PHARMACEUTICAL INSPECTION CONVENTION

PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 009-3
25 September 2007

AIDE-MEMOIRE

INSPECTION OF UTILITIES

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1. DOCUMENT HISTORY

Adoption by Committee	24 April 2002
Entry into force	1 July 2002

2. INTRODUCTION

2.1 Technological and technical progress have increased in the pharmaceutical industry in the last decades. Progress has not only been made in the area of production equipment, technology and quality control but also in the area of auxiliary systems such as HVAC and media systems.

2.2 PIC/S has paid due attention to these systems for the manufacture of medicinal products. In 2001, the annual PIC/S Seminar was devoted to the inspection of utilities used by the manufacturer of pharmaceuticals (Prague, Czech Republic).

3. PURPOSE

3.1 The purpose of this document is to provide guidance for GMP inspectors to use for training purposes and in preparation for inspections.

3.2 The Aide-Memoire is the direct result of the 2001 PIC/S Seminar and was drafted with the aim of facilitating the effective planning and conduct of GMP inspections of utilities. The Aide-Memoire should enable the inspector to make both an optimal use of the inspection time and an optimal evaluation of GMP compliance.

4. SCOPE

4.1 The following Aide-Memoire describes different areas which could be evaluated during the GMP inspection of HVAC systems, pharmaceutical water, steam and medicinal gases. However, the Aide-Memoire should be considered as a non-exhaustive list of areas to be looked at during an inspection.

4.2 At the time of issue, this document reflected the current state of the art. It is not intended to be a barrier to technical innovation or the pursuit of excellence. The advice in this Aide-Memoire is not mandatory for industry. However, industry should consider PIC/S recommendations and aide-memoires as appropriate.

5. AIDE MEMOIRE

1.	Area of operation/Items **HVAC for medicinal products**	Notes	Crucial questions	Supporting documents
1.1	Key design parameters[1]	▪ Need for separate systems ▪ Level of filtration (Filter specifications) ▪ Recirculation or make-up air ▪ Location of filters ▪ Position of inlet and air return, dust extractors ▪ Temperature ▪ Humidity ▪ Air changes ▪ Pressure differentials ▪ Design of ducting ▪ Easy and effective cleaning ▪ Alarm system ▪ Air flow direction- LAF and/or turbulent	▪ How do you prevent cross contamination by air?	PIC/S GMP Guide 3.10, 3.14, 5.10, 5.11, 5.18, 5.20. Annex 1- 29-31, Annex 2 -9,10,14,15, Annex 15- 9,10 ISO 14644-4: Clean rooms and associated controlled environments – Part 4: Design and construction. International Organisation for Standardisation ISO, Geneva (April 2001) EN 1822: High efficiency particulate air filters (HEPA and ULPA): Part 1 – Requirements, testing, marking; Part 2 – Aerosol production, measuring equipment, particle counting statistics; Part 3 – Testing the planar filter medium; Part 4 – Testing the filter element for leaks (scan method); Part 5 – Testing the efficiency of the filter element. European Committee for Standardisation, Brussels (parts 1-3 were ratified in March 1998, parts 4-5 in August 2000). EN 779: Particle air filters for general ventilation – Requirements, testing, marking. European Committee for Standardisation, Brussels (July 1993).
1.2	Qualification of HVAC systems[1]	▪ DQ, IQ, OQ a PQ ▪ Average speed and uniformity of airflow ▪ Pressure differentials ▪ Air changes ▪ Integrity and tightness of terminal installed final filters	▪ How have you implemented recommendations and correct deviations mentioned in qualification reports? ▪ Who is responsible for evaluating if requalification is necessary?	Guide - 4.26, 5.21, 5.22, 5.24, 5.37, Annex 1-30, Annex 15 – 2-18. EN ISO 14644-1: Clean rooms and associated controlled environments Part 1: Classification of air cleanliness. International Organisation for Standardisation ISO, Geneva and European

[1] Important for the introductory inspection

1.	Area of operation/Items **HVAC for medicinal products**	Notes	Crucial questions	Supporting documents
		▪ Number of particles ▪ Recovery tests ▪ Air temperature ▪ Smoke tests ▪ Requalification (parameters for requalification) ▪ Change control	▪ What are the requirements for regular requalification? ▪ Show me your deviations and change control reports for HVAC?	Committee for Standardisation CEN, Brussels (May 1999). EN ISO 14644-2: Clean rooms and associated controlled environments Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1. International Organisation for Standardisation ISO, Geneva and European Committee for Standardisation (September 2000).
1.3	Walk round tour Confront differences between design specifications, drawings (in SMF) and reality, unplanned maintenance and change control and following items	▪ Are rooms for the production of medicinal products equipped with HVAC in accordance with GMP requirements[1]? ▪ Location of filters ▪ Position of inlets and air return ▪ Dust extractors, ▪ Pressure differences (across filters, between production and adjacent rooms) ▪ Logbooks-maintenance and calibration ▪ Monitoring of other process parameters ▪ HVAC alarm systems function	▪ How do you challenge your alarm systems? ▪ Place and procedure for sampling? ▪ Where and how do you weigh and refill starting materials?	Guide - 3.6, 3.7, 3.12, 4.27 Annex 1 -29, Annex 2-14
1.4	Monitoring of HVAC systems	▪ Environmental monitoring (particles, micro organ, humidity, temperature) ▪ Chemical residue testing		Guide 4.15, Annex 1 4-6,
1.5	Maintenance and calibration of HVAC systems	▪ Maintenance program ▪ Calibration program ▪ SOP´s ▪ Records ▪ Breakdown/Emergency including challenges of alarm systems	The interaction between unplanned maintenance and requalification	Guide 3.41

1.	Area of operation/Items **HVAC for medicinal products**	Notes	Crucial questions	Supporting documents
1.6	Documentation for HVAC systems	▪ Technical data ▪ SOP, records-maintenance, calibration, validation, monitoring, deviations, change control ▪ Validation protocols and reports ▪ As–built engine drawing		Guide 4.1, 4.26, 4.28, 4.29

2.	Area of operation/Items **Pharmaceutical water system**	Notes	Crucial questions	Supporting documents
2.1	Key design parameters	**WFI** ▪ Weld quality ▪ Passivation of pipeworks ▪ Vent filters **All kinds of pharmaceutical water** ▪ Suitability of construction materials ▪ Slope of pipeworks ▪ Recirculation at adequate velocity and temperature ▪ Sanitary joints ▪ Capacity x daily demand ▪ Valves ▪ Draining /flushing ▪ Samplings ports	▪ What are the design features that prevent entrainment? ▪ Who owns the system?	Guide 3.10 FDA- Guide to Inspection of Highly Purified Water Systems Annex 1-35 Annex 15 –9,10
2.2	Qualification	**DQ, IQ, OQ, PQ AND COMPUTER VALIDATION IF NEEDED** ▪ Drawing, with all sampling points ▪ Setting operation and cleaning parameters-I. Stage ▪ CONSISTENTLY PRODUCING WATER OF DESIRED QUALITY	▪ All qualification completed? ▪ For existing systems, show me deviation and change control reports? ▪ Does staff understand what, how and why the work is performed? ▪ What do signatures mean?	3.3.4, 3.38, 5.22, 5.24 Annex 15 – 2-18.

2.	Area of operation/Items **Pharmaceutical water system**	Notes	Crucial questions	Supporting documents
2.3	Walk round inspection Is water for injection produced and used according to requirements of Note for Guidance on Quality of Water for Pharmaceutical Purposes and Ph Eur? Confront differences between drawings and reality, unplanned maintenance and change control. Follow the system from pre-treatment to user points: in each part, check leaks, sampling points (access), who does what, start up and shutdown, cleaning / disinfection / sterilisation), quantities produced.	▪ Water quality grade and purposes of its use ▪ feed water ▪ pre- treatment ▪ distillation – sight glass ▪ storage tank-filter, break valve, Q-spray ball ▪ distribution loop-temp, conductivity, TOC ▪ heat exchanger-integrity ▪ user points-number, design and location ▪ control system-alarms, record of action, set points and demonstration ▪ monitoring print outs ▪ DISINFECTION? HOT WATER? STEAM? CONTINUOUS RECIRCULATION**?**	▪ How is the system kept in a validated state? ▪ Let me have a look in the sight glass! ▪ Show me records of alarms that have occurred!	Ph. Eur. current edition CPMP - Note for Guidance on Quality of Water for Pharmaceutical Purposes Annex 1 –35
2.4	Quality control testing	▪ PROGRAMME, INCLUDING TEST METHODS ▪ SCHEDULE? ▪ SAMPLING, WHO TAKES SAMPLES, TRAINING, VOLUME SAMPLED, HANDLING OF SAMPLES ▪ Limits (micro, chemical, endotoxin) ▪ Out of spec. results (OOS) ▪ Trending of results ▪ Check that all points are sampled over time, accessibility to sampling points	▪ How do you perform sampling (handling, volume, done by, all points covered)? ▪ What are alert, action limits? ▪ Source water testing?	Ph. Eur. current edition CPMP – Note for Guidance on Quality of Water for Pharmaceutical Purposes Guide 3.43, 4.15, 4.22, 6.7
2.5	Monitoring	▪ Temperature ▪ Speed ▪ Vent filters ▪ DI column regeneration ▪ pH ▪ UV light (PW) ▪ Conductivity ▪ Leakage ▪ TOC	By whom and how are corrective actions made?	Guide 4.15 Annex 1 –44

2.	Area of operation/Items **Pharmaceutical water system**	Notes	Crucial questions	Supporting documents
2.6	Maintenance and calibration of water systems	▪ Maintenance program ▪ Calibration programme ▪ SOP´s ▪ Records ▪ Breakdown/Emergency including challenges of alarm systems	The interaction between unplanned maintenance and requalification	Guide 3.41
2.7	Documentation	▪ Drawing – up to date (SMF?) ▪ OOS evaluation ▪ Deviation reports ▪ Change control reports ▪ Operation of the system ▪ Cleaning / sanitation / sterilisation ▪ Logbook – monitoring parameters- see 1.6, incidents, filter changes, shut down periods, cleaning/sanitation, maintenance		Guide 5.38 Guide 4.1, 4.26, 4.28, 4.29

3.	Area of operation/Items **Pharmaceutical steam systems**	Notes	Crucial questions	Supporting documents
3.1	Key design parameters	▪ entrainment prevention ▪ cross contamination- factory/ clean steam ▪ non condensable gases reduction ▪ slope of pipeworks ▪ no dead legs		Guide 3.10 Annex 15 – 9-10
3.2	Qualification	DQ, IQ, OQ, PQ AND COMPUTER VALIDATION IF NEEDED THE SCOPE OF VALIDATION	▪ All qualification completed? ▪ For existing systems, show me deviation and change control reports	3.3.4, 3.38, 5.22, 5.24 Annex 15- 2-18
3.3	Walk round tour What kind of steam is used for manufacture of pharmaceutical products – factory, clean steam generator)? What kind of source water is used for production of steam? Confront differences	▪ FEED WATER-TYPE, LEVEL, TEMPERATURE ▪ Sample points- location, number, access ▪ System for removal of air loop		

3.	Area of operation/Items **Pharmaceutical steam systems**	Notes	Crucial questions	Supporting documents
	between drawings and reality, unplanned maintenance and change control. Follow the system in logical order. Pay attention to leaks, sampling points (access), who does what, start up and shutdown, cleaning / disinfection / sterilisation), quantities produced.			
3.4	Monitoring	▪ control of entrainment ▪ level control of feed water ▪ pressure control inside still ▪ temperature ▪ filters ▪ blown down frequency ▪ emergency shutdown and start up		Guide 4.15
3.5	Quality control testing	▪ methods (contains non condensable gases and additives) ▪ limits ▪ sampling ▪ OOS results ▪ Trending results		Guide 3.43, 4.15, 4.22, 6.7 Annex 1- 68
3.6	Maintenance and calibration of the system	▪ Maintenance program ▪ Calibration programme ▪ SOP´s ▪ Records ▪ Breakdown/Emergency including challenges of alarm systems	The interaction between unplanned maintenance and requalification	Guide 3.41
3.7	Documentation	▪ Drawing – up to date (SMF?) ▪ OOS evaluation ▪ Deviation reports ▪ Change control reports ▪ Operation of the system ▪ Cleaning / sanitation / sterilisation ▪ Logbook - monitoring parameters - see 1.6, incidents, filter changes, shut down periods, cleaning / sanitation, maintenance		Guide 4.1, 4.26, 4.28, 4.29

4.	Area of operation/Items **Pharmaceutical gases**	Notes	Crucial questions	Supporting documents
4.1.	Key design criteria (compressed air)	▪ air inlet-source, contamination risks ▪ filters (pre – final) ▪ suitability of materials ▪ welding ▪ prevention of contamination (receiver vessel) ▪ valves		Guide 3.10. Annex 15- 9-10
4.2.	Qualification	▪ (DQ, IQ, OQ? PQ) ▪ solid contaminants, water, oil limits ▪ capacity, filter pressure drops, alarm operation	▪ how do you assure that filters are replaced in time?	Guide 3.34, 3.38 ISO 8573 Compressed air 1-7 Annex 15- 2-18
4.3.	Walk round inspection Identify all used gases with the risk for medicinal products. Confront differences between drawings and reality, unplanned maintenance and change control Follow the system in logical order	▪ contact with the product or with the "process equipment" ▪ type of the product - non sterile (terminally sterilised, aseptic procedures) ▪ labelling and identification of the system ▪ Connections-risk of mix up ▪ Identify all other used gases		
4.4.	Operating the system	▪ Changing system for filters ▪ SIP system ▪ Back-up systems ▪ Capacity-consumption		
4.5.	Monitoring of the system	▪ Leakage tests ▪ Filter integrity tests ▪ Pressure control		Guide 4.15
4.6.	Quality control	▪ Pollution - oil, water, particles, bio burden		Guide 3.43, 4.15, 4.22, 6.7
4.7.	Maintenance and calibration of the system	▪ Maintenance program ▪ Calibration programme ▪ SOP´s ▪ Records ▪ Breakdown/Emergency including challenges of alarm systems	The interaction between unplanned maintenance and requalification	Guide 3.41

4.	Area of operation/Items **Pharmaceutical gases**	Notes	Crucial questions	Supporting documents
4.8	Documentation	▪ Line drawings (pipeline, flow, valves, filters, rooms) ▪ Deviation and corrective actions ▪ Cleaning / sanitation / sterilisation ▪ Logbook – monitoring parameters – see 1.6, incidents, filter changes, shut down periods, cleaning / sanitation, maintenance		

6. REVISION HISTORY

Date	Version Number	Reasons for revision
1 July 2004	PI 009-2	Change in the Editor's co-ordinates
25 September 2007	PI 009-3	Change in the Editor's co-ordinates