Pürifiye Su Sistemleri Validasyonu

Istanbul, Turkey
May 31, 2001

Peter Drechsler
Aventis Pharm- Frankfurt , Germany

Aventis Pharma

allegra
fexofenadine HCl 60 mg

Exubera™ Inhaled Insulin

LOVENOX® CLEXANE®
enoxaparin sodium

Actonel™
(risedronate sodium)

TAXOTERE®
(docetaxel)

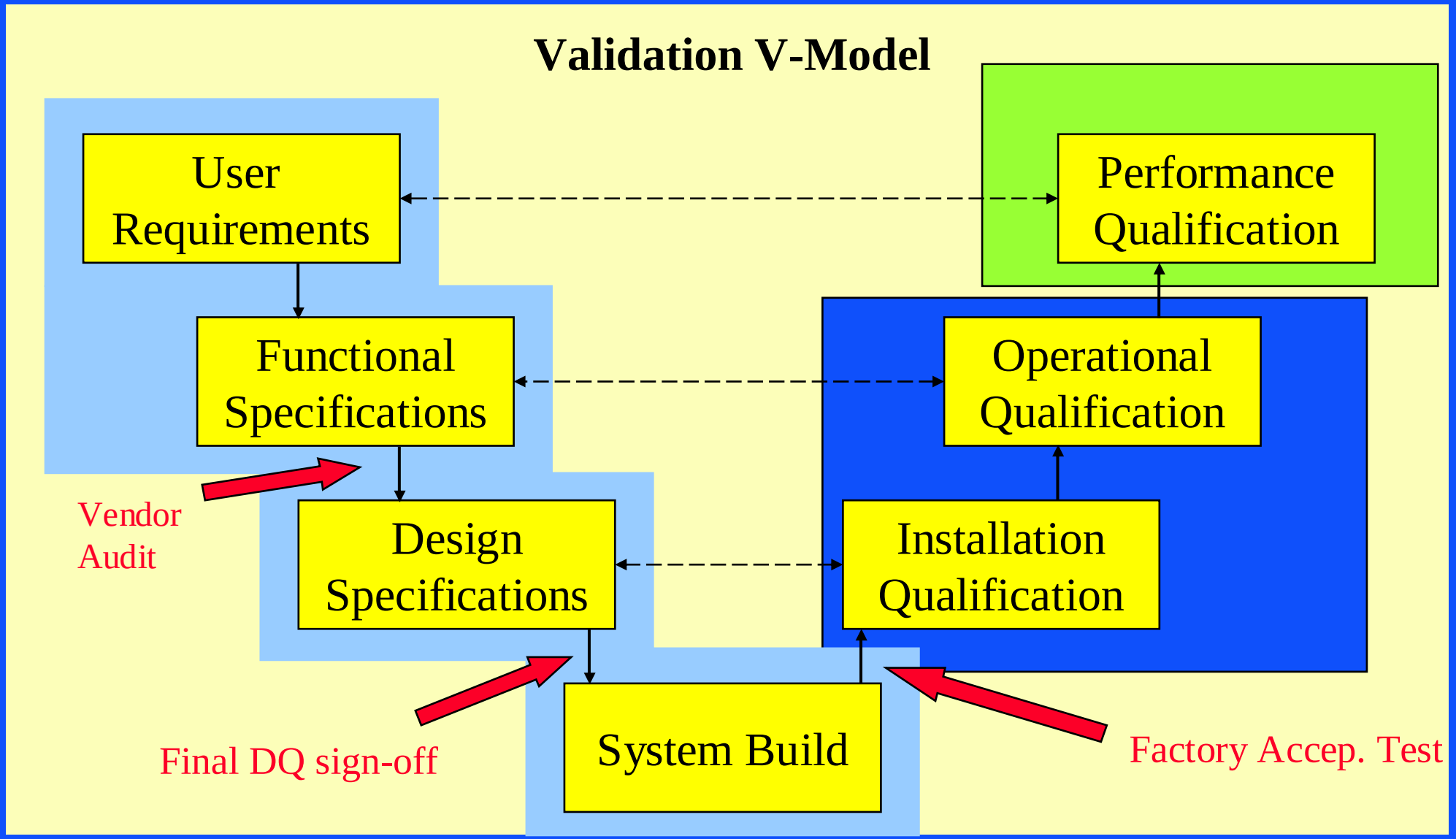
LANTUS®
insulin glargine

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Table of content for Presentation:

* Validation V-Model
* Validation Working Model
* Water Validation- How and Where to Start
* Elements of Validation- DQ, IQ, OQ, PQ
* 3 Phase Approach for PQ
* Critical Parameters and Acceptance Parameters
* Conclusion for the PQ
* Typical Water Validation Common Problems/Issues

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com



AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Istanbul May 31, 2001

VALIDATION PROGRAM SUMMARY AND OVERVIEW

Performance Qualification (PQ)
•Testing of Critical Quality Parameters
•SOP's to Monitor Critical Parameters

Operational Qualification (OQ)
•Test for Proper System Operation
•SOP's for Systems or Equipment

Installation Qualification (IQ)
•Preventive Maintenance
• Validated Drawings
• Instrument Audit & Logbook

Design Qualification (DQ)
•User Requirements
•Functional Specification
•Vendor Audit / Factory Acceptance Test

Validation Plan

• Scope of Validation
• System Description
• System Capacity
•Blockflow Diagram

SOP
Specific SOP
to monitor critical
Quality Parameters

SOP
Specific SOP to
document the operation
of the Validated System

SOP
Core SOPs
That are common to
all Validation Reports:

• Preventive Maintenance
• Instrument Audit
•Equipment Logbook
• Validated Drawings

CHANGE CONTROL

Change Control System documents changes to a Qualificed Equipment and Validated System.

The „Change Control Looks at:

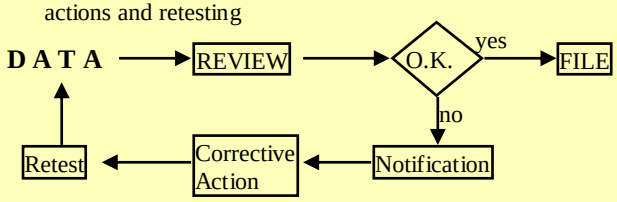
* Qualification Report
* Validation Report
* Related SOP's

And determines what needs to be document for the change. The SOPs need to be reviewed and updated as needed, if a change occures. Additional IQ/OQ/PQs need to be completed.

Validation Report
(Utilities, Computers, Packaging lines)
- •Validation Plan
- •DQ
- •IQ
- •OQ
- •PQ

Qualification Report
(Manufacturing Equipment, Facilities)
- •DQ
- •IQ
- •OQ

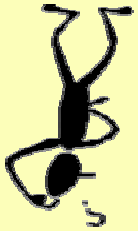
SOP compliance creates **D A T A**
The **D A T A** is review to ensure it meets predetermined acceptable limits. Failure to meet the limits requires notification, corrective actions and retesting



DIAGRAM

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Purified Water Validation



How and Where to Start ?

1. Write a Validation Plan

2. Draw a simple Blockflow Diagram of the system

3. Develop a Simple Summary Table from the Blockflow Diagram and identify which parts/ equipment will be included in the Qualification.

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

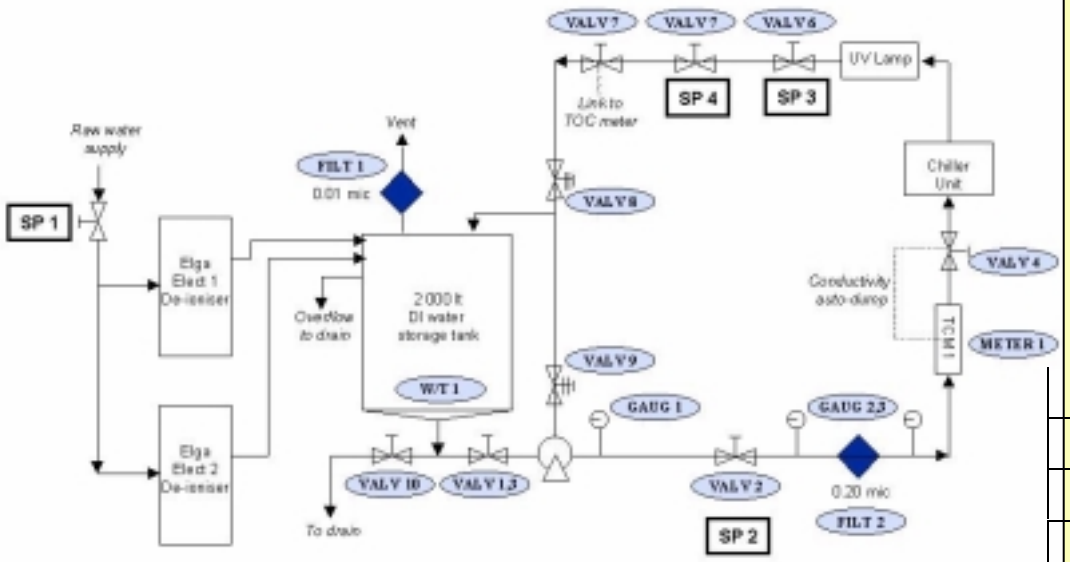
Validation Plan

Brief Documentation (3-5 pages) that describes the scope of the Validation and general approach that will be followed.

- System Description
- System Capability
- Project Timeline and Project Team

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Purified Water Validation- How and Where to Start



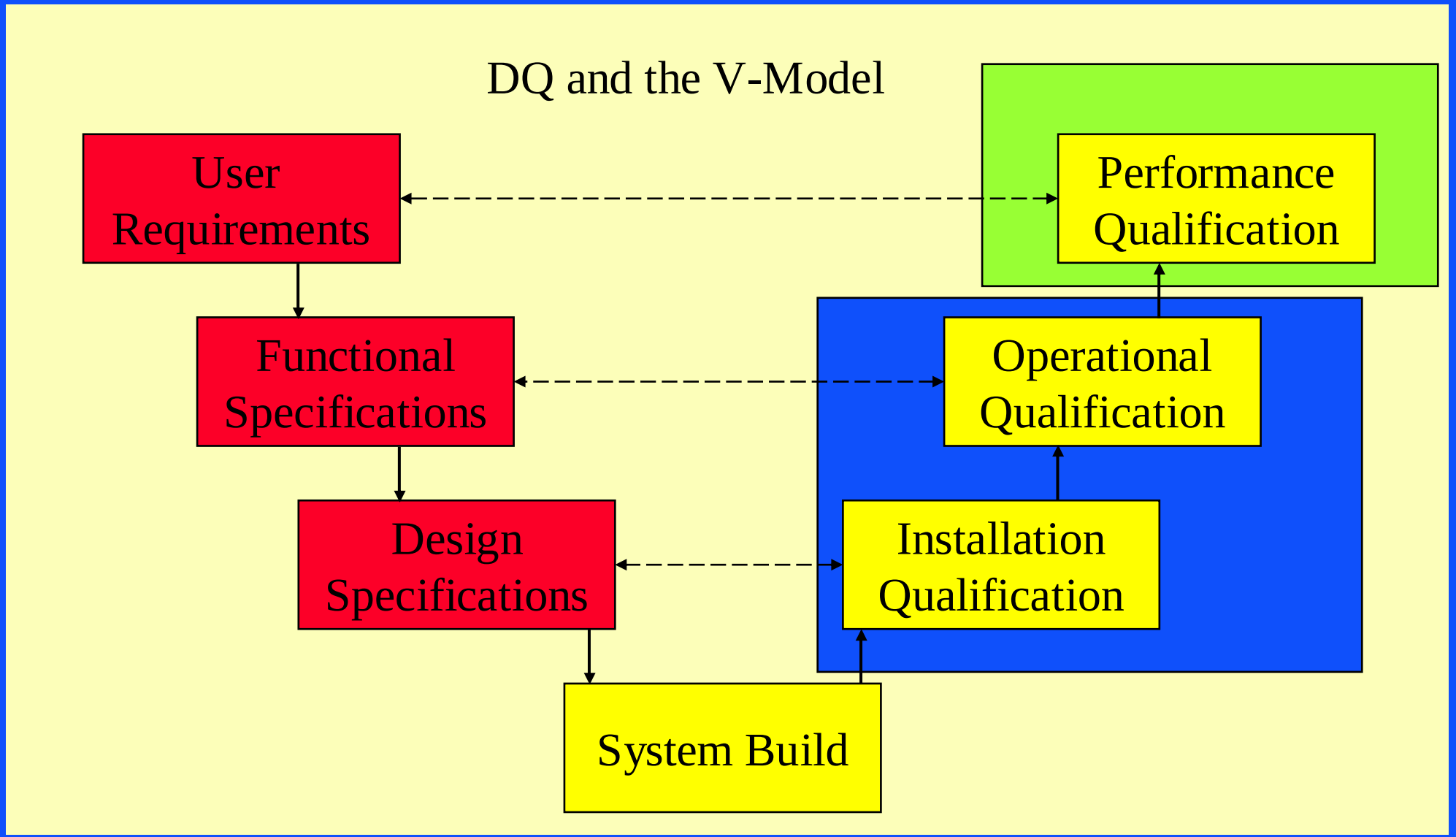
Block flow Diagram for a Typical Water System

Validation Summary Table

	IQ	OQ	PQ
Deionizer	X	X	
Valve	X	X	
Storage Tank	X		
Filters	X	X	
UV Lamps	X	X	
Pump	X	X	
Pipe	X		
Purified Water			X

Note: DQ is also required were it applies

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com



AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

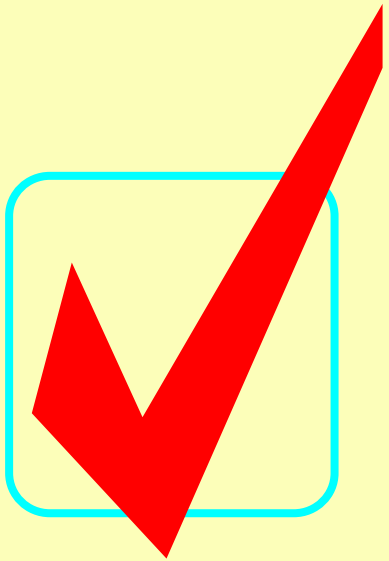
Design Qualification Definition:

- Providing documented evidence that the design of facilities, equipment, services and operation is suitable for the intended purpose and meets Quality and GMP requirements.

Reference:Baseline®Pharmaceutical Engineering Guide Series: Introduction of Qualification and Commissioning Draft 3, November 23, 1998

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Documents for the DQ



- Pipe and Instrument Diagram (P&ID)
- Technical Drawings
- Functional Description
- Specification of Material
- Specification of Surfaces
- Material- / Personnel Flow
- Clean Room Classes
- Filter Specification
- etc.

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Design Qualification - A step by step Example

- **User Requirements**
  - Purified Water to meet USP
- **Functional Specification**
  - RO System that is sanitized by Steam
- **Design Specification** (Vendor)
  - Double sheet 316L SS heat exchanger
- **Design Qualification**
  - Formal check that the Design is o.k. and User Requirements are met

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

DQ DOCUMENTATION EXAMPLE

SYSTEM DESCRIPTON:

SYSTEM CAPABILITY:

SYSTEM CAPACITY:

FLOW DIAGRAM (INCLUDING INSTRUMENT AND SAMPLE POINTS

	Date	Signoff
1.1 User Requirements	_____	_____
1.2 Functional Specifications	_____	_____
1.3 Vendor Specifications	_____	_____
1.4 Vendor Audit Report	_____	_____
1.5 Finalized DQ	_____	_____

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Installation Qualification (IQ)

Documentation that a building area, system, equipment, process and/or instrument is constructed according to the specific design in terms of **static** attributes. For Engineering purposes, the IQ includes:

- Construction material and finish
- Drawings of record
- Utility connections
- Statement including suitability to function

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

IQ DOCUMENTATION EXAMPLE

EQUIPMENT/SYSTEM _____

1. IDENTIFIERS: ( ) See Attached

1.1 Major Equipment Purchase Order Number?
1.2 Equipment Numbers Affixed to Equipment?
1.3 Logbooks Created?
1.4 Operator Training Checklist Created?
1.5 Block Flow Diagram?

2. ENGINEERING SPECIFICATIONS: ( ) See Attached

2.1 Equipment Specifications & Requirements
2.1.1 Product-Contact Surface Area
2.2 List Materials in Product-Contact
2.3 List all Product-Contact Lubricants _____

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

IQ DOCUMENTATION EXAMPLE

3. UTILITY INSTALLATIONS (Per Spec or Requirement):

- 3.1 Field Identification and Labeling Satisfactory:
- 3.2 Electrical Installation Satisfactory:
- 3.2.1 Record Motor Data:
- 3.3 Compressed Air Connection Satisfactory:
- 3.4 Nitrogen Connection Satisfactory:
- 3.5 Vacuum Connection Satisfactory:

4. INSTRUMENT CALIBRATION: ( ) See Attached

- 4.1 All Critical Instruments in Instrument Audit Program

5. PREVENTIVE MAINTENANCE: ( ) See Attached

- 5.1 New Requirements Entered in PM Program

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

IQ DOCUMENTATION EXAMPLE

6. CHANGE PARTS AND TOOLING: ( ) See Attached
6.1 List all New Change Parts and Tooling

7. SERVICE DOCUMENTS: ( ) See Attached
7.1 Spare Parts List
7.2 Copies of Owner's Manuals
7.3 Copies of Operating Instructions
7.4 Process Control Program Hard Copy
7.5 Others

8. ASSOCIATED EQUIPMENT: ( ) See Attached
8.1 Have all Associated Equipment Been Qualified?

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

IQ DOCUMENTATION EXAMPLE

9. SPECIAL PROCEDURES: ( ) See Attached

9.1 Initial Degreasing
9.2 Passivation
9.3 Initial Cleaning
9.4 Initial Sanitization

10. FINAL ENGINEERING DRAWINGS: ( ) See Attached

10.1 Update all Drawings per Actual Installation
10.2 Drawings on File in Engineering Dept.

11. INSTALLATION QUALIFICATION TESTING: ( ) See Attached

11.1 Safety Interlocks Checked _____ _____
11.2 Static Grounding Acceptable
11.3 Control Loop Checks Complete

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Operation Qualification (OQ)

Documentation that a system or sub-system performs as intended when compared to a predetermined set of **dynamic** attributes. Dynamic attributes may include conformance to performance specifications such as:

- Critical Micro and chemical parameters
- Water flow velocity
- Sanitization Temperature
- etc.

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

OQ DOCUMENT EXAMPLE

OPERATIONAL Qualification Protocol: EXAMPLE FORMAT AND CONTENT:				
Utility or Equipment Name or number	Bldg	Protocol Number	Page	Date
			1 of	

1. Identification of Test

2. Rational

3. Description of Test

4. Method of Sampling

5. Acceptance Criteria

6. Test Results

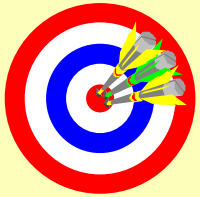
7. Conclusion

Person who performed Test: _____ Signature of Supervisor _____

Date Test was Performed: ---------- Date reviewed and signed ----------
Instrument(s) Used For Test: ----------
Date of Calibration & Due date ----------

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Qualification Documentation



In order to start a Performance Qualification it is required that the Installation Qualification as well as the Operation Qualification for the system to be PQ'd have been successfully completed and signed off. This ensures that there can not be any unauthorized changes to the layout or functioning of the system.

Description	Doc no.	Edition Date	Location	Checked	Signature
Installation Qualification				Complies	
Operation Qualification				Complies	

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Performance Qualification (PQ)

Documentation that a system or sub-system performs as intended AND meets all the User Requirements. The PQ includes the following Topics:

- Equipment & Process Description
- Validation Approach
- Critical Parameters
- Sampling Rational
- Testing Procedures
- Acceptance Parameters
- Conclusion / Summary

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

3 Phase Approach for the PQ

The PQ takes place in three phases. There will be 2 phases of 10 days (*phase 1 and phase 2*) during which the water will be *monitored, chemically and microbiologically on a daily basis*, and one phase of one year (*phase 3*), during which time the water will be monitored *chemically and microbiologically on a bi-weekly basis* for both user points and the other points once a week.

The 12-month period will enable the performance of the system to be qualified during the whole period (thereby taking seasonal changes into account).

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

3 Phase Approach for the PQ

The PQ takes place in three phases over a 1 year period.

Phase 1

10 Consecutive days of Chemical and Micro monitoring

Phase 2

10 Consecutive days of Chemical and Micro monitoring following Phase 1

Phase 3

52 weeks of Chemical and Micro monitoring following Phase 2

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Critical Parameters for the PQ

Two types of monitoring of the purified water produced by the system can be distinguished:

Chemical
Microbiological

Critical Parameters :	Acceptable Criteria and Tests Used :
CHEMICAL Parameters	*As per USP XXIII*
MICROBIOLOGICAL Parameters	*As per USP XXIII*

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Sampling Rational for the PQ (example)

To facilitate representative monitoring of the system, the sampling for samples for Micro monitoring will include **ALL** points of use as well as the sampling port just in front of the 0.2 µ inline filter and some points in the water manufacturing process (for example: before and after the RO units).

The feed water should also be monitored to assist with possible correlation between micro results in the ring main system and the feed water.

In order to simulate normal operations water must be drained every day prior to sampling to simulate water usage.

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Summary of Sampling for the PQ

Critical Parameters :	Duration and Frequency of Sampling :	Sample volume
CHEMICAL Parameters	*Phase 1 Daily online* *Phase 2 Daily online* *Phase 3 Bi-weekly online*	*Online sampling except for pH measurement which will be 100 ml sample*
MICRO Parameters	*Phase 1 Daily* *Phase 2 Daily* *Phase 3 Bi-weekly*	*Sample size for each point is 500 ml*

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Summary of the Duration of the Different Tests

Phase	Monitoring Type	Periodicity	Duration
1	Chemical Microbiological	Every point every day	10 days
2	Chemical Microbiological	Every point every day	10 days
3	Chemical Microbiological	Every point Bi-weekly	52 weeks

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Chemical Monitoring

- **Total Organic Carbon (TOC)** – The USP XXIII specifies a maximum TOC content of the Purified Water at 500 ppb.
- **Conductivity** – The system will meet the requirements for conductivity as specified USP XXIII for Purified Water. Note that this value will be uncompensated conductivity.
- **Temperature** – The temperature is important in order to determine the correct specification for the uncompensated conductivity.
- **pH Value** – The measured value of the 100ml sample, after the addition of 0.30 ml of saturated potassium chloride solution, should be between 5.0 and 7.0

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Microbiological Monitoring

The Microbiological testing/monitoring will be done to ensure that the water meet the requirements for USP XXIII specifications for Purified water.

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

USP XXII Acceptance Criteria

Chemical Testing Acceptance Criteria (USP XXIII) & EP				
Sample point	**TOC**	**Conductivity**	**Temperature**	**pH**
Online	500 ppb	As per USP & EP Table	Used to determine conductivity specification	
Any sampling point				5.0 – 7.0
Microbiological Testing Acceptance Criteria (USP XXIII)				
Sample point	**R2A TPC**	**CASO TPC**	**Endo**	**Cetrimide**
Valv 2	<100 CFU / ml	<100 CFU / ml	E.coli Not Detected	P.aeruginosa ND
Valv 6	<100 CFU / ml	<100 CFU / ml	E.coli Not Detected	P.aeruginosa ND
Valv 7	<100 CFU / ml	<100 CFU / ml	E.coli Not Detected	P.aeruginosa ND
Feedwater	<500 CFU / ml	<500 CFU / ml	E.coli Not Detected	P.aeruginosa ND

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Test Summary / Conclusion for the PQ

The summaries of the Chemical and Micro testing must be completed for each phase of the PQ.

Once a phase has been completed, a conclusion has to be written indicating whether the Chemical and Micro specifications were complied to.

There will be a Phase 1, Phase 2 and a Phase 3 Test conclusion Section in the Purified Water Validation Document.

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Common Problems / Issues during Validation

* Scope of the Validation Plan is not Clear

* Special attention must be give to the filters:
  - Check and document filter size
  - Pressure differential meters across filters
  - establish change schedule for filters
  - Don’t forget any tank vent filters

* Critical Instruments must be calibrated before the PQ begins

* Lab equipment used for the PQ must be Calibrated

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Common Problems / Issues during Validation

* Operational SOP's are not clearly established
* Collection of Data from the systems in not clear (charts, print-outs)
* The sanitization cycle was not tested in the OQ (temperature and time)
* Critical Equipment is not in the Preventive Maintenance Program
* UV lights- the time to change the lamps has not been established
* The Documents are not signed (missing signatures)
* The raw data or lab data is not included in the PQ Report
* The final Conclusion after PQ 3 is missing

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

Istanbul May 31, 2001

Example - Site Topkapı / TOC - Validation

- **Team :** Quality Control / Quality Assurance / Engineering
- **Duration:** 6 months (Change Control)
- **Qualification :**
  * System Suitability Test Analysis (sucrose, frequency)
  * Calibration (Benzoquinone, certif.)
  * Cont. monitoring (accuracy)
- **Parallel Testing :**
  * TOC (Ca, Cl, Vap.Res., Total Hardness, Si…)
  * Well water, full testing
  * Periodic traditional
- **Benefits :**
  * Environment (less reagent & waste)
  * Reduced (USP, EP allowed)
- **Current Analysis :**
  * TOC
  * Conductivity
  * Nitrates
  * Appearance
  * Heavy Metals

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com

THANK YOU FOR YOUR TIME

GOOD LUCK !!!

ANY QUESTIONS ?????

AVENTIS Pharma, Frankfurt, Germany
Peter Drechsler contact: peter.drechsler@aventis.com