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

<table>
<thead>
<tr>
<th>1.</th>
<th>Area of operation/Items</th>
<th>Notes</th>
<th>Crucial questions</th>
<th>Supporting documents</th>
</tr>
</thead>
</table>
| 1.1 | Key design parameters | • 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  
| 1.2 | Qualification of HVAC systems | • 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?  

---

1 Important for the introductory inspection
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<tr>
<th>1. Area of operation/Items</th>
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</table>
| HVAC for medicinal products | • 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.  

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?  
• 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

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<th>Notes</th>
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<tr>
<td><strong>HVAC for medicinal products</strong></td>
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</table>
| **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

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<tr>
<th>Notes</th>
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<tbody>
<tr>
<td><strong>Pharmaceutical water system</strong></td>
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</tbody>
</table>
| **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  
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<th>2.</th>
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</table>
| 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 | | | |
| 2.5 | Monitoring | | | |

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<td>system</td>
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<td>Maintenance and</td>
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<td>Guide 3.41</td>
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<td>calibration of water</td>
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<td>The interaction</td>
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<td>between unplanned</td>
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<td>requalification</td>
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<td>2.7</td>
<td>Documentation</td>
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<td>Guide 5.38</td>
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<td>Guide 4.1, 4.26, 4.28, 4.29</td>
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<td>3.1</td>
<td>Key design parameters</td>
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<td>Guide 3.10</td>
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<td>Annex 15 – 9-10</td>
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<td>3.2</td>
<td>Qualification</td>
<td>DQ, IQ, OQ, PQ AND COMPUTER</td>
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<td>VALIDATION IF NEEDED</td>
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<td>THE SCOPE OF VALIDATION</td>
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<td>All qualification completed?</td>
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<td>For existing systems, show me deviation and change control reports</td>
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<td>3.3</td>
<td>Walk round tour</td>
<td>FEED WATER-TYPE, LEVEL,</td>
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<td>TEMPERATURE</td>
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<td>Sample points-</td>
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<td>location, number, access</td>
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<td>System for removal of</td>
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<td>air loop</td>
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<td>Pharmaceutical steam systems</td>
<td>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.</td>
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<td>3.4</td>
<td>Monitoring</td>
<td>• control of entrainment&lt;br&gt;• level control of feed water&lt;br&gt;• pressure control inside still&lt;br&gt;• temperature&lt;br&gt;• filters&lt;br&gt;• blown down frequency&lt;br&gt;• emergency shutdown and start up</td>
<td></td>
<td>Guide 4.15</td>
</tr>
<tr>
<td>3.5</td>
<td>Quality control testing</td>
<td>• methods (contains non condensable gases and additives)&lt;br&gt;• limits&lt;br&gt;• sampling&lt;br&gt;• OOS results&lt;br&gt;• Trending results</td>
<td></td>
<td>Guide 3.43, 4.15, 4.22, 6.7&lt;br&gt;Annex 1- 68</td>
</tr>
<tr>
<td>3.6</td>
<td>Maintenance and calibration of the system</td>
<td>• Maintenance program&lt;br&gt;• Calibration programme&lt;br&gt;• SOP’s&lt;br&gt;• Records&lt;br&gt;• Breakdown/Emergency including challenges of alarm systems</td>
<td>The interaction between unplanned maintenance and requalification</td>
<td>Guide 3.41</td>
</tr>
<tr>
<td>3.7</td>
<td>Documentation</td>
<td>• Drawing – up to date (SMF?)&lt;br&gt;• OOS evaluation&lt;br&gt;• Deviation reports&lt;br&gt;• Change control reports&lt;br&gt;• Operation of the system&lt;br&gt;• Cleaning / sanitation / sterilisation&lt;br&gt;• Logbook - monitoring parameters - see 1.6, incidents, filter changes, shut down periods, cleaning / sanitation, maintenance</td>
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<td>Guide 4.1, 4.26, 4.28, 4.29</td>
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<td>4.</td>
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</tbody>
</table>
| 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 | - 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**

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#### 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

<table>
<thead>
<tr>
<th>Date</th>
<th>Version number</th>
<th>Reasons for revision</th>
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