Pharmaceutical Steam Sampling
Overview of ISPE Good Practice Guide

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Operations

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Safety Moment

Steam at any pressure is dangerous
It is at elevated pressures and elevated temperatures
So please be aware of and respect the hazards

- Condensate temperature can be > 180°F
- Saturated pure steam is often at pressures of 30 - 60 psig (temperatures between 274 – 307°F)
- Saturated plant steam is often at pressures around 150 psig (temperature of 366°F)
- Superheated steam can be at much higher temperatures

Serious injuries, including burns and death, are possible.

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Steam Types

- **Plant Steam:**
  - Non-product contact, non-direct impact system
  - Produced from potable water
  - Produced using industrial steam boiler (uses boiler chemicals)
  - Industry uses: non-direct contact process heating

- **Chemical-Free Steam (CFS):**
  - Non-direct impact steam system
  - Produced from pretreated water (no volatile boiler chemicals)
  - Non-volatile boiler additives meet FDA Generally Recognized as Safe (GRAS) or other international standard.
  - Industry uses: non-product contact applications such as humidification
Steam Types (cont’d)

• **Process Steam:**
  - Direct-impact steam
  - When condensed meets quality characteristics of potable water
  - Industry uses: direct inject heating and sterilization

• **Pure Steam or Clean Steam:**
  - Direct-impact steam
  - Produced by specialized steam generator
  - When condensed meets quality characteristics of USP/EP water for injection (WFI)
  - Industry uses: sterilization (autoclave or SIP)
  - May require meeting EN 285 requirements

Steam Cautions

• **Pure steam is typically operated between 30 – 45 psig.**
  - This corresponds to a temperature of between 275 - 292°F

• **Do not operate your steam generator at higher pressures than dictated by your requirements. Large pressure reductions can result in superheating issues.**
  - Make sure to size lines properly.
  - Reminder: many autoclaves have pressure reducing valve inside the skid boundary.
Compendial Requirements

THE JAPANESE PHARMACOPOEIA
SEVENTEENTH EDITION

Official from April 1, 2016

Pure Steam vs. Clean Steam

- Is it Pure Steam or Clean Steam?
- Technically the answer is both as these terms are used interchangeably.
- USP 39
  - “Pure Steam” is also sometimes referred to as “clean steam”
- ISPE Baseline® Guide Volume 4: Water and Steam Systems
  - Official requirements for “pure steam” (also referred to as “clean steam”) are provided in the monographs included in USP.
USP Mongraph

“Pure Steam is water that has been heated above 100°C and vaporized in a manner that prevents source water entrainment. It is prepared from water complying with the EPA National Primary Drinking Water Regulations, or with drinking water regulations of the European Union or of Japan, or with WHO drinking water guidelines. It contains no added substance. The level of steam saturation or dryness and the amount of non-condensable gases are to be determined by the Pure Steam application.”

USP 39–NF 34 Monograph for Pure Steam

“Pure Steam quality is difficult to assess in its vapor state; therefore, the attributes of its condensate are used to test its quality. The process used to create and collect the condensate for analysis must not adversely impact these quality attributes.”

<table>
<thead>
<tr>
<th>Attribute</th>
<th>USP Monograph limits for Pure Steam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conductivity (μS/cm at 25°C)</td>
<td>&lt;645&gt;</td>
</tr>
<tr>
<td>TSC (mg/l)</td>
<td>&lt;643&gt;</td>
</tr>
<tr>
<td>Bacterial Endotoxins (EU/ml)</td>
<td>&lt;85&gt;</td>
</tr>
</tbody>
</table>

Notes:
1. Stage 1 limit of 1.3 μS/cm at 25°C
2. Stage 2 limit of 2.1 μS/cm at 25°C
3. Stage 3 measure pH and refer to monograph table
4. Instrument response (Rd-Rf) to 0.50 mg/L standard
5. <0.25 EU/mL
Question

How many folks test their clean / pure steam systems for Bioburden?

WHY?

USP Pure Steam (cont’d)

• Follows the compendial requirements for water for injection with one exception – Microbiological requirements.
• So what about bioburden?
• Per USP 39 General Chapter <1231>

“Finally, because Pure Steam is lethal to microbes, monitoring of microbial control within a steam system is unnecessary, as is microbial analysis of the steam condensate.”
Special Requirements

EN 285: 2016

- Outlines requirements for steam used for Sterilization — Steam sterilizers — Large sterilizers

- Requirements for: Dryness, Superheat, Non-Condensable Gases
Non-Condensable Gases

- Non-Condensable Gas: excessive non-condensable gases in the steam may prevent attaining sterilization conditions in parts of the sterilizer load.

- Acceptance Criteria: up to 3.5 % V/V when tested according to EN 285.
- Test apparatus per EN 285 Figure 7
- Minimum of 3 tests required, maximum result must meet EN 285 requirements.

Ref. EN 285-2016 section 21.1

EN 285 Non Condensable Gas

Equation 4

The calculation of the concentration of non-condensable gas as a percentage is then made using the following equation:

\[ C_n = \left( \frac{V_b}{V_c} \right) \times (100\%) \]

where:

- \( C_n \) = concentration of non-condensable gases in %
- \( V_b \) = volume of water displaced from the burette, in ml
- \( V_c \) = volume of water collected in the graduated cylinder, in ml

Ref. EN 285-2016-02 section 21.1
EN 285 Dryness

- **Dryness**: excess moisture in saturated steam can cause damp loads while too little moisture cannot prevent the steam from becoming superheated during expansion into the autoclave.

- **Acceptance Criteria**: (dryness value)
  - Metal Loads 0.95
  - Other Loads 0.90

Ref. EN 285-2016-02 section 21.2
EN 285 Dryness Equation 5

The calculation of the dryness concentration is then made using the following equation:

\[ D = \frac{(T_1 - T_2)C_{pw}(m_2 - m_1) + A}{L(m_f - m_1)} \]

where:

\[ L \] = latent heat of dry saturated steam at temperature \( T_1 \) in kilojoules per kilogram

\( m_s \) = mass of the Dewar flask and stopper, pipes and tube, in kilograms

\( m_h \) = mass of the Dewar flask, water charge stopper, pipes and tube, in kilograms

\( m_w \) = mass of the flask, water charge, condensate, stopper, pipes and tube in kilograms

\( T_i \) = initial temperature of the water in the Dewar flask, in degrees Celsius

\( T_f \) = final temperature of the water and condensate in the Dewar flask, in degrees Celsius

\( T_d \) = temperature of dry saturated steam delivered to the sterilizer, in degrees Celsius

\( C_{pw} \) = specific heat capacity of water (4.18 kJ/kg°C)

\( D \) = dryness value of the steam

\( A \) = effective heat capacity of the apparatus (0.24 kJ/kg)

EN 285 Figure 8: Pilot tube

Dimensions in millimetres

<table>
<thead>
<tr>
<th>Steam pressure (kPa)</th>
<th>Bore a (mm ± 0.02)</th>
<th>Key</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 300</td>
<td>up to 2</td>
<td>1</td>
</tr>
<tr>
<td>up to 400</td>
<td>up to 3</td>
<td>2</td>
</tr>
<tr>
<td>up to 700</td>
<td>up to 6</td>
<td></td>
</tr>
</tbody>
</table>

Key:
1. silver solder
2. pipe thread ISO 228-G 1/4 A

NOTE: The values given in the table are for guidance only. When the steam pressure is not within the ranges given, the bore ‘a’ size can be determined by extrapolation.
EN 285 Figure 9: Dryness Test

Key
1. Pitot tube
2. Temperature probe entry gland
3. Rubber tube
4. Rubber stopper assembly
5. 1L dewar flask
6. To temp measurement instrument
7. To sterilizer
8. From steam service
9. Pipe for temp probe and vent
10. Sample pipe

EN 285 Superheat

- **Superheat**
  - Steam that is at an elevated temperature for its saturation pressure
  - Acceptance Criteria: ≤ 25°C*
    - when the steam is expanded to atmospheric pressure
- **EN 285 – reduce pressure drop ratios to less than 2:1**
- **Risk to sterilization process due to superheat**
  - Steam will not condense and provide moisture until the steam temperature has reduced to the saturation temperature.
  - As a result, the steam acts as hot air and at the temperatures present, will have little or no sterilizing effect.
- **Pharmaceutical** 121°C for ~15 mins
- **Hospital** 134°C for ~3 mins
  - Result is less time for de-superheating to occur

Ref. EN 285-2016-02 section 21.3
EN 285 Superheat Expansion Tube

Key
1. Pitot tube (from dryness apparatus)
2. Temperature probes fitting
3. Expansion tube
4. To temperature measurement instrument
5. To sterilizer
6. From steam service
T-h Phase Diagram
Water to Steam


Sample Locations
Pure Steam Distribution

- ASME BPE design based distribution systems
- Materials of construction typically 316L SS
- Slope horizontal lines in direction of flow
- Must ensure sagging of pipes does not occur
- Ideally all components shall be self draining
- Trap installation critical to system performance.
- Install traps
  - at least every 100 feet,
  - upstream of control valves
  - upstream of isolation valves
  - bottom of vertical risers
  - all low points
  - expansion loops

Distribution (cont’d)

- Condensate must freely drain to traps and from traps
- Avoid dead legs.
- Branch lines should be routed from top of header.
- Sampling points should be located to be representative of system:
  - generator outlet
  - header ends
  - autoclaves
  - SIP stations
  - other critical points of use
System Isometric (ASME BPE)

Fig. SD-4.2.2-1 Typical Clean Steam System Isometric

**GENERAL NOTE:** Provide steam traps
(a) where line transitions from horizontal to vertical (at the bottom of the vertical run)
(b) at least every 100 ft (30 m)
(c) at end of each header or branch
(d) at thermal expansion loops or transitions
(e) where steam is sampled

Point of Use Design (ASME BPE)

Fig. SD-4.2.2-2 Clean Steam Point-of-Use Design
Steam Traps (ASME BPE)

Fig. SD-3.12-1  Steam Traps for Clean Steam Systems

(a) Serviceable Trap
(b) Welded Trap

Steam Sampling
Steam Sampling

- Requirements for Pure Steam
  - Total Organic Carbon (TOC)
  - Conductivity
  - Bacterial Endotoxin
- In the past EN 285 was specific to products sold in Europe. However recent revisions to USP now state “The level of steam saturation or dryness and the amount of non-condensable gases are to be determined by the Pure Steam application.”
- So don’t forget the EN 285 Requirements
  » Dryness
  » Superheat
  » Non-condensable gas

Sampling Location Schematic

[Diagram of steam sampling location]
Portable Sample Coolers

- Take care to ensure that the sample cooler does not contaminate the sample.
- Design the sample cooler to be sterilized.
- If using portable coolant source, be sure it does not contaminate your clean room.
- Make sure to calculate the required latent heat to condense the steam.

Sample Plans
Sample Plans

- Sampling pure steam should be determined based on the state of the system such as:
  - restoration from scheduled/unscheduled shutdown
  - maintenance
  - validation
  - normal routine operation
- Risk analysis principles (e.g., Hazard Analysis Critical Control Points [HACCP]) can be used to develop a sampling rationale that takes into account the:
  - criticality of the POUs on the system
  - their frequency of use
  - reasonable accessibility
  - historical performance

Sampling Plans (cont’d)

Sampling Plan Example

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Test</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly</td>
<td>Endotoxin, Nitrates, TOC, Conductivity</td>
<td>Generator</td>
</tr>
<tr>
<td>Monthly</td>
<td>Endotoxin, Nitrates, TOC, Conductivity</td>
<td>One-Way Distribution most distant points</td>
</tr>
<tr>
<td>Biannually</td>
<td>Endotoxin, Nitrates, TOC, Conductivity</td>
<td>All Use Points</td>
</tr>
<tr>
<td>Annually</td>
<td>Steam Quality (non-condensable gas, superheat, dryness)</td>
<td>Autoclave Use Points</td>
</tr>
</tbody>
</table>
Sample Valves

- Most common type of sample valve found on continuous duty pure steam systems is a stainless steel sanitary ball valve.

- Some equipment may utilize diaphragm valves, however diaphragm pressure and temperature limits exist.

- Sample equipment may utilize stainless steel needle valves for flow control.
Sample Valve (cont’d)

- **ASME BPE SD-4.2.3 Clean/Pure Steam Valves**
  - SD-4.2.3 covers isolation, regulation, and control valves that are part of the steam system and are subject to continuous steam service.
    - Valves for steam service shall be designed for drainability and should have minimal fluid holdup volumes.
    - Ball valves are an acceptable industry standard for isolation purposes on continuous steam service. Three-piece-body ball valves should be used instead of single-body designs for both cleanability and maintainability. The bore of the ball valve assembly shall match the inside diameter of the tube (see Fig. SG-2.3.1.3-1).
    - All components shall be suitable for continuous steam service at the temperatures and pressures specified by the owner/user.

### Diaphragm Valve Cautions

<table>
<thead>
<tr>
<th>Diaphragm</th>
<th>Material/Design</th>
<th>Diaphragm size</th>
<th>Liquid media</th>
<th>Temperature range [°C]</th>
<th>Sterilisation</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPDM</td>
<td>Ethylene-propylene-diene rubber</td>
<td>8 - 100</td>
<td></td>
<td>max. 150°C ¹</td>
<td>max. 60 min, per cycle</td>
<td>13/9A</td>
</tr>
<tr>
<td>EPDM</td>
<td>Ethylene-propylene-diene rubber</td>
<td>8 - 100</td>
<td>-10 - 100</td>
<td>max. 150°C ²</td>
<td>max. 180 min, per cycle</td>
<td>17</td>
</tr>
<tr>
<td>PTFE/EPDM</td>
<td>Fully laminated PTFE diaphragm with EPDM back</td>
<td>8, 10, 100</td>
<td>-10 - 100</td>
<td>max. 150°C ³, no time limit per cycle</td>
<td></td>
<td>50/5A</td>
</tr>
<tr>
<td>PTFE</td>
<td>Convex two-piece PTFE diaphragm with loose EPDM back</td>
<td>25, 40, 50, 60</td>
<td>-10 - 100</td>
<td>max. 150°C ³, no time limit per cycle</td>
<td></td>
<td>5E</td>
</tr>
</tbody>
</table>

¹ The sterilisation temperature is valid for steam (saturated steam) or superheated water.
² If the sterilisation temperature limits are applied to the EPDM diaphragms for longer periods of time, the service life of the diaphragms will be reduced. In these cases, maintenance cycles must be adapted accordingly. This also applies to PTFE diaphragms exposed to high temperature fluctuations.
³ PTFE diaphragms can also be used as moisture barriers; however, this will reduce the service life. The maintenance cycles must be adapted accordingly.
⁴ GEMO 555 and 505 globe valves are particularly suitable for use in the area of steam generation and distribution. The following valve arrangement for interfaces between steam pipes and process pipes has proven itself over time. A globe valve for shutting off steam pipes and a diaphragm valve as an interface to the process pipes.
Sample Techniques

• **Equipment considerations**

  • When condensing pure steam for sampling, the equipment should not contribute contaminants to the sample.
  
  • The equipment should be designed to allow for complete cleaning and drainage.
  
  • It should be possible to sterilize the equipment and for it to be de-pyrogenated to ensure that no endotoxins are contributed to the sample.
  
  • In addition, the equipment typically requires a cooling source (such as chilled water) to facilitate condensation.
Sample Techniques (cont’d)

• **Sample containers**
  - When taking samples, efforts should be made to ensure that sampling containers do not introduce measurable contaminants.
    - TOC samples should use TOC collection vials.
    - Pyrex® glass, sterile polypropylene plastic, or inert fluoropolymer containers are the most common container material for collecting condensed steam samples for conductivity and or pH.
    - Bioburden samples (if required*) must be taken in sterile containers, typically an inert plastic such as polypropylene or a suitable fluoropolymer.
    - Endotoxin sampling should be done using pyrogen-free containers of either glass or inert plastic.

*USP does not require bioburden samples, however some still take them.

Sample Handling
Sample Handling

• Develop equipment-specific sampling procedures for all required samples.
• Train sample collectors.
  • Include witnessed sample collection activities
  • Common to require trainees to demonstrate that they can collect a minimum of three distinct sets of samples
    »one set per day for each type of collection and each unique location from which they will be required to collect samples
  • Monitor sample collector performance
• Verify that proper sample containers are utilized.

Sample Handling (cont’d)

• Samplers should label all samples with:
  • sample identification
    »point of use (include system ID and building, if required)
  • type of sample (e.g., condensed steam) and indicate if repeat sample
  • date and time of sampling
  • analysis required
  • sampler’s name

• Travel time
  • For the most accurate test results, samples should be transferred to the laboratory and placed on test within an hour of collection.
Resources

- ISPE Baseline® Guide Volume: 4 Water and Steam Systems
- ASME BPE Bioprocessing Equipment
- United States Pharmacopeia (USP)
- European Pharmacopoeia (EP)
- EN 285 Sterilization — Steam sterilizers — Large sterilizers
- HTM 2010 Sterilization: Good Practice Guide
- Spirax Sarco Design of Fluid Systems Hook Ups (Red Book)

Questions?

Please use the microphone indicated so our recording includes audio of your question
Contact Information

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