the use of rapid/alternative methods

Bioburden: RMMs

- Days to hours for results
- Correlation to plate counts
- Faster turnaround time for production

Endotoxin: Microfluidics

- Minimal analyst hands on
- Less pipetting
- Reagent sustainability

Reference: EU GMP Annex 1, Manufacture of Sterile Medicinal Products. Finalized August of 2022 by the European Commission.

Real-Time Release Testing and Monitoring Strategies

TOC, Conductivity, Bioburden, and BET

Implementing Real-Time Release/Monitoring

Types of validation:

1. Process Validation
2. Alternative Method Validation

Assess

- Accuracy
- Precision
- Specificity
- Linearity
- Limit of Detection
- Limit of Quantitation
- Range

COMPENDIAL REQUIREMENTS FOR PHARMA WATER	
USP <1231>, EP 9.2 & 9.7	WATER FOR PHARMACEUTICAL PURPOSES
USP <643>, EP 2.2.44	TOTAL ORGANIC CARBON
USP <645>, EP 2.2.38	WATER CONDUCTIVITY
USP <61> &<62>, EP 2.6.12	MICROBIOLOGICAL EXAMINATION OF STERILE AND NONSTERILE PRODUCTS: MICROBIAL ENUMERATION TESTS
USP <85>, EP 2.6.14	BACTERIAL ENDOTOXINS TEST
USP <1223>, EP 5.1.6	VALIDATION OF ALTERNATIVE METHODS

Implementing Real-Time Release Testing

Process Validation Step 1: Method Transfer

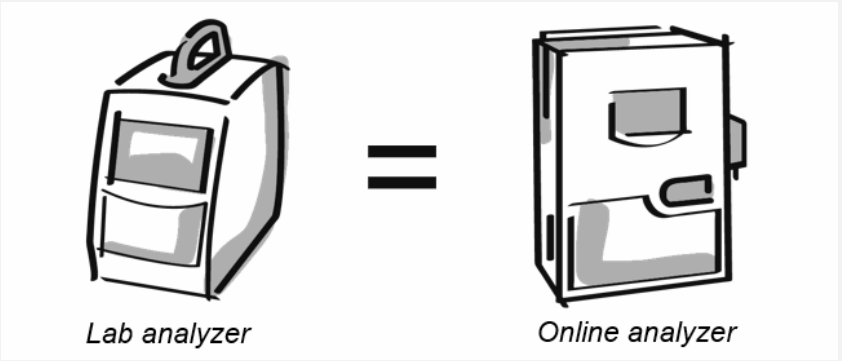
Purpose: To demonstrate instruments “like-for-like”

Process Validation Step 2: Equivalency Study

Purpose: To ensure the online instrument for RTT performs “equivalent or better” than the laboratory instrument

Process Validation Step 3: Point-of-Use Comparability Study

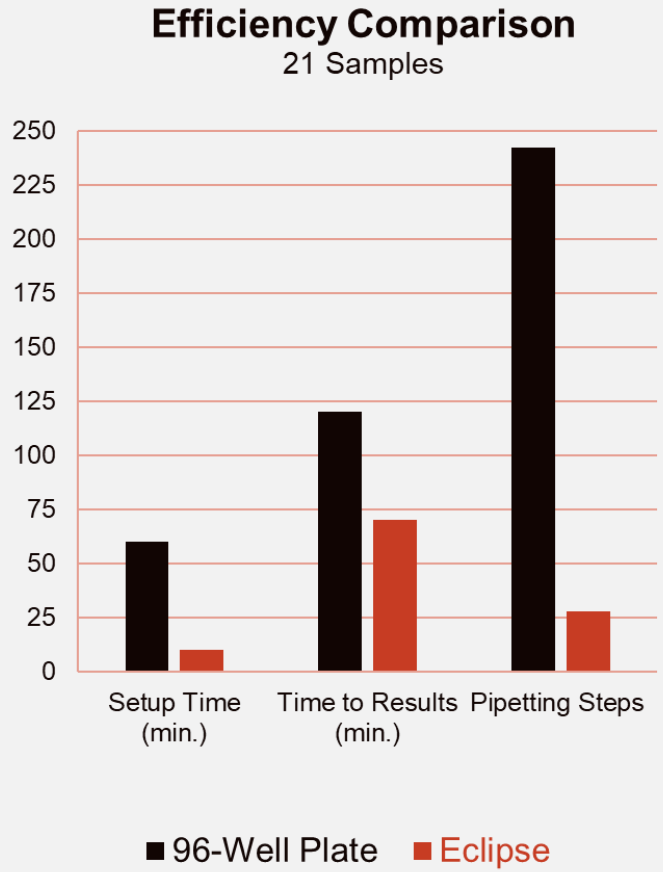
Purpose: To evaluate whether the RTT instrument measurements are reflective of the riskiest POU



How microfluidics can help a CCS using RTRT for BET

“Faster release times, minimal training, and sustainability.”

- Less analyst hands on time = less chance of manual errors
- Easily train at line production technicians on simpler, faster bioburden and endotoxin testing procedures
- New technologies should be considered to reduce the risk of microbial contamination



How RMMs can help a CCS prevent microbial ingress

- CCS should **identify critical points** in the manufacturing process where contamination can occur
- **Routine monitoring** of raw materials, intermediates, CV, and final products is necessary for a CCS
- **Fast turn around time endotoxin and bioburden solutions > Mitigate production risk**
    - No delay in production
    - At line testing can provide results quickly to control the manufacturing process

Cleaning Validation

Comparison of Sampling Modes for Cleaning Validation (CV)

	Advantages	Disadvantages
Lab	• Standard process • Low cost • Highly flexible • Ability to run swabs	• Sampling handling errors • Delayed equipment release • Duplication of review/ approval • Samples queued with other QC testing
At-Line	• Lower initial cost • Highly flexible • Instrument dedicated to cleaning samples • Ability to run swabs	• Sample handling (less than lab) • Data must be transferred
Online	• Total automation • Data integration • Rinse down profile • Process control • Reduced human factors	• Higher initial cost • Low flexibility • No swabs

At-line TOC & Conductivity

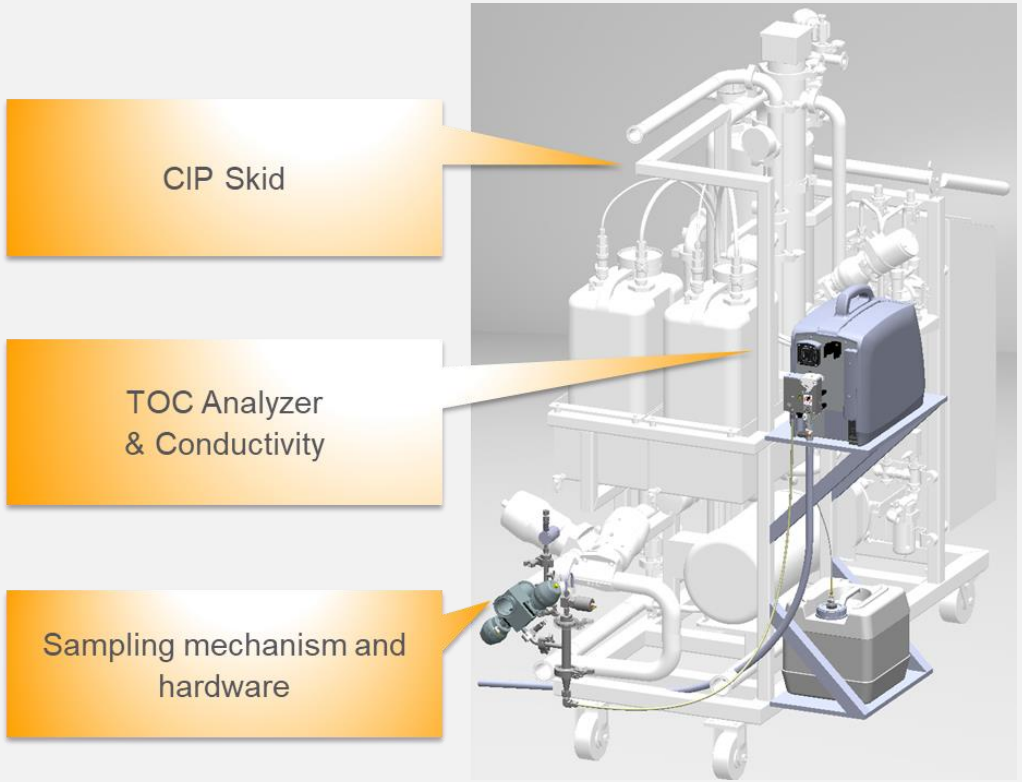
- **Reduced failures** due to sample handling
- **Removes delays** due to QC workflow
- **Removes duplication** of documentation/review/approval
- **Reduced turnaround time** for equipment
- Testing of rinse and swab samples
- Combined **conductivity** and **TOC** sample
- Easy to transfer out the lab method to the plant
- Low capital cost for implementation

Step 1
TOC instrument to production equipment

Step 2
Analyse and generate result

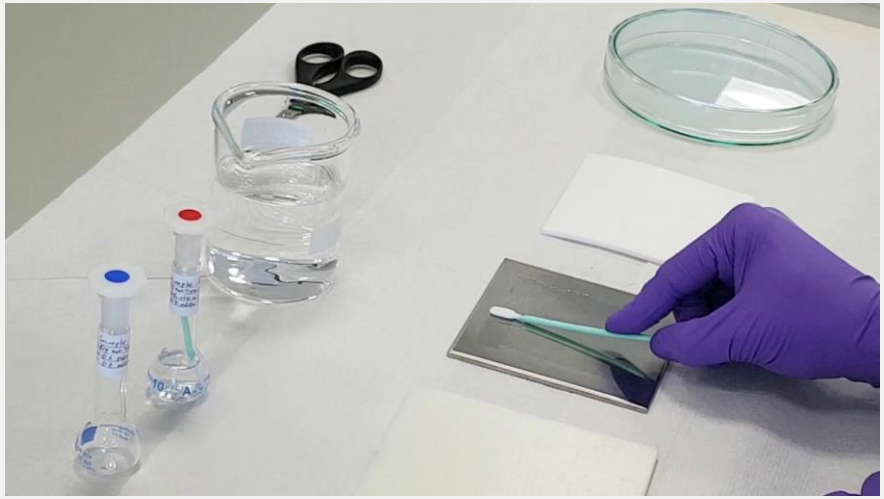
Online TOC & Conductivity

- Trending and Control **(in real time)**
- **Continuous verification** of the validated state
- **Reduced sample variability** (e.g. sampling error)
- Cleaning process **optimization**
- **Removes delays** due to QC workflow
- **Faster release** of equipment



Endotoxin and Bioburden for Cleaning Validation (CV)

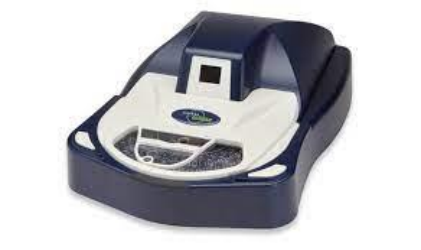
- Testing CV samples for **endotoxin** and **bioburden** is prevalent in the manufacturing of parenteral drugs
- **Mitigate risk** of microbial contamination and carryover
- Apply sanitization step for CV to **reduce microbial contamination**
- **Trend data overtime** by taking a risk-based approach to understanding process capability levels of cleaning program
- Re-validate CV program when new products and/or equipment is introduced to ensure worst-case CV limit is reflective of process changes



Global Solution!!

TOC & Conductivity (Lab & Online):

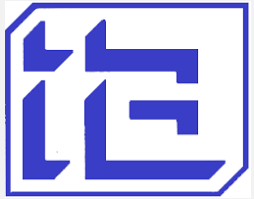
Endotoxin & Bioburden:



Data Management:

Questions?

GRACIAS POR SU ATENCIÓN!



Expertos en Soluciones en Industria Farmacéutica

Cualquier consulta, presentación, demo, no dude en contactar

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References

1. *Annex 1 Manufacture of Sterile Medicinal Products*. European Commission, Aug. 2022
2. *How to Develop and Document a Contamination Control Strategy. ECA Task Force, ECA Foundation, Dec. 2022*