EUROPEAN PHARMACEUTICAL REVIEW

WEBINAR

IMPLEMENTING PHARMA 4.0 ON WATER SYSTEMS

it's time to prepare for Pharma 4.0

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USP <643> & EP 2.2.44, Total Organic Carbon (TOC)

TOTAL ORGANIC CARBON

What is TOC and how does it work?

- Non-specific method
- Intrinsic organics referred to as inorganic carbon (IC)
- Extraneous organics referred to total organic carbon (TOC)
- Total carbon (TC) and inorganic carbon (IC) are measured independently
- TOC = TC - IC

REGULATION

UPW, WFI, Water for Haemodialysis or Pure Steam

- Can be performed online or offline with limit of 500 ppb TOC
- LOD = 0.05 ppm TOC or lower
- System suitability %response efficiency criteria between 85-115%
- % Response efficiency $= 100\,\frac{Rss - Rw}{Rs - Rw}$

"TOC can also be used as a process control attribute to monitor performance of the purification and distribution system." – USP <643>

Regulations Supporting Real-Time Testing

1. **ASTM E2656 “Standard Practice for Real-Time Release Testing of Pharmaceutical Water for the Total Organic Carbon Attribute”**
2. **ICH Q9 Quality Risk Management**
3. **FDA “Guidance For Industry PAT- A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance”**
4. **EMA Guideline on Real Time Release Testing**
5. **EuDraLex Vol 4 Annex 1**

Pharma 4.0

PAT Process Analytical Technology

QbD Quality by Design

RTT / RTRT Real-Time Release Testing

"RTRT is a system of release that gives assurance that the product is of **intended quality**, based on the information collected during the manufacturing process, through product knowledge and on process understanding and control."

29 March 2012
EMA/CHMP/QWP/811210/2009-Rev1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Real Time Release Testing (formerly Guideline on Parametric Release)

Pharma 4.0

RTT / RTRT Real-Time Release Testing

+

21 CFR Part 11 & Data Integrity; data collection, evaluation, trending and retention by suitable IT systems

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Pharma 4.0

EudraLex, Vol. 4, Annex 1 DRAFT

Manufacture of Sterile Medicinal Products

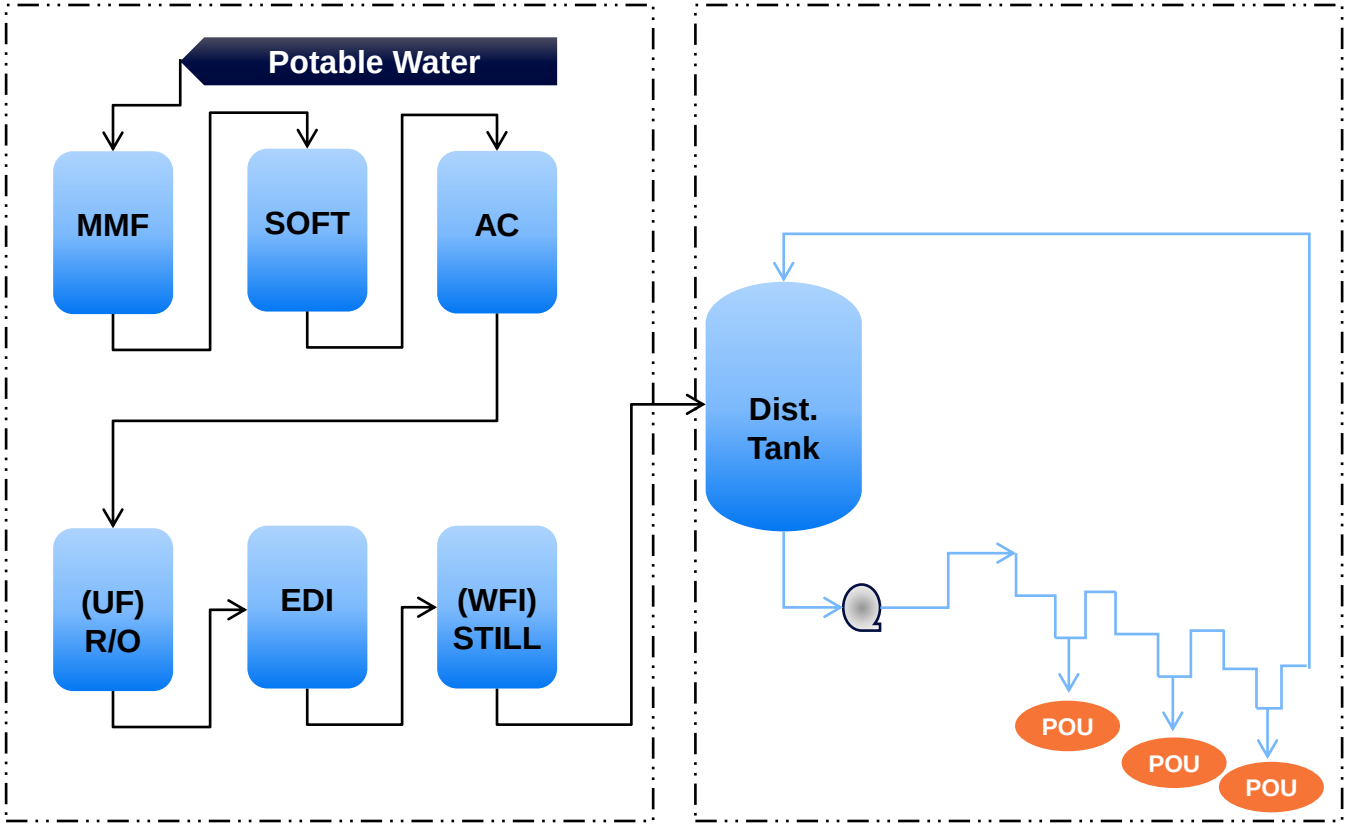
“6.13 Regular ongoing chemical and microbial monitoring of water systems should be performed. Alert levels should be based on the qualification or a review of **ongoing monitoring data** that will identify an adverse trend in system performance. Sampling programs should reflect the requirements of the CCS and include:

i. All points of use, at a specified interval, to ensure that representative water samples are obtained for analysis on a regular basis.
ii. Potential worst case sampling locations.
iii. A sample from the point at the end of the distribution loop each day that the water is used.”

“6.15 WFI systems should include **continuous monitoring systems** such as Total Organic Carbon (TOC) and conductivity, (unless justified otherwise) as these may give a **better indication of overall system performance** than discrete sampling. Sensor locations should be based on risk and the outcome of qualification.”

Generation
(Service Ports)

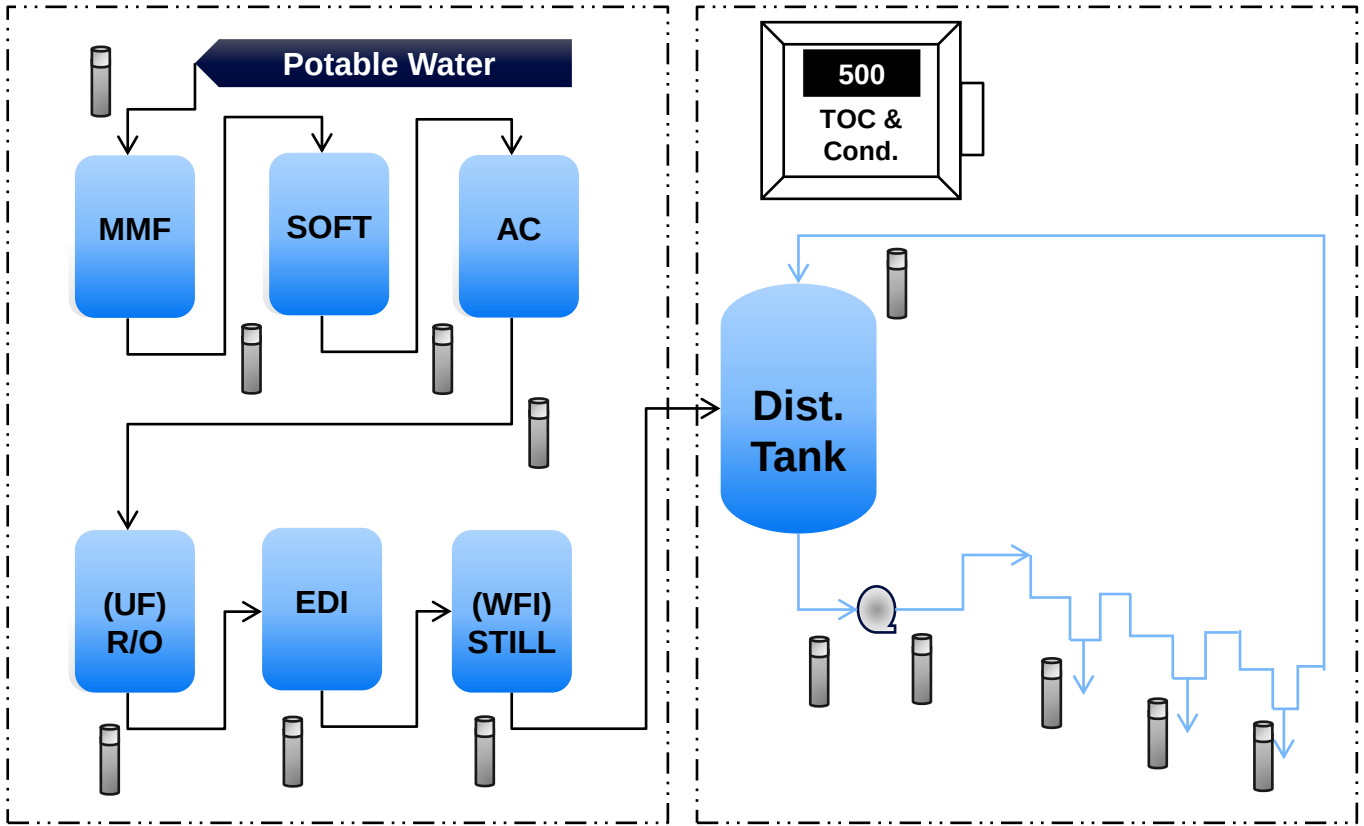
Storage & Distribution
(POU's)



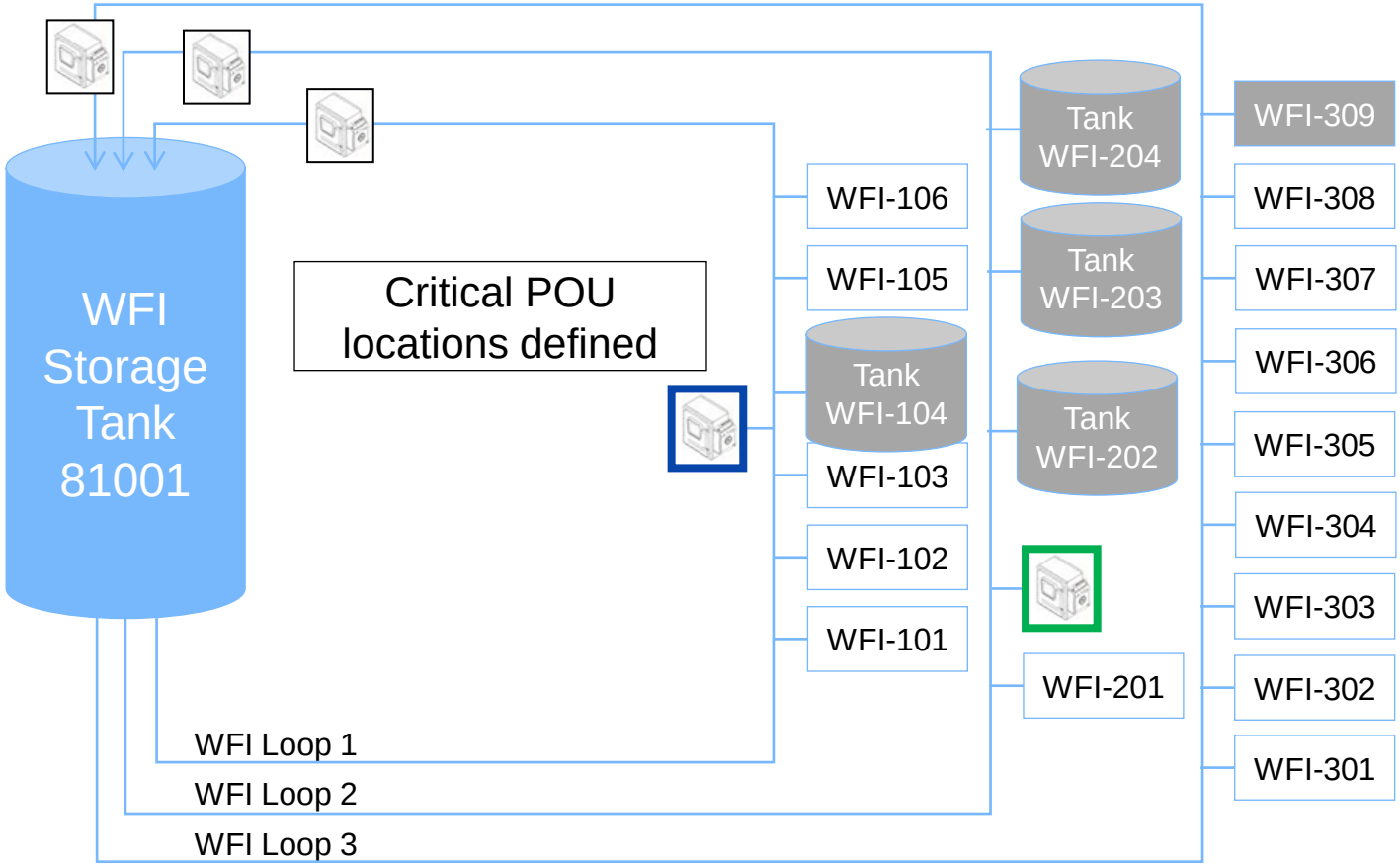
First steps to RTT/RTRT

TOC meters are often located on the return loop of the distribution system, prior to recirculation back to the storage tank.

(Best Practices – See also ASTM E2656)



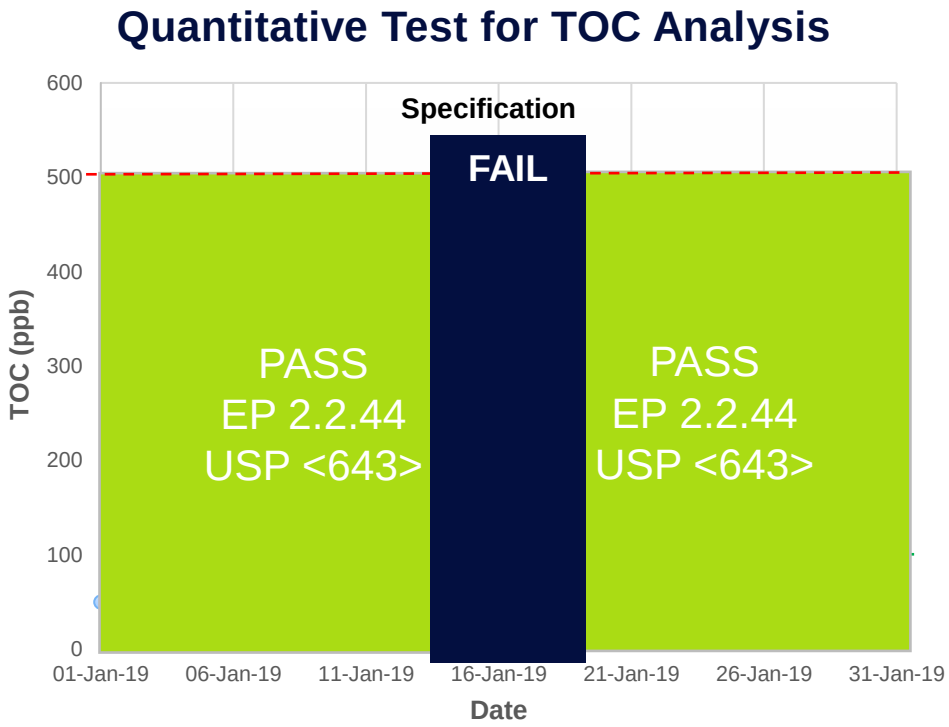
Future State Mapping: OLTOC Locations



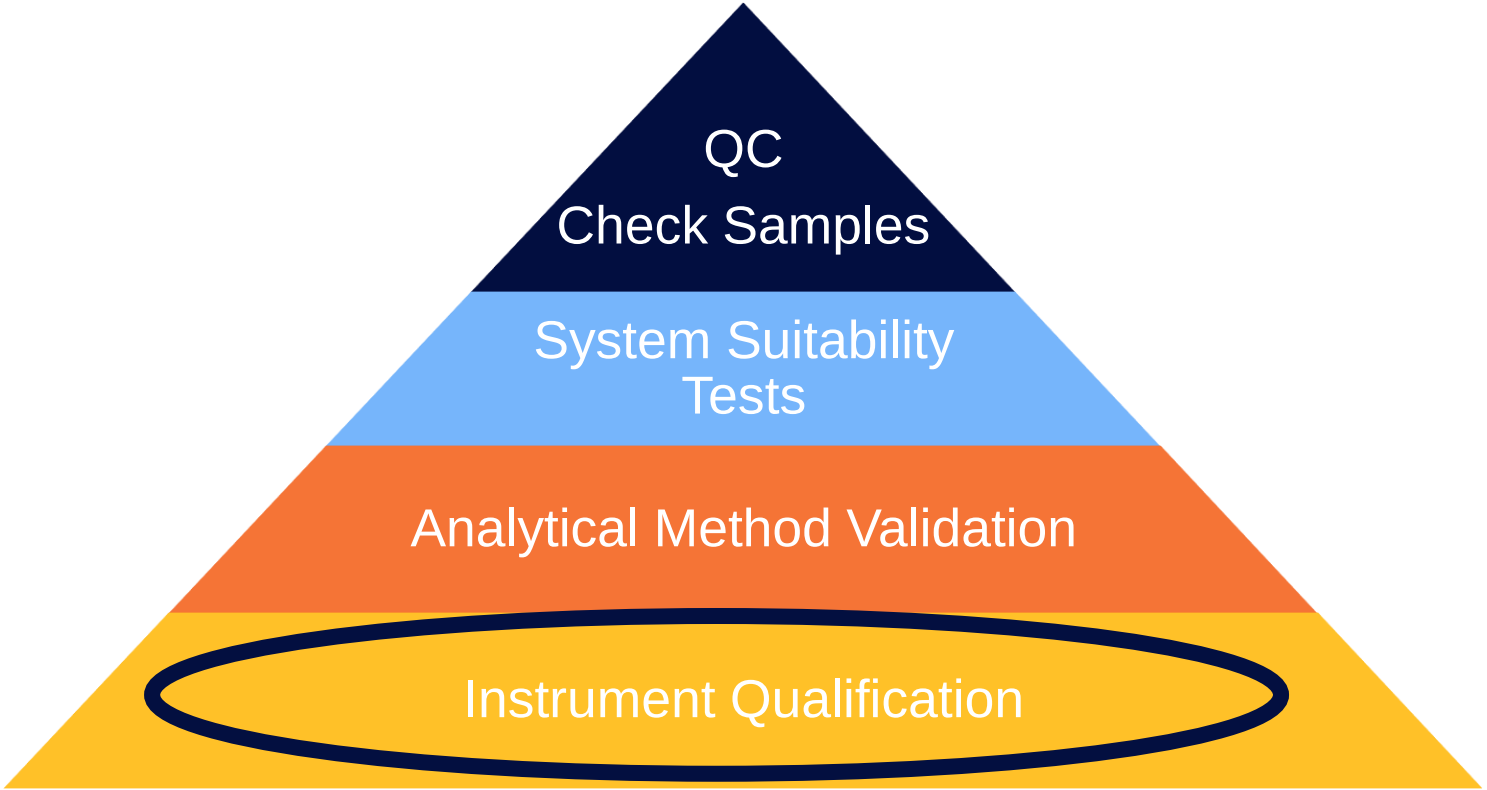
First steps to RTT/RTRT

"To control, trend, and monitor on-line systems and to release water in real-time using quantitative data, the analytical method requires the use of quantitative data, so the analytical method shall be validated to the requirements of the quantitative tests."

- ASTM E2656



Foundational components of data quality – USP <1058>



Installation Qualification

Purpose	Documented evidence that the instrument is properly installed and that the environment is suitable for the instrument
Typical Testing	➢ Receipt Verification ➢ Component Verification ➢ Utility Verification ➢ IT Verification for data storage & compliance ➢ Firmware qualification ➢ COTS qualification

Operation Qualification

Purpose	Documented evidence that demonstrate the instrument can function according to operational specifications in a selected environment
Typical Testing	➢ Functional Testing ➢ COTS Software Qualification ➢ Firmware Qualification ➢ Demonstration of data storage, back-up, archiving, audit trails ➢ Draft SOPs

Performance Qualification (ICH Q2 R1 and USP <1225>)

Purpose	Documented evidence that the system consistently performs according to user specifications
Typical Testing	➢ Repeated testing per SOP ➢ Linearity ➢ Precision ➢ Accuracy ➢ Robustness ➢ Specificity ➢ Limit of Detection & Limit of Quantitation

Best Practices: Data Analysis

USE ALL OF THE DATA AT YOUR DISPOSAL!

- OOS Support
- Process optimization, understanding, & control

	Process In Control	Inorganic Ionic Contamination	CO2 Contamination	Organic Ionic Contamination	Organic Non-ionic Contamination
Conductivity	→	↗	↗	↗	→
Inorganic Carbon (IC)	→	→	↗	→	→
Total Organic Carbon (TOC)	→	→	→	↗	↗
Contamination Source Examples		**Potassium Chloride (KCl)**	**Process open to atmosphere**	**Citric Acid ($C_6H_8O_7$)**	**Sucrose ($C_{12}H_{22}O_{11}$)**

Data Requirements and Handling

ADVANCED DATA MANAGEMENT:

- **supports** 21 CFR Part 11 & ALCOA+ Data Integrity regulations and guidance
- **exports** data in encrypted and password protected legible file formats
- **ensures** data retention by data management software that allows digital signatures, reporting and collection of data from analyzers and access to GMP data throughout the retention period

Key Points

- RTRT with TOC ensures quality of in-process and/or final product based on process data
- Limits based on process performance to enable process control
- Robust process analytical technology to generate validated quantitative data
- Robust materials of construction resistant to challenging compounds
- The power of validated data enables enhanced process troubleshooting and diagnostics
- Today it’s all about data!

Advancing the SIEVERS legacy

The Sievers M500 Online TOC Analyzer revolutionizes online detection of organics by bringing new **performance, design, and data management** features to the industry-leading Sievers TOC platform.

accuracy. efficiency. integrity.

Sievers M500: Designed for Today's Data

The Sievers M500 supports compliance to 21 CFR Part 11 and adherence to US FDA and other Pharmacopoeia Data Integrity guidelines using new digital features:

DATA TRANSFER

- Remote access
- Ethernet and WiFi
- Advanced communications using 4-20 mA, Modbus, Profinet, and binary

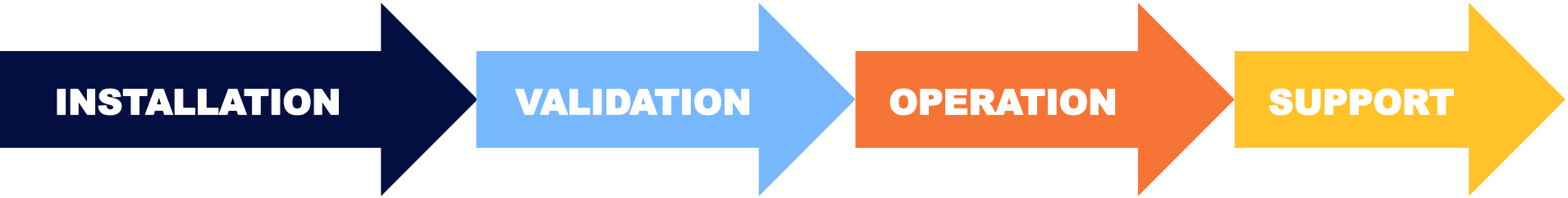
DATA SECURITY

- Password protection
- Data encryption
- Customizable access, roles, and permissions

WEB-BASED DATA MANAGEMENT

- Closed system architecture
- Customizable data transfer and export

Full Lifecycle Support and Services



- Field Service Engineers (FSE)
- Onsite installation
- Training
- Documentation
- Software

- Field Service Engineers (FSE)
- Validation Packages
- Onsite validation services

- Certified reference materials
- Vials and consumables
- Customized reference standards
- Preventive Maintenance Agreements (PMA)

- Technical support
- Diagnostics
- Onsite repairs
- Failure Analysis Reports (FAR)
- Application Support
- Warranty
- Upgrades

Online Resources

- **WWW.SUEZWATERTECHNOLOGIES.COM/SIEVERS**
  - Pharmaceutical solutions
  - M500 TOC Analyzer
  - Vials & Standards
  - Cleaning Validation
  - RTRT
  - HPLC vs TOC
  - On-Demand webinar series
  - Sign up to receive emails (1-2 month max) with product updates, services, webinars, and events
- **DOCUMENT LIBRARY**
  - WTS & AI case studies, technical paper, app notes, brochures, etc.
- **YOUTUBE**
  - 1-4 minute videos on Sievers technology, pharma solutions, cleaning validation, M500 Analyzer, TOC, more
- **LINKEDIN**
  - Analytical Instruments page
  - SUEZ - Water Technologies & Solutions page

Attendee Q&A