QUALITY CONTROL TESTING INSTRUMENTATION SOLUTIONS FOR GMP MANUFACTURING

- Raw Materials QC
- Production QC
- Final Product QC

"Data integrity refers to the completeness, consistency and accuracy of data. Complete, consistent and accurate data should be attributable, legible, contemporaneous recorded, original or true copy and accurate (ALCOA)." [1]

CHARACTERIZED *by ingenuity.*

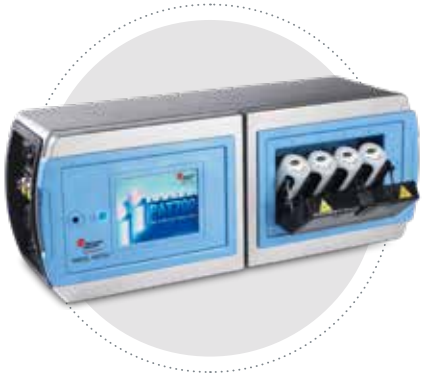
BECKMAN COULTER Life Sciences

Purified Water (PW) Testing

Purified Water is used to produce nonparenteral preparations and other pharma applications, including tests/assays for which water is indicated.

SOP parameters can be pre-programed into the instrument and automated for testing to meet EP 2.2.44 Total Organic Carbon, USP<645> Water Conductivity, USP <643> Total Organic Carbon Analysis, and International Conference on Harmonization (ICH) Q2 standards. Pharmacopoeial requirements for PW production include:

- Must meet requirements for ionic and organic chemical purity, and be protected from microbial contamination
- Source water can be purified via deionization, distillation, reverse osmosis or other suitable purification process
- Purified water systems must be validated to ensure they reliably/consistently produce water of acceptable quality
- Systems operated under ambient conditions require monitoring and frequent sanitization



Use the ANATEL PAT700 for on-line release testing for Conductivity and TOC Analysis

Use the QbD1200 for point-of-use grab sample analysis for TOC Analysis

Water for Injection (WFI) Testing

WFI is used to produce parenteral and other preparations where endotoxin content must be strictly controlled

SOP parameters can be pre-programed into the instrument and automated for testing to meet EP 2.2.44 Total Organic Carbon, USP<645> Water Conductivity, USP <643> Total Organic Carbon Analysis, and International Conference on Harmonization (ICH) Q2 standards. Pharmacopoeial requirements for WFI production include:

- WFI must meet all requirements for Purified Water—plus specifications for bacterial endotoxins prone to inhabit water
- Tests for total organic carbon (TOC) and water conductivity apply to WFI produced onsite for use in manufacturing
- Action Levels for WFI in USP <1231> (10 cfu/100 mL) are considered to represent a level above which the water is unfit for use
- On-line testing can avoid contamination risks and provide immediate analysis and opportunities for real-time control/intervention

Use the ANATEL PAT700 for on-line release testing for Conductivity and TOC Analysis

Use the QbD1200 for point-of-use grab sample analysis for TOC Analysis

Active Pharmaceutical Ingredient (API)/ Excipients Powder Granule Sizing

Formulations include APIs, excipients (non-active ingredients), such as diluents (an active filler to achieve a reasonable final pill size), and disintegrating agents to regulate the tablet's dissolution time after administration[2]

- Granule sizing consistency ensures pills dissolve at the right time and they don't crumble under pressing
- SOP parameters pre-programed into the instrument and automated for detection of: homogeneous mixture of API and excipients, detection of 'fines' (particles <1micron in size) in tablet manufacturing, correct size distribution for formulation, etc.

Particle size is a critical component to efficient efficacy, our product solution is the LS 13 320 XR particle size analyzer.

Instrument	Application	Regulation	A	L	C	O	A
ANATEL PAT700	On-line Water for Injection (WFI), Purified Water (PW) Total Organic Carbon (TOC), Temperature and Conductivity	USP<643> USP<645> EP2.2.44 EP2.2.38	Multi-level, individual User Name and Password for all users	Legible, secure PDF export for Alarm Trail, Audit Trail, Measurement Results	Secure PDF created on day of sample analysis	Original electronic record created directly from the instrument	SOP parameters pre-programed into the instrument and automated
QbD1200	Grab-sample point of use testing for Water for Injection (WFI), Purified Water (PW) Total Organic Carbon (TOC),	USP<643> EP2.2.44	Multi-level, individual User Name and Password for all users	Legible, secure PDF export for Alarm Trail, Audit Trail, Measurement Results	Secure PDF created on day of sample analysis	Original electronic record created directly from the instrument	SOP parameters pre-programed into the instrument and automated
LS 13 320 XR	Active Pharma-ceutical Ingredient, Excipients	ISO 13320	Multi-level, individual User Name and Password for all users	Legible, secure PDF export as well as Audit Trail and Measurement Results	Secure PDF created on day of sample analysis	Original electronic record created directly from the instrument	SOP parameters pre-programed into the instrument and automated

Raw Materials — WFI Treatment Facility — Bioreactor Production Bulk Drug Product — Final Product Cleanroom — Drug Stability Formulation Testing — Final Product Quality Control

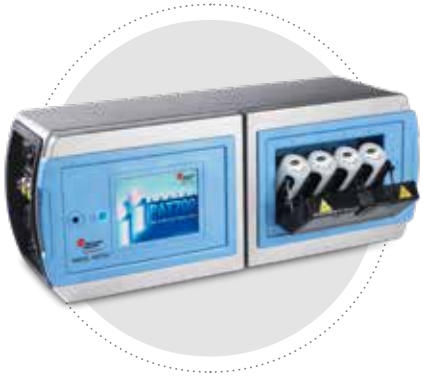
Clean-in-Place (CIP) Processes

CIP systems are becoming standard for pharmaceutical manufacturing facilities regulated by good manufacturing practices (GMP)

- CIP systems can be fully or semi-automated to require minimal operator intervention
- Parameters such as time, action, concentration (of cleaning agents) and temperature (TACT) determine CIP process outcomes
- Carefully controlling TACT parameters—and documentation for process validation and product-batch release—help ensure consistent success of CIP protocols
- Automating QC processes for CIP systems (e.g., monitoring total organic carbon) can help avoid production delays

Use the QbD1200 during CIP program development, validation, and/or for final rinse grab sample analysis for validated CIP programs

Use the ANATEL PAT700 for fast on-line testing of final rinse in validated CIP programs in order to release cleaned vessels back into production quicker than waiting for manual grab samples analysis.



Monitoring Cell Viability

Providing assessment of concentration of viable cells for biopharmaceutical manufacturing and pharmacology research, e.g. cancer research.

The trypan blue dye exclusion method, which identifies live cells based on membrane integrity, is a proven technique used for a variety of important research purposes, including:

- Characterizing cell line growth patterns to identify the fastest-growing lines
- Monitoring cell proliferation to determine growth rates
- Conducting cytotoxicity studies to track the speed of cell death
- Optimizing cell feeding strategies to ensure the most cost-effective use of resources

Use the Vi-CELL BLU for high-throughput cell viability analysis

Mammalian Cell Bioreactor Media Health

Detect small changes in metabolic activity in different cell types

- The Vi-CELL MetaFLEX has 3 dedicated QC solutions
  - Automatic failure detection and resolution
  - Continuous system and analysis checks including automatic lockout of parameter(s) that fail QC
  - Customizable QC schedule

Use the Vi-CELL MetaFLEX for fast, accurate analysis of bioreactor media health.

Instrument	Application	Regulation	A	L	C	O	A
Vi-CELL BLU	Mammalian cell viability and concentration	USP <1046>	Multi-level, individual User Name and Password for all users	Legible, secure PDF export for measurement results	Secure data records stored and tracked at time of measurement	Original electronic record created directly from the instrument	SOP parameters pre-programed into the instrument and automated
Vi-CELL MetaFLEX	Mammalian cell bioreactor media health		Multi-level, individual User Name and Password for all users	Legible, reports can be printed or viewed on the instrument	Secure data records stored and tracked at time of measurement	Original electronic record created directly from the instrument	SOP parameters pre-programed into the instrument and automated
MET ONE 3400	Routine environmental monitoring (air particulates) in sterile manufacturing cleanrooms	EU GMP Annex 1 CGMP ISO 14644-1 & -2	Multi-level, individual User Name and Password for all users	Legible, secure PDF export for Measurement Results including metadata	Secure PDF created on day of sample analysis	Original electronic record created directly from the instrument	SOP parameters pre-programed into the instrument and automated
MET ONE Facility Monitoring System	Sterile manufacturing cleanroom continuous air particulate monitoring	EU GMP Annex 1 CGMP ISO 14644-2	Multi-level, individual User Name and Password for all users	Legible, secure PDF export for Alarm Trail, Audit Trail, Measurement Results	Secure data records stored in database at time of measurement	Original electronic record created directly from the instrument	Your SOPs pre-programmed into the User Interface and automated. No manual data entry or Pass/Fail calculations

Raw Materials — WFI Treatment Facility — Bioreactor Production Bulk Drug Product — Final Product Cleanroom — Drug Stability Formulation Testing — Final Product Quality Control

Cleanroom Monitoring

Parenteral/injectable drugs must be manufactured in a controlled environment according to EU GMP Annex 1 and CGMP where particulate levels in the air are controlled.

Routine environmental SOP parameters can be pre-programed into the instrument and automated for testing to:

- EU GMP Annex 1 Manufacture of Sterile Medicinal Products
- CGMP Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice
- ISO 14644-1 Cleanrooms and associated controlled environments Part 1: Classification of air cleanliness by particle concentration
- ISO 14644-2 Cleanrooms and associated controlled environments

Use MET ONE Portable Air Particle Counters to reduce complexity of cleanroom environmental monitoring programs.

Facility Monitoring Systems (FMS)

Particle monitoring for GMP compliant pharmaceutical manufacturing

- Particle size and concentration monitoring compliant with EU GMP Annex 1 and FDA 21 CFR Part 11
- Built in Audit Logging
- Custom reports to record results
- IQ/OQ documentation for simple validation
- Small scale, rapidly deployed pre-packaged software and hardware for isolators and small production line
- Batch workflow system for one or more production lines with several monitoring points
- Custom workflow optimized solutions for monitoring complex production methods across several production lines

The MET ONE FMS Systems can incorporate the MET ONE 3400, MET ONE 6000, MET ONE 6000P, MET ONE 7000, and the MET ONE Manifold particle counting system

Use MET ONE FMS Systems for continuous and routine environmental monitoring

Final Quality Testing

QC FOR INJECTABLES/PARENTERALS

When performing final quality testing for injectable drugs, it's easy to contaminate samples and produce costly errors in Pass/Fail calculations.

SOP parameters pre-programed into the instrument and automated for testing to demonstrate compliance to USP<787>, USP<788>, etc.

- Liquid particle counters (e.g., the HIAC 9703+ instrument) help minimize false-positive fails
- The HIAC 9703+ Pharmaceutical Liquid Particle Counter can simplify QC by automatically recommending actions if:
  - Sensors have been contaminated
  - Bubbles may have affected QC results
  - Calibration or routine service is required

VISIBLE PARTICULATE INSPECTION

Stability studies are often conducted on parenteral formulations to characterize size distributions

The Multisizer enables Coulter-based counting and sizing of particles independently of their interaction with light

- SOP parameters can be programmed into the instrument to enable automated testing to demonstrate compliance to USP<788>
- The Coulter principle can be used as a complementary, orthogonal technique for USP <788> and USP <790>

Instrument	Application	Regulation	A	L	C	O	A
HIAC 9703+	Final product sub-visible particulate counting in parenteral drug products	USP<787> USP<788> USP <789>	Multi-level, individual User Name and Password for all users	Legible, secure PDF export for Alarm Trail, Audit Trail, Measurement Results	Secure PDF created on day of sample analysis	Original electronic record created directly from the instrument	SOP parameters pre-programed into the instrument and automated
Multisizer 4e	Final product visible particulates counting in parenteral drug products		Multi-level, individual User Name and Password for all Users	Legible secure PDF export for Audit Trail, Measurement Results	Secure PDF created on day of sample analysis	Original electronic record created directly from the instrument	SOP parameters pre-programed into the instrument and automated

References:

1. U.S. Department of Health and Human Services Food and Drug Administration, Data Integrity and Compliance with Drug cGMP Questions and Answers Guidance for Industry, FDA-2018-D-3984, December 2018, page 4. **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-integrity-and-compliance-drug-cgmp-questions-and-answers-guidance-industry**
2. Roossin, Paul. Pill Manufacturing - A Second Revolution? April 1, 2015. Research and Development Magazine. **https://www.rdmag.com/article/2015/04/pill-manufacturing-%E2%80%93-second-revolution**

Drug Production Applications

- Purified Water PW QC
- Water for Injection WFI
- Clean in Place CIP
- Cleanroom Environmental Monitoring
- Monitoring Cell Viability

Final Product Quality Testing Applications

- Protein Stability testing
- Cleanroom Monitoring
- Final Quality Testing Particulate Matter

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