Water For Injection Skid

1. Introduction of injection water equipment system

Water for injection (Water For Injection, hereinafter referred to as WFI) system is composed of generating device (multi-effect distilled water machine), storage-distribution system, etc. This paper only involves the storage-distribution system.

WFI storage-distribution system (WFI Storage and Distribution System) is composed of storage tanks, delivery pumps, stainless steel pipeline, heat exchanger, water point valves and some testing equipment. The system should be designed to effectively prevent the breeding and contamination of microorganisms and bacterial endotoxins, facilitate the system sterilization, and meet the requirements of sterile production water.

2. Overall design requirements of the WIF storage-distribution system

Overall design requirements for the WIF Storage-Distribution system:

(1) The WFI system adopts circulating pipeline design. The low storage temperature of the whole WFI storage and distribution system shall not be lower than 85℃, and the low temperature of circulation temperature shall not be less than 70℃.

(2) The design of the circulation pipeline shall always ensure that the WFI flow rate back to the storage tank is not less than 1.0 m / s on the premise of meeting the production requirements of each water use point.

(3) The design of the system should avoid the generation of dead corners, and the blind tube should at least meet the "3d" standard, so as to prevent the breeding of microorganisms caused by water retention.

(4) The design of the system shall achieve full emptying, and the horizontal pipe shall guarantee 0.5% 1% inclination (depending on the length of the horizontal pipe).

(5) Always maintain the relative positive pressure of the system.

(6) The system can realize the sterilization function.

(7) When the conductivity of the backwater exceeds the standard and the TOC value fails the standard, the pipeline has the function of automatic discharge.

(8) The system should have reliable insulation measures, and the insulation material should be a non-fibrous material.

(9) The design and construction of the system shall comply with the relevant regulations of ISPE and ASME BPE-2009 (TheAmerican Society of Mecha - nical Engineers / American Mechanical Engineering Association, Bioprocessing Equipment / Bioprocessing equipment).

3. Requirements for the construction of the components of the WFI storage-distribution system

3.1 The WFI storage tank

3.1.1 Tank volume

The determination of the tank volume mainly depends on three requirements:

(1) Take into account the water production speed of water production equipment and the changing water consumption of production to ensure sufficient buffer room.

(2) Ensure that the water production equipment can operate continuously for most of the time, and avoid reducing the utilization rate of the utility system due to the frequent startup and shutdown of the water production equipment, so that the equipment is adversely affected.

(3) In the event of water production equipment failure or water production cannot be produced due to system disinfection, short-term reserve water quantity can be provided. When determining the reserve allowance, a batch of products, a working cycle, or other appropriate requirements should be considered.

3.1.2 Form of the storage tank

The form of storage tank is mainly vertical tank and horizontal tank 2 kinds.

The advantages of vertical tank are large usable volume (effective volume), low manufacturing cost, small footprint, easy internal clean emptying, spray ball design is relatively simple.

The advantage of horizontal tank is that it is low and limited by the height of the water station room. But its covers an area of large area, the design of internal cleaning with spray ball difficulty is big, install at least 2 spray ball commonly.

Specific selection of vertical tank or horizontal tank, to combine the water tank design volume, site area and room height and other factors of comprehensive consideration. If the spatial influence factors are not considered, generally, vertical tank is less than 10t, and horizontal tank is more than 10t.

3.1.3 Material and surface treatment of the storage tank

The materials of cans and parts directly or indirectly in contact with WFI shall be AISI 316L stainless steel confirmed by the supplier, and the corresponding national standard grade is OOCrl 7Ni 14Mo2.

The surface of the tank needs to be electropolished, and the surface roughness is Ra <0.4 M, m. Meanwhile, all surfaces in contact with WFI should be free of any cracks and sharp edges and gaps that may hinder proper cleaning.

The effect of the insulation material is reliable, the insulation material should be completely sealed in the insulation layer, the outer surface is covered with AISI 304 stainless steel plate, the thickness is not less than 1.5 mm, and the corresponding national standard grade is 06Crl9Nil0.

3.1.4 Tank temperature and pressure

The design temperature of WFI storage tank is 0135 ° C, and the design pressure is not lower than 0.4 MPa. WFI storage tanks shall comply with the relevant regulations of the design, manufacture and testing of national pressure vessels, and shall have a third-party testing certificate.

3.1.5 Tank accessories

3.1.5.1 Breathing apparatus

The respirator is equipped with 0.22 | xm hydrophobic PTEF filter, can sterilize in place, have integrity test interface, equipped with electric heating device to ensure the dry filter element at all times.

3.1.5.2 Sprouting ball

The design of the spray ball should ensure that the spray falls into every part of the tank. The supplier should do the riboflavin spray experiment before delivery and provide the verification documents on the cleaning effect.

3.1.5.3 Blasting plate and safety valve

A lasting plate or safety valve must be installed on the tank. The lasting plate and safety valve are sanitary design. Blasts are recommended on WFI tanks, which are relatively simple for the future maintenance.

3.1.5.4 Level meter

At present, there are mainly three kinds of liquid level meters used on the WFI storage tank, which are static pressure type, capacitance type and differential pressure type. Either form of liquid level meter should meet the sanitary design.

The static pressure level meter shows too much error and is not recommended. The installation of the capacitive liquid level meter requires the height of the room, because if the room is too short and the storage tank is very high, the liquid level meter can not be removed from the tank once the storage tank is in place, resulting in future maintenance difficulties. However, the price of capacitive level meter is low, and if the tank volume is small, it is suitable to use capacitive level meter. The differential pressure level gauge reading is accurate and is not limited by the installation space. Although the price is slightly higher, it is suitable for WFI storage tanks.

3.1.5.5 Temperature sensor and pressure transmitter

WFI storage tank should be equipped with temperature sensor and pressure transmitter, both of which should have signal output function, and belong to the sanitary design.

3.2 Circulating water pump

3.2.1 Key technical points

WFI water system generally uses centrifugal water pump, and must choose the

sanitary structure design products.

   The pump is made of AISI316L stainless steel, electropolishing and passivation. The pump is self-lubricated without additional lubricant, and the gasket resists the temperature of the system sterilization (121 ° C). To drain the water in the pump head, the pump outlet should be tilted up 45° to avoid air cav.

3.2.2 Reynolds number and backwater flow rate

In order to ensure the formation of turbulence in WFI pipeline, the general design value of Reynolds number office is around 4600. The Reynolds number calculation formula: $Re = dwp / \mu$

In the formula

The d —— pipe diameter (m);

W- - - -Flow rate (m/s)

The p —— density (kg/m3);

μ —— Fluid viscosity (Pa.s)。

  In the actual engineering implementation process, because the Reynolds number cannot be measured, so the backwater flow rate is used to assess the turbulence in the WFI line.

The WFI storage-water distribution system requires the return flow rate of large water consumption, at least should not be less than 1 m/s. Because the water consumption is constantly changing, the pump of WFI system must be equipped with frequency conversion controller, constantly adjust the frequency of the pump according to the signal of the return flowmeter, control the speed of the pump, and always ensure that the return flow rate of WFI system is within the design range.

3.2.3 Standby pump

  At present, some pharmaceutical factories use the practice of online arranging standby pumps, which can install two pumps in parallel or in series. This method is not recommended in this paper. The practice of installing standby pumps online is also worth discussing. Because when the running pump fails, the pipeline is directly connected to the standby pump installed side by side, although it can save the time of system maintenance and troubleshooting the fault, but this practice does not meet the requirements of GMP requirements. When the system is connected to a new water pump, in order to ensure the quality requirements of the whole WFI sterile safety production, the whole WFI storage-distribution system must be cleaned and sterilized, so the workshop shutdown time is not shortened.

  A good solution is configured quality within the WFI system.

  Double tube plate heat exchanger has high safety, WFI pipe process, cooling water shell process. In case of leakage between the seamless stainless steel pipe and the B

plate seal, the cooling water will seep out from here, and can never mix with the WFI in the pipe process. Even if the seal between the seamless stainless steel pipe and plate A leaks, the WFI will ooze from here and will not mix with the cooling water. So the double tube plate heat exchanger provides a safe heat exchange solution for the WFI system.

The disadvantage of double plate heat exchanger is low heat transfer efficiency, and due to the high processing difficulty, the cost of double plate heat exchanger is very high. Since realizing the same heat transfer capacity of the double-tube plate heat exchanger requires more installation space, this factor needs to be considered in advance during the construction of the project.

3.4 Stainless steel line

3.4.1 Pipe Material Requirements
Stainless steel pipe must be made of AISI 316L stainless steel pipe. The inner wall of the pipe shall be electropolished according to ISO2037 or ASME BPE, with surface roughness of Ra at 0.4 pm, and degreasing, pickling and passivation. The supplier must be required to provide the material certificate for all lines.

3.4.2 Requirements for system design
  The design pressure of the system is not less than 0.6 MPa. After installation, the water pressure shall be tested and the pressure is 1.5 times of the design pressure and maintained for at least 30 min. The water used for pressure test shall not contain chloride ion.
  A slope of at least 0.5% should be considered in the design of the whole pipeline system, and the low point of the system ensures that the liquid storage * in the water system can be drained away.
WFI lines should be designed to avoid "cecal pipes" as far as possible, if not, according to the principle that the valve center to the outer wall of the main pipe is at 3d.

3.4.3 Requirements for pipeline installation
  WFI system pipes are installed using TIG automatic track welding whenever possible, minimizing manual welding and clamp connection. Each solder joint must be coded, and the layout drawing of the solder joint should be drawn. The tested position of the solder joint should be clearly marked on the drawing.
  At least 20% of the total weld examination; when manual welding, 100 weld shall have color endoscope examination, all results shall be taken into CD, and the welding

standard shall refer to the standard of ASME BPE-2009.

At least 10% of the total weld joints for X-ray inspection, specific sampling location proposed by the supplier and must be confirmed by the demand side and indicated on the layout diagram of the final solder joints.

The outer wall of WFI pipe needs to be insulated. The insulation material should be * sealed in the insulation layer, and the outer wall is marked by water flow. The insulation in the purification area is AISI304 stainless steel, which is beautiful and reliable.

3.5 Valve

3.5.1 Valve body material

All valves in the WFI storage-distribution system must be of AISI 316L sanitary diaphragm valves.

3.5.2 Valve body form

Diaphragm valve body has forging and forging 2 forms, the price difference is nearly 3 times. The operating pressure of WFI system does not exceed 0.3 MPa, so it is a low pressure pipe, and the casting diaphragm valve is sufficient. In addition, using diaphragm valve forged valve or casting diaphragm valve is not the focus of GMP.

3.5.3 Films

3.5.3.1 Silicone diaphragm sheet

Silicone diaphragm is cheap, which is widely used on the diaphragm valve of most domestic pharmaceutical plants. However, its heat resistance is relatively poor. WFI needs high temperature cycle and regular sterilization, so the silicone diaphragm is easy to age and needs to be replaced frequently.

3.5.3.2 EPDM (EPDM) diaphragm

The elasticity, temperature resistance and aging resistance of this diaphragm are better than that of silicone diaphragm, which is more suitable for WFI system. But in fact, this kind of diaphragm is suitable for use in purified water (Purified Water, PW) pharmaceutical water system operating at room temperature. At present, foreign pharmaceutical enterprises use EPDM diaphragm in the preparation, storage and distribution of purified water.

3.5.3.3 EPDM + PTFE composite diaphragm

PTFE (PTFE) has the reputation of plastic, has high temperature resistance, acid and alkali resistance, organic solvent resistance, aging resistance and many other advantages. But its disadvantage is that the hardness is too high, ductility and elasticity is too poor, so can not be used alone as diaphragm diaphragm valve. A new practice has been developed abroad, combining very thin PTFE diaphragm (about 0.4 mm) and normal thickness EPDM diaphragm together, so that it has the elasticity of EPDM and the high temperature resistance of PTFE, and the performance is very superior. At present, the WFI system has been widely used in foreign pharmaceutical enterprises.

3.6 On-line conductivity detector and online TOC detector

3.6.1 On-line conductivity detector

According to the regulations of the new GMP, the WFI system must detect the change in the water quality of the WFI in the storage-distribution system in real time according to the on-line conductivity detector. The online conductivity meter should be installed in front of the WFI return pipe inlet tank, so as to fully detect the possible abnormal conditions in the whole pipeline system.

The unqualified water discharge valve. When the WFI water quality is abnormal and the conductivity value exceeds the standard, the control system PLC shall alarm on the HMI, automatically close the WFI inlet valve and open the bypass discharge valve, so that the unqualified WFI can be discharged outside the system in time and will not pollute the WFI in the storage tank.

3.6.2 Online TOC Tester

Total organic carbon TOC (Total Organic Carbon) is an indicator reflecting the total amount of organic pollutants in water quality. Compared with the traditional chemical oxygen demand (COD) measurement, TOC technology is simple and fast. The analysis time of the TOC analyzer is generally 46 min. If it is an online detector, the WFI water quality can be monitored continuously for 24 h.

The 2020 Chinese Pharmacopoeia stipulates that TOC testing of WFI is mandatory, TOC testing of PW is optional (easy oxide or TOC), and TOC qualification limit of WFI and PW is 500 micrograms per liter.

Although the 2020 edition of Chinese Pharmacopoeia stipulates that online monitoring of TOC and offline laboratory measurement of TOC are allowed, the pharmacopoeia also indicates the possible pollution caused by offline testing, indicating the advantages of online testing: " On-line monitoring can facilitate the real-time measurement of water quality and real-time process control of the water system; and the off-line measurement may bring many problems. Since the

production of water is carried out in batches or in continuous operation, the conditions and specific conditions of water production should be determined by choosing the offline measurement or the online measurement."

The online TOC detectors should be installed in front of the WFI return pipe inlet tank for the same reason as the online conductivity detectors, so they are usually installed together.

When the WFI water quality of WFI is abnormal and the TOC value exceeds the standard, just with the conductivity value, the control system should alarm, close the WFI tank valve and open the discharge valve, so that the WFI with T0C value exceeds the standard can be discharged outside the system in time without polluting the WFI in the storage tank.

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