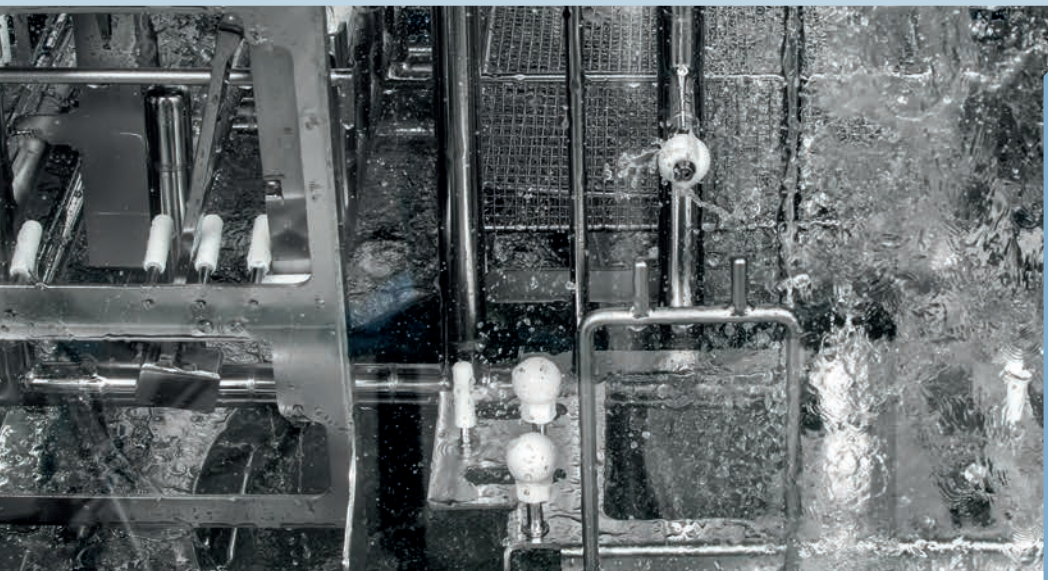

NEW ANNEX 1

How IWT can support its compliancy

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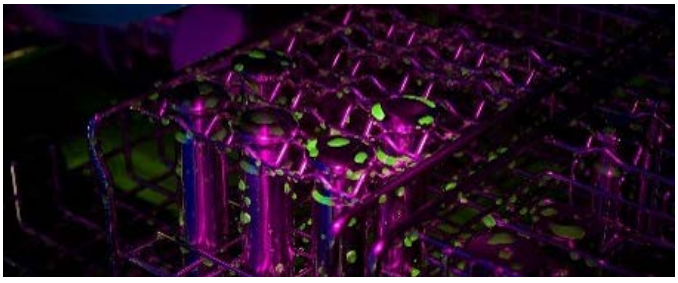
INTRODUCTION

IWT supports pharmaceutical enterprises' in their aim to minimize any risk of microbial, particulate and endotoxin/pyrogen contamination as demanded by the latest ANNEX 1 regulatory enhancements.
The designing of any IWT cleaning equipment is managed in accordance with Quality Risk Management (QRM) principles to provide a proactive means of identifying, evaluating and controlling potential risks to quality on final sterile and non-sterile products manufactured by our business partners.

ANNEX 1

"Automatic Cleaning operations, in order to establish robust assurance of contamination prevention, are an essential element of any accurate Contamination Control Strategy (CCS) implemented across the facility to manage risks to medicinal product quality and safety"

(ref. new ANNEX 1 section 2.5 xiii)



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DOCUMENTATION, CERTIFICATES AND TRACEABILITY

1

ANNEX 1

5.1 A written, detailed description of the equipment design should be available (including process and instrumentation diagrams as appropriate). This should form part of the initial qualification package and be kept up to date

6.5 Records of utility system installation should be maintained throughout the system's life-cycle. Such records should include current drawings and schematic diagrams, construction material lists and system specifications. Typically, important information includes attributes such as:

i. Pipeline flow direction, slopes, diameter and length.
ii. Tank and vessel details.
iii. Valves, filters, drains, sampling and user points

Full Design Qualification, Certification and Validation packages are available for IWT equipment:

- HDS, MDS, FDS and SDS;
- FDA and 3.1 Certificates, with related traceability and cross-reference on equipment drawings, for materials in contact with process fluids;
- Datasheets as per electrical and process diagrams;
- RTM (Requirements Traceability Matrix) with all references between IWT documentation and URS

  in a matrixial format to track the completeness of the relationships
- Welding book (WPS, WPQR, Welders' test certificates, welding and inspection log), endoscopic inspections, welds traceability by mean of drawing maps and indelible tagging on machine piping;
- Factory Acceptance Tests and on-site qualification packages (SAT, IQ, OQ, PQ);
- Riboflavin test protocol, execution and related report.

(ref. new ANNEX 1 section 5.1, 6.5)

CLEANING VALIDATION AND PROCESS CONTROL

2

ANNEX 1

5.4 The cleaning process should be validated to be able to:
i. Remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used.
ii. Minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.

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

IWT high performing cleaning equipment is qualified to effectively sanitize and disinfect the specific batch load. Powerful mechanical action to remove residue and debris; an accurate detergent and/or disinfecting agent dosage; in-process conductivity monitoring and temperature control; contact parts punctual, repeatable, fully drainable positioning on washing racks: these are the key factors for validated results. Up to 20 phases among wash, rinse by recirculation and/or single pass rinse with WFI, drying and cooling can be totally tuned (time, temperature, detergents concentration, water quality, final and in-process conductivity monitoring) during cycle development to achieve the expected results.

(ref. new ANNEX 1 section 5.4, 6.15)

CRITICAL PARAMETERS MONITORING AND PROCESS CONTROL

3

ANNEX 1

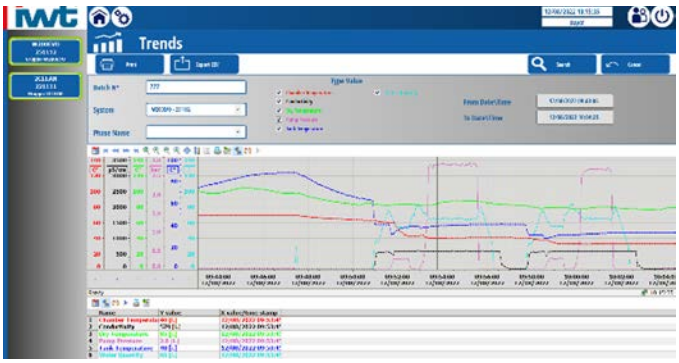
6.3 Utilities should be designed, installed, qualified, operated, maintained and monitored in a manner to ensure that the utility system functions as expected.

6.4 Results for critical parameters and critical quality attributes of high risk utilities should be subject to regular trend analysis to ensure that system capabilities remain appropriate.

Data collection, storage and related data integrity needs to be guaranteed as part of pharmaceutical regulatory compliancy. IWT capabilities for reports and traceability allow for 21 CFR part 11 regulations and Annex 11 EU GMP to be met with a greater degree of accuracy and quality control.

Audit trail, batch information and GMP critical process parameters trends (ERES Electronic Records and Signatures), machine status, alarm and cycle logs, I/O status are directly manageable via IWT CleanView SCADA system for routinary analysis or root-cause verifications.

(ref. new ANNEX 1 section 6.3, 6.4)



SAMPLING POINTS

4

ANNEX 1

6.1 The nature and extent of controls applied to utility systems should be commensurate with the risk to product quality associated with the utility. The impact should be determined via a risk assessment and documented as part of the CCS.

6.2 In general, higher risk utilities are those that: Directly contact product e.g. water for washing and rinsing, gases and steam for sterilisation; Contact materials that will ultimately become part of the product.

Water inlets used for washing and rinsing, being in direct contact with process items, are a potential source of risk to final product. Their monitoring and controlling should be an integral part of properly developed CCS, regardless of original water quality type (RO, PW, WFI), via QA regular sampling and analysis.

IWT offers a set of standard solutions directly equipped on-board of its washing equipment to manually or automatically sample incoming water lines and process solution to allow Quality Representative an easy, quick and safe batch collections for planned controls.

(ref. new ANNEX 1 section 6.1, 6.2)

SERVICEABILITY

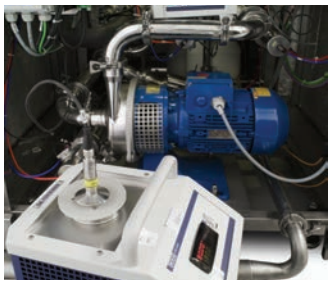
5

ANNEX 1

5.3 As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance, and repairs can be performed outside the cleanroom. If maintenance has to be performed in the cleanroom, and the required standards of cleanliness and/or asepsis cannot be maintained, then precautions such as restricting access to the work area to specified personnel, generation of clearly defined work protocols and maintenance procedures should be considered.

IWT equipment is designed to be installed flushed between separation walls either on loading and unloading ends. A dedicated bioseal can be equipped to prevent crossflows between differently classified areas (cleanrooms and technical spaces). Accessibilities for maintenance and service activities are engineered to be performed either from side technical area or mezzanine. Particular attention is placed in the ease of intervention with aid tools to improve components reachability without compromising the general equipment compactness.

(ref. new ANNEX 1 section 5.3)



MAINTENANCE

6

ANNEX 1

5.6 All equipment such as sterilisers, air handling systems (including air filtration) and water systems should be subject to qualification, monitoring and planned maintenance. Upon completion of maintenance, their return to use should be approved.

7.3 All personnel including those performing cleaning, maintenance, monitoring and those that access cleanrooms should receive regular training, gowning qualification and assessment in disciplines relevant to the correct manufacture of sterile products.

Preventive maintenance and calibrations accordingly to the scheduled service program, as described in the Original Instructions for Use of IWT equipment, are mandatory steps to ensure efficiency and efficacy along time of any automatic washing system.

All required yearly Wear&Tear components, including filtering units where the status is constantly monitored by differential pressure readers, are bundled by serial number in organized sets to guarantee smooth, quick and safe on-site activities.

IWT performs regular training and certification of field technicians and engineers with the aim to keep up the pace with either the latest technical innovations and client's good practices and procedures to access operating classified areas.

(ref. new ANNEX 1 section 5.6, 7.3)