GENERAL SPECIFICATION

TECHNICAL & VALIDATION DOCUMENTATION

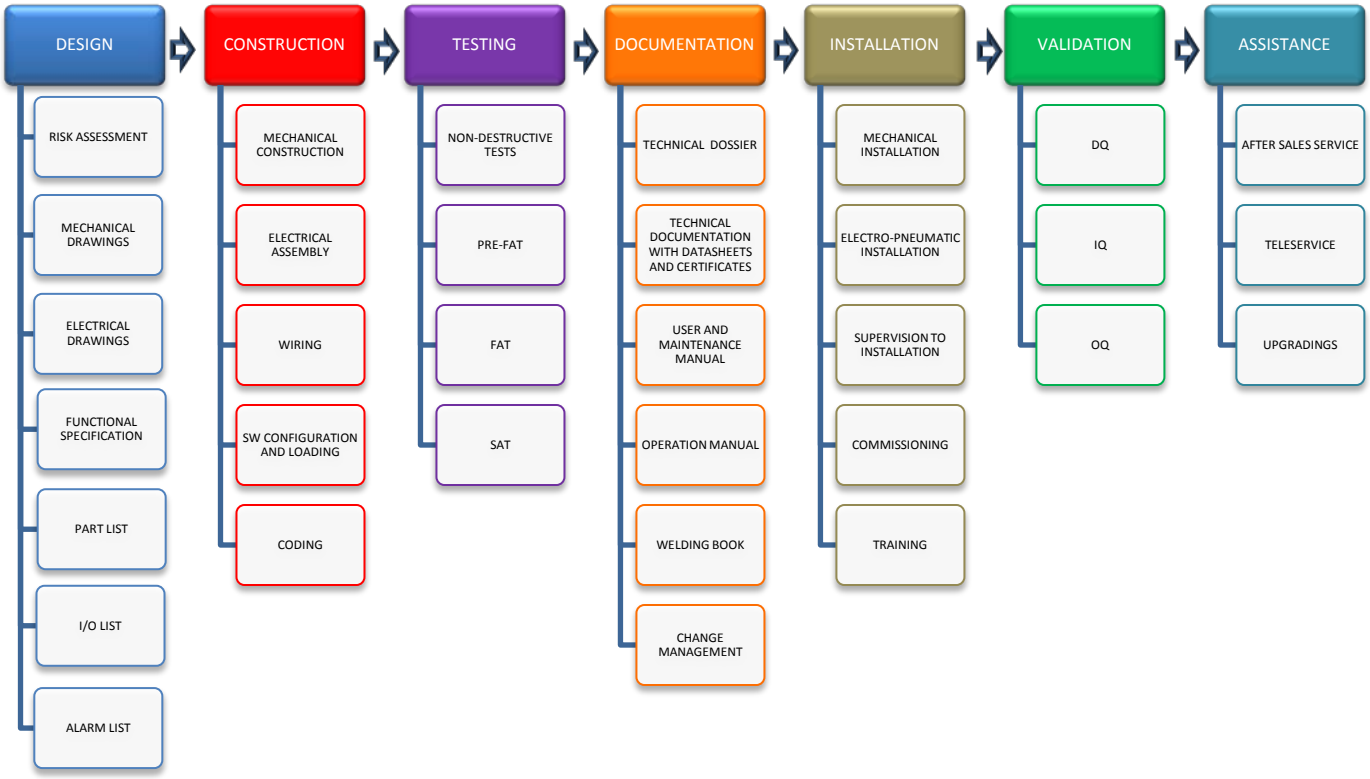
EQUIPMENT

REVISIONS HISTORY					
#	Date	Description	Issued	Verified	Approved
0	06.08.2013	First issue	Cristina Opl	Francesca Fresegna	Gianni Opl
1	26.09.2014	General revision	Cristina Opl	Francesca Fresegna	Gianni Opl
2	26.02.2015	General revision	Cristina Opl	Valentina Cucci	Gianni Opl

CONTENTS

1. ACTIVITIES FOR PROJECT DEVELOPMENT

BRAM-COR develops the turn-key project in compliance with GMP manufacturing practices according to following scheme:



BRAM-COR S.p.A. activities are regulated by BRAM-COR Corporate Quality System and described in the Quality Manual, detailed by the relevant Standard Operating procedures. The following list defines main BRAM-COR certified Quality System Procedures and main Operating Instructions regulating Design, Construction, Testing and Project Managing activities.

Activity	Procedure	Title
Design	PO 73_01	Design Management
Purchase	PO 74_01	Purchase Management
	PO 74_02	Supplier's Assessment
Production and Installation	PO 75_01	Job Management
	PO 75_02	Customer's Properties
	PO 75_03	Assistance
	PO 75_04	Identification and Traceability
	PO 75_05	Process Control
	PO 75_06	Delivery and Commissioning
	PO 75_08	Machines Construction
	PO 75_09	Sanitary Piping
	PO 75_10	Technical Documentation
Inspection & Monitoring	PO 76_01	Measuring Instruments Management
	PO 83_01	CAPA Management

2. GMP REGULATORY STANDARDS

A list of GMP reference standards for BRAM-COR activities includes:

- ISPE Guideline: "Sterile Manufacturing facilities" Vol. 3
- ISPE Guideline: "Water & steam systems" – Vol. 4
- European Pharmacopoeia 8th edition
- 2006/42/CE European Directive for Machinery
- EudraLex -The Rules Governing Medicinal Products in the European Union-Volume 4 Good Manufacturing Practice-Medicinal Products for Human and Veterinary Use
- USP 38
- GAMP 5: "A risk-based approach to compliant GXP computerized systems"
- 21 CFR part 11
- ASME BPE-2014 "Bioprocessing Equipment"
- UNI EN ISO 9606:2013 "Qualification of welders" - Manual welding
- UNI EN 14732:2013 "Qualification of welders" - Automatic welding
- ASTM A -270 "Standard Specification for Seamless and Welded Austenitic Stainless Steel Sanitary Tubing"
- ASTM A 967-01 "Standard Specification for Chemical Passivation Treatments for Stainless Steel Parts"
- CEI EN 60204-1:"Electrical safety of machinery"
- CEI EN 61439-1 , 61439 "Low-voltage switchgear and controlgear assemblies"
- IEC 1131-1: "Programmable Controllers - General Information
- ISPE Baseline: Sterile Product Manufacturing Facilities" Vol. 3 2011
- FDA Guidance for Industry: "Sterile Drug Products Produced by Aseptic Processing" cGMP.
- ISPE baseine: Water ans Steam Systems" Vol 4. 2011
- ISPE Guideline: "Testing GXP"
- ISPE Guideline: "Commissioning and Qualification"Vol. 5 2001
- ISPE Guideline: "Commissioning and Qualification of Water and Steam Systems" Vol. 5
- ISPE Guideline: "Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems) 2014
- ISPE Guideline: "Calibration Management"
- UNI 10893: "Technical Documentation of Product"
- ASTM C- 795 –" Standard Specification for Thermal Insulation for Use in Contact with Austenitic Stainless Steel"
- UNI 5634 "Identification of piping for fluids"
- ASTM A 380-99 "Standard Practice for Cleaning, Descaling, and Passivation of Stainless Steel Parts, Equipments and Systems"

3. DOCUMENTATION & VALIDATION PLAN

All project steps from design to final validation will be accompanied by the relevant GDP documentation, according to following sequence:

- Design Qualification - within contractual terms
- Technical Documentation with manuals- submitted during FAT
- Factory Acceptance Test (Protocol preparation & execution) - at FAT
- Installation Qualification (Protocol preparation) - submitted before commissioning
- Operational Qualification (Protocol preparation) - submitted before commissioning
- Performance Qualification (Protocol preparation) -optional

4. RISK ASSESSMENT

Risk assessment is issued for each equipment/process step using the FMEA method, according to GAMP 5.

Typically, BRAM-COR Risk Assessment documents include

- Overview
- Scope and application
- Main references
- Terminology and abbreviation
- Key parameters for risk assessment
- Severity index assignment criteria
- Occurrence index assignment criteria
- Detection index assignment criteria
- Risk assessment method
- Control strategy
- Risk assessment for each item/criticality/possible failure

The risk assessment is included in the technical documentation of the equipment.

5. DESIGN QUALIFICATION PROTOCOL

Each DQ protocol includes:

- Signatures page
- Overview
- Scope and application
- Change control
- Responsibilities
- Protocol approval
- Terminology and abbreviations
- Regulatory standards
- BRAM-COR S.P.A. Quality system procedures
- Reference documentation
- Design assumptions for water quality
- Performance, consumption and utilities requirements
- System & process description
- Mechanical components description
- Electric components & instruments
- Hardware design specification
- Functional and software design specification:
    - Sequences
    - Phases
    - Operator functions
    - Interfaces
    - Data storage
    - Passwords
    - Non-functional attributes
    - Maintainability
- Documentation and testing list
- Approval page

6. TECHNICAL DOCUMENTATION

All equipment is supplied with a complete technical documentation including:

SECTION 1: GENERAL DOCUMENTATION AND CONSTRUCTIVE SPECIFICATIONS:

1.1 Design qualification
1.2 P&ID reading key
1.3 P&ID
1.4 Tie-in/lay out
1.5 Technical specifications
1.6 Conformity declaration of equipment
1.7 Quality declaration

SECTION 2: COMPONENTS DOCUMENTATION

2.1. Components list and specifications
2.2. Manufacturers data sheets and technical documentation

SECTION 3: VALVES DOCUMENTATION

3.1 Valves list and specifications
3.2 Manufacturers' data sheets and technical documentation

SECTION 4: INSTRUMENTS DOCUMENTATION

4.1 instruments list and specification
4.2 manufacturer data sheets and technical documentation

Note: conductivity, redox and oxygen probes are calibrated by the manufacturer with a buffer solution on 1 point. This type of standard certificate is named "Manufacturer's certificate".
Factory/Site calibration of measurement chains is performed upon URS specifications and contract agreement.

SECTION 5: ELECTRICAL DOCUMENTATION

5.1 Electrical scheme
5.2 Electrical components list and specifications
5.3 Control board isolation declaration

SECTION 6: HARDWARE AND SOFTWARE DOCUMENTATION

6.1 Hardware design specification
6.2 Hardware technical documentation & manuals
6.3 Declaration of software conformity to 21 CFR part 11 (where applicable)
6.4 Alarm list and action
6.5 Input/output list
6.6 PLC/HMI software identification form
6.7 PLC software recovery procedure
6.8 HMI software recovery procedure

SECTION 7: PIPING, FITTINGS AND WELDING DOCUMENTATION (WHERE APPLICABLE)

7.1.2. Piping and fitting certificates
7.1.1. Materials list
7.2.2. Materials certificate
7.2.1. Welding documentation
7.3.1. Quality declaration of the welding
7.2.2. Qualification declaration of the welders
7.2.3. Pickling and passivation report
7.2.4. WPS: welding procedure specification (for manual welding)
7.2.5. WPQR: welding procedure qualification record (for manual welding)
7.2.6. WPQ: welding performance qualification (for manual welding)
7.2.7. WPS: welding procedure specification (for orbital welding)
7.2.8. WPQR: procedure qualification record (for orbital welding)
7.2.9. WPQ: welding performance qualification (for orbital welding)
7.2.10. Filler material (for manual welding)
7.2.11. Gas Argon Certificate

SECTION 8: OPERATING AND MAINTENANCE INSTRUCTIONS

8.1. User and maintenance manual, including following main contents:

- General information
- Safety information
- Equipment description
- Information for transportation and installation
- Use and management of the system
- Maintenance and cleaning operations
- Troubleshooting

8.2. Operating manual, including following main contents:

- Preliminary operation
- Introduction
- Operator interface
- Software architecture
- General information
- Data processing
- Passwords management
- HMI panel structure
- Generator procedure
- Operative mode
- Report and parameters
- Alarms management

8.3. Spare parts list

7. FACTORY ACCEPTANCE TEST

FAT protocols will be issued for each unit/machine and submitted to Customer's approval before the Factory Acceptance Test, to be performed in Italy, as per Contract terms, using local utilities, where applicable.

F.A.T. activities include:

Test A: Mechanical Components Acceptance Test

- P&ID verification
- TIE-IN drawing verification
- Part List Verification
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Test B: Electrical Hardware Acceptance Test

- Verification of pneumatic connections
- Verification Hardware Components
- Verification Electrical Connections.

Test C: Software Acceptance Test

- Input / Output verification
- Verification of access security
- Simulation of Alarms & Interlocks

Test D: Functional Test

- Plant performance verification.
  NOTE: Reverse osmosis plants are "dry" tested during FAT to avoid contamination of membranes and filters, while preparation plants and thermic equipment (PS generators or distillers) are usually tested with pretreated (demi) water.

8. SITE ACCEPTANCE TEST

When included in the contract, the same tests executed during Factory Testing, can be repeated in the final location of the equipment, under real operating conditions and using local utilities.
SAT protocols are usually issued by BRAM-COR when IQ-OQ execution is not included in the contract (unless otherwise agreed) and are filled-in by BRAM-COR technician during commissioning.

9. QUALIFICATION PROTOCOLS PREPARATION

BRAM-COR will prepare a customized validation protocol for each validation phase (i.e. Installation and Operational Qualification), when included in the contract.

The protocols will be issued in the language defined by contractual terms following our standard. The Protocols will take into account all the requirements coming from reference GMPs standards. The protocols will be submitted to the Customer before commissioning and approved by the Customer's key Representatives (usually from Manufacturing, Quality Assurance, Engineering Departments) before "field" activity can start

10. INSTALLATION QUALIFICATION PROTOCOL

- Documentation verification
- AS BUILT verification
- Components verification
- Instrument verification
- Hardware verification
- Software installation verification
- Materials in product contact verification
- Safety aspect verification
- Utilities & boundaries connection verification

11. OPERATIONAL QUALIFICATION PROTOCOL

- HMI software verification
- Inputs & Outputs test
- Passwords verification
- Alarm & Interlocks test
- Functional test (including status verification, functional sequences verification, critical production parameters verification, as left settings records, emergency devices verification)
- Equipment-specific tests (filters verification, fluorescein test, pumps speed verification, Reynolds number verification, etc.)
- Power Failure Verification
- Training verification

12. PERFORMANCE QUALIFICATION PROTOCOL (optional)

For preparation plants

- SOPS VERIFICATION
- Verification of solution homogeneity
- Verification of cleaning process effectiveness
- Verification of sterilization process effectiveness

For water systems:

- SOPS VERIFICATION
- Verification of chemical and microbiological quality
- Verification of cleaning process effectiveness (where applicable)
- Verification of sterilization process effectiveness (where applicable)

13. GLOSSARY

CAPA = Corrective & Preventive Actions
DQ = Design Qualification
Eu. Ph= European Pharmacopoeia
FAT = Factory Acceptance Test
FMEA = Failure Mode & Effect Analysis
GMP = Good Manufacturing Practice
HW = Hardware
HMI= Human-Machine Interface
I/O = Input/Output
IQ = Installation Qualification
ISPE = International Society of Pharmaceutical Engineering
OQ = Operational Qualification
P&ID= Piping and Instrumentation Diagram
PLC = Programmable Logic Controller
PQ = performance Qualification
SAT = Site Acceptance Test
SOP = Standard Operative Procedure
SW = Software
TIE IN=Utilities & boundaries connections diagram
URS= User Requirement Specification
USP =United States Pharmacopoeia
VMP = Validation Master Plan