GB

NATIONAL STANDARD OF THE

PEOPLE'S REPUBLIC OF CHINA

ICS 11.120.30

C 90

GB/T 36030-2018

General technical requirements of CIP and SIP for pharmaceutical machinery

制药机械（设备）在位清洗、灭菌通用技术要求

Issued on: March 15, 2018 **Implemented on: October 01, 2018**

Issued by: General Administration of Quality Supervision, Inspection and Quarantine of the People's Republic of China;

Standardization Administration of the People's Republic of China.

Table of Contents

General technical requirements of CIP and SIP for pharmaceutical machinery

1 Scope

This Standard specifies the general technical requirements for pharmaceutical machinery implementing cleaning in place and sterilization in place in the “Good Manufacturing Practice (2010 Revision)”.

This Standard is applicable to the pharmaceutical machinery implementing cleaning in place and sterilization in place during the pharmaceutical production process.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

GB 28670 General rule of pharmaceutical machinery conforming to good manufacturing practice

JB/T 20158 Pharmaceutical cleaning in place equipment

Quality Management Regulations for Pharmaceutical Production (revised in 2010) (Ministry of Health of the People's Republic of China)

Pharmacopoeia of the People's Republic of China (2015 Edition) (National Pharmacopoeia Commission)

3 Terms and definitions

For the purpose of this document, the following terms and definitions apply.

3.1

cleaning in place; CIP

Cleaning of system or equipment in the original installation position, without disassembling or moving.

GB 28670.

4.2 The CIP and SIP process shall be effective and reproducible, and the data shall be traceable.

4.3 The installation environment, location and space, floor structure and process piping of CIP and SIP for pharmaceutical machinery shall meet the requirements of CIP and SIP process and validation.

4.4 The validity of the process certification documents and batch record documents shall be confirmed before implementing CIP and SIP for pharmaceutical machinery.

4.5 The CIP pharmaceutical machinery shall be cleaned at the specified time after used. Non-sterile drug production equipment shall be dried after cleaning; sterile drug production equipment and aseptic operation area production equipment shall be sterilized at the specified time after cleaning. The exposed opening after cleaning, sterilization and drying shall be closed.

4.6 Sterile drug production equipment shall be sterilized after complete assembly. Equipment, pipes, connecting points, valves, and sealing devices that are in direct contact with the materials should be cleaned in place and sterilized in place.

4.7 CIP shall ensure that there is no dead space in the cleaning range. The cleaning solution pressure, flow rate, temperature, and cleaning time shall be guaranteed and verified before implementation.

4.8 For CIP pharmaceutical machinery which is difficult to determine the residue limit standard, the surface in contact with the material shall be sprayed with the specified drug. After cleaning, the residue limit of the sprayed drug shall be used as the validation index.

4.9 The type of cleaning agent used in CIP pharmaceutical machinery, the concentration of cleaning fluid, and the order of use shall be verified before putting into use.

4.10 Pharmaceutical machinery cleaned with acidic or alkaline water shall have a sewage disposal facility.

4.11 Pharmaceutical machinery cleaned with organic solvents shall have an explosion-proof facility.

4.12 The validation of CIP devices consisting of one or more systems shall include microbial challenge tests under the most adverse conditions.

4.13 Sterile drug production equipment and aseptic operation area production

The minimum limit value calculated by one of the above three methods is taken as the acceptance standard for the residue per unit area by wipe sampling.

8.1.12 It shall make clear the dry storage conditions after cleaning.

8.1.13 It shall make clear the validity period after cleaning.

8.1.14 The cleaning procedures shall be able to guide each operator to work.

8.2 Selection of cleaning agent

8.2.1 The cleaning agent shall have simple composition, stable quality and exact effect.

8.2.2 The cleaning agent shall dissolve the residue effectively, not corrode the equipment, and be easily removed. The recovery rate shall not be less than 50 %.

8.2.3 The biological activity or toxicity parameters in the cleaning agent shall be clear.

8.2.4 The cleaning agent shall be environmentally friendly or harmless.

8.2.5 The name, formula and operating parameters of the cleaning agent shall be determined according to factors such as residue's solubility, activity or toxicity, stability, viscosity, adsorption, concentration of the active ingredient, daily dose range, production batch, influence of auxiliary materials on cleaning effect, chemical compatibility of cleaning materials and cleaning agents.

8.2.6 The selection of the cleaning agent shall avoid introducing new impurities.

8.2.7 For cleaning agents that need to be recycled, the quality of the recycled cleaning agent shall be monitored and proved to have no adverse effect on the quality of the drug.

8.2.8 In order to prevent the cleaning agent from causing tolerance to spores and microorganisms, the cleaning agent shall be replaced regularly.

8.2.9 The cleaning water shall meet the quality standards for pharmaceutical water as specified in the Pharmacopoeia of the People's Republic of China. The condensed water of pure steam shall meet the quality standards for pharmaceutical water as specified in the Pharmacopoeia of the People's Republic of China. The last cleaning water for sterile pharmaceutical equipment shall be water for injection, and the last cleaning water for non-sterile pharmaceutical equipment shall be at least purified water.

8.3 Determination of cleaning parameters

9 Sterilization

9.1 Sterilization procedures

9.1.1 It shall make clear the interval between the end of the cleaning and the start of sterilization.

9.1.2 It shall make clear the method of sterilization.

9.1.3 It shall make clear the location of the coldest spot and use the table or icon to indicate the location of the temperature probe and indicator.

9.1.4 It shall make clear the name and requirements of biological indicator.

9.1.5 It shall make clear the procedure for sterilization.

9.1.6 It shall make clear the quality requirements for sterilization media.

9.1.7 It shall make clear monitor the instrumentation and accuracy requirements of the sterilization parameters and have a calibration record.

9.1.8 It shall make clear the operational steps and precautions.

9.1.9 It shall make clear the sampling method and sampling location and sample preservation method.

9.1.10 It shall make clear the quality standards for sterilization;

9.1.11 It shall make clear the storage conditions after sterilization and drying.

9.1.12 It shall make clear the validity date after sterilization.

9.1.13 The sterilization procedures shall be able to guide each operator to operate safely.

9.2 Sterilization and sterilization parameters

9.2.1 The sterilization object in this Standard is the pharmaceutical machinery and equipment after cleaning in place, which has good thermal stability and is suitable for high temperature steam sterilization.

9.2.2 The temperature and time of steam sterilization shall be greater than or equal to 121 °C for 15 min.

9.2.3 The steam sterilization process shall be monitored and recorded.

9.2.4 The sterilization in place shall be subjected to the challenge qualification

Through validation, it is confirmed that the cleaning and sterilization of CIP and SIP pharmaceutical machinery meet the “Good Manufacturing Practices (2010 Revision)”, meet the requirements of the pharmaceutical production process, and achieve the specified cleaning and sterilization effects.

12 Cleaning and sterilization quality standards

12.1 The cleaning effect shall ensure that the total amount of the specified residue is so low that it does not affect the quality of the next batch of drugs. The sterilization effect shall reach the sterility assurance value of sterile drugs.

12.2 The residue limit indicators after cleaning of pharmaceutical machinery for the production of non-toxic, non-high-activity, non-hypersensitizing drugs shall meet the following requirements:

a) It shall not have visible residues by visual inspection; it shall be dry and odorless;

b) The content of the drug residue in the previous preparation checked in the sampling eluent shall not exceed 1/1000 of the minimum treatment daily dosage.

c) The residual content of the previous batch of API checked in the sampling eluent shall be less than 10×10^{-6};

d) The residual content of the cleaning agent checked in the sampling eluent shall be less than 10×10^{-6};

e) The residual limit standard for sampling by wipe sampling method shall regard the minimum value calculated by the three calculation methods of 8.1.11 as the acceptance standard for the residue per unit area by wipe sampling.

12.3 The microbiological indicators after cleaning shall meet the following requirements:

a) The sampling of rinsing water for rinsing with water for injection is in accordance with the criterion for microbiological and endotoxin for water for injection specified in the Pharmacopoeia of the People's Republic of China (2015 Edition). The microbial limit shall be less than 10 CFU/100 mL; the endotoxin shall be less than 0.25 EU/mL; TOC ≤ 0.5 mg/L.

b) The sampling of rinsing water for rinsing with purified water is in accordance with the criterion for microbiological and endotoxin for purified water specified in the Pharmacopoeia of the People's Republic of China (2015 Edition). The microbial limit shall be less than 100 CFU/mL; TOC ≤

This is an excerpt of the PDF (Some pages are marked off intentionally)

------ The End ------