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Process Design of CDMO Aseptic Formulation Workshop for PD-1 Antibody and Protein Products

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Abstract. With the rapid development of biotechnology and the improvement of global health awareness, the biopharmaceutical industry has developed rapidly. The CDMO model has become an important means for many biopharmaceutical enterprises to optimize resource allocation and improve research and development efficiency. The aim of this study is to provide a scientific and cost-effective sterile formulation workshop design scheme that meets GMP requirements. The study aims to avoid potential risks to materials during the CIP process by conducting an overall CIP/SIP process with the filling machine after material filling in the liquid mixing process. Based on the first law of thermodynamics, energy balance is calculated to determine the thermal load of the equipment or device, and further determine the type, quantity, and main process dimensions of the heat transfer equipment. This study aims to ensure product quality, improve production efficiency to cope with global market competition and the complexity of supply chains, as well as the development of personalized and precision medicine.

Keywords: biopharmaceuticals; CDMO mode; GMP requirements; Sterile preparation workshop; Liquid preparation process.

1. Introduction

With the rapid development of biotechnology and the improvement of global health awareness, the biopharmaceutical industry has developed rapidly. The CDMO model has become an important means for many biopharmaceutical enterprises to optimize resource allocation and improve research and development efficiency [1]. The aim of this study is to provide a scientific and cost-effective sterile formulation workshop design scheme that meets GMP requirements. This study aims to ensure product quality, improve production efficiency to cope with global market competition and the complexity of supply chains, as well as the development of personalized and precision medicine. The main content of this design includes design basis and design foundation; Process description; Production system; Material calculation; Selection of main process equipment; Main raw and auxiliary materials; Consumption of process utility engineering; Workshop layout, etc.

This design task is to design the process of CDMO sterile preparation workshop for protein products. The production scale and quality standards of the product are clearly defined, as shown in Table 1:

Table 1 Production Scale and Quality Standards

Product Name	Production scale	specifications
PD-1 antibody	15 million units per year	10 mL/bottle
Protein products	2 million units per year	5 mL/bottle

Product Name: PD-1 Antibody and Protein Products; Dosage forms: small volume injection and freeze-dried injection; Registration classification: Therapeutic biological products; Product function

and use: PD-1 antibody is an antibody drug used for non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis. This drug effectively controls the progression of the disease by clearing CD20 positive B cells [2]. Protein products can reduce fat, promote digestion, enhance immunity, strengthen muscles, protect the brain, regulate endocrine functions [3], and more.

The raw materials and quality standards are shown in Table 2:

Table 2 Raw Materials and Quality Standards

name	quality standard
PD-1antibody biological stock solution	The white concentration is 100 mg/mL
Protein product stock solution	The protein concentration is 50 mg/mL
Tween 80	Current Chinese Pharmacopoeia
sucrose	Current Chinese Pharmacopoeia

Design principle: Under the premise of meeting the basic requirements of production tasks, the process flow should comprehensively consider multiple technical and economic indicators such as energy consumption and operating costs, as well as factors such as environmental protection, safety, and land occupation, and be designed reasonably; The process design needs to fully consider the concepts of health, safety, environmental protection, and energy conservation, minimize the clean area area as much as possible, and achieve mechanization, automation, and good human-machine engineering design of process equipment and material operation equipment in workshop operation; Equipment selection should be based on the properties of materials and material balance results, selecting reasonable, advanced, safe and reliable new equipment that meets the system GMP requirements; The entire design process is always carried out in conjunction with the manufacturing process, ensuring quality control during the production process and fully considering safety, environmental protection, and personnel protection issues.

2. Ease of use

2.1. Process Description

2.1.1. Process Overview

The process route and flowchart of PD-1 antibody are shown in Figure 1 (see Appendix 1 for the color diagram)

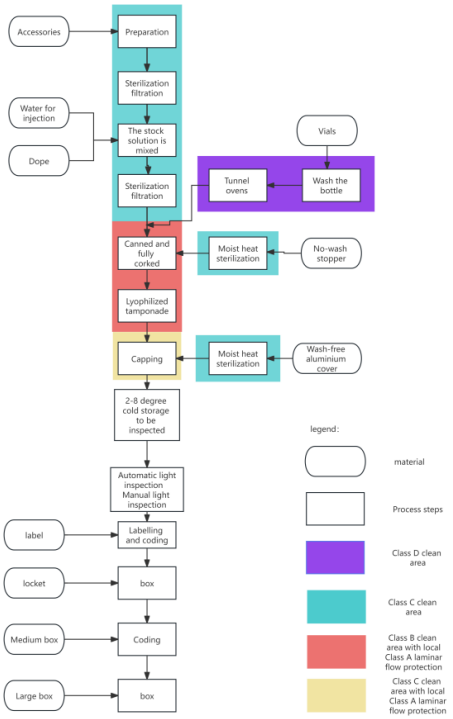

Figure 1 Process flowchart of PD-1 antibody

The process route and flowchart of protein products are shown in Figure 2 (see Appendix 2 for the color diagram)

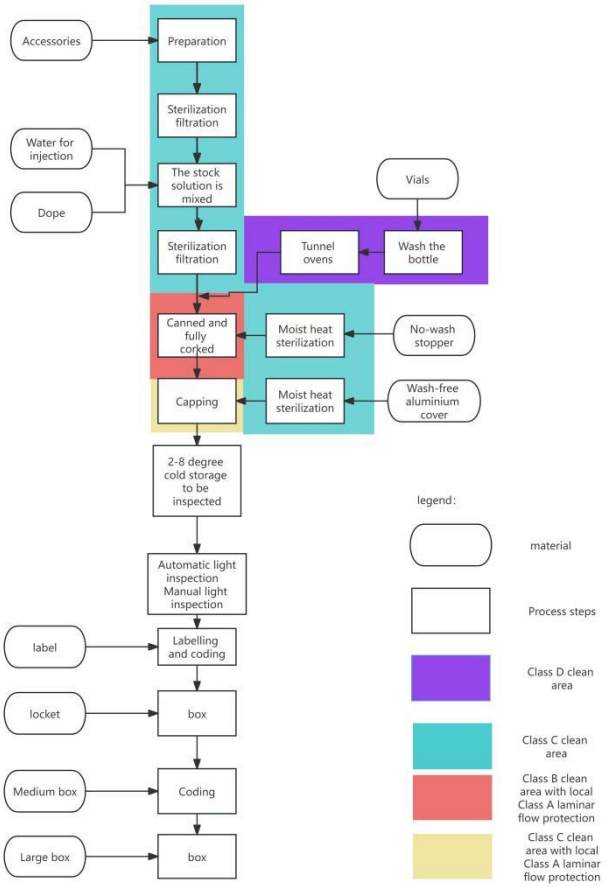

Figure 2 Process flowchart of protein products

2.1.2. Process

The following design is carried out for the liquid preparation process: add a certain amount of room temperature injection water to the auxiliary material preparation tank, add sucrose solid according to the proportion, stir at room temperature for 30 minutes, completely dissolve, then add Tween 80 according to the proportion, stir evenly, and transfer to the semi-finished product preparation tank after primary sterilization and filtration for later use. The volume of the excipient solution for the prepared PD-1 antibody is 7 times the volume of the original PD-1 antibody solution to be added, and the volume of the excipient solution for the prepared protein product is 3 times the volume of the original protein product solution to be added. Add the original solution to the semi-finished product mixing tank, stir at room temperature for 30 minutes, stir evenly, add room temperature injection water to a constant volume, and then transfer it to the semi-finished product temporary storage tank through primary sterilization filtration. Then, transfer it to the filling machine for filling after secondary sterilization filtration. The cleaning process of the liquid dispensing and filling system: The components of the liquid dispensing and filling system include the liquid dispensing tank, semi-finished product temporary storage tank, filling machine, and corresponding material pipelines. In order to avoid potential risks to the materials during the CIP process, after the materials are filled, the liquid dispensing system and the filling machine perform CIP/SIP as a whole. The program running time for the entire CIP/SIP is 8 hours [4]. The content of finished raw materials is shown in Table 3 and Table 4.

Table 3 Table of raw material content for each PD-1 antibody finished product

Number	component	content
1	PD-1 antibody protein	100 mg/tube
2	sucrose	400 mg/tube
3	Tween 80	2.0 mg/tube

Table 4 Table of raw material content for each finished product of biological product A

Number	component	content
1	Biological product A protein	50 mg/tube
2	sucrose	200 mg/tube
3	Tween 80	1.0 mg/tube

Note 1: The original solution is transported to this workshop through a disposable storage bag and is not within the scope of this design.

Note 2: During the solution preparation process, the solid solute dissolves in the solvent and has already formed a solution. The volume is calculated as unchanged.

Note 3: The working range of stainless-steel liquid dispensing containers is 25-75% of the container volume.

2.2. Production system

2.2.1. design requirement

The production system can be set as a three-shift system, with 8 hours per shift; For processes that take less than 16 hours, a two-shift system can be established, with 8 hours per shift; The process that lasts less than 8 hours can be designated as a single shift system. Design scale: As shown in Table 3-1. Design annual working days: 300 days; Production shift system: Except for the freeze-drying and plugging position, which is a three-shift system, all other operating procedures are a two-shift system;

8 hours per shift. The specific production shift system for each process is determined according to the operating cycle.

Design scale: As shown in Table 5:

Table 5 Design Scale Table

Product Name	Design scale
PD-1 antibody	15 million units per year
Biological product A	200 million units per year

(1) Design annual working days: 300 days

(2) Production shift system: Except for the freeze-drying and plugging position, which is a three-shift system, all other operating procedures are a two-shift system; 8 hours per shift. The specific production shift system for each process is determined according to the operating cycle.

2.2.2. Cycle allocation

As can be seen from the previous text, the annual working day is 300 days. Due to the designed workshop being used for CDMO, the number of alternations for different products throughout the year is considered to be 8, and a 24-hour cleaning is required for product switching. The annual production days are 292 days. Considering the stability of the equipment, a single unit with a specification of 25 meters is selected ² the freeze-drying machine produces protein products, but its loading capacity for penicillin bottles is limited. Therefore, when determining the production days and batches of two types of products, priority should be given to meeting the freeze-drying scale of protein products.

The diameter of the 15R penicillin bottle is 24 mm, estimated to be 25 m ² Loading capacity of freeze-drying machine: 25/ (0.024 x 0.024) ≈ 43403 pieces; If the packaging quantity is calculated as 43000 pieces, the annual production batch of protein products is approximately 2000000/43000 ≈ 50 batches. Considering the losses during the production process, the annual production batch of protein products is determined to be 50 batches.

Due to the long freeze-drying cycle, the production of protein products is done in batches every three days, and the annual production days are 50 x 3=150 days.

The annual production days of PD-1 antibodies are 292-150=142 days. The PD-1 antibody is calculated on a daily basis, with an annual production batch of 142 batches.

The initial allocation of annual production times is 4 times for PD-1 antibodies and 4 times for protein products. The specific production days are based on the actual production tasks.

2.2.3. Production shift system

The production shift system is determined based on the actual production time of the process, as shown in Table 6 and Table 7.

Table 6 Production Shift System of PD-1 Antibody Production Workshop

Production process	Production shift
Liquid preparation process	Two shift system
Aluminum cover and rubber plug treatment process	Two shift system
Processing process of penicillin bottles	Two shift system
Filling process	Two shift system
Capping process	Two shift system
Lamp inspection, labeling and outsourcing process	Two shift system

Table 7 Production Shift System of Biological Product A Production Workshop

Production process	Production shift
Liquid preparation process	Two shift system
Processing process of penicillin bottles	Two shift system
Freeze drying and plugging process	three-shift system
Filling process	Two shift system
Capping process	Two shift system
Lamp inspection, labeling, and outsourcing processes	Two shift system

2.3. Material balance

2.3.1. Fundamentals of Accounting

The theoretical basis of material balance: The theoretical basis of material balance is the law of conservation of mass [5], which means that the total amount of material entering a system must be equal to the total amount of material leaving the system, plus the loss during the process and the accumulation in the system. Use this law to derive material balance equations for various processes:

$$\sum G_i = \sum G_O + G_A \tag{1}$$

In the formula: $\sum G_i$ —The total amount of materials input into the system

$\sum G_o$ —Total material quantity of the output system

G_A —The total accumulation of materials in the system

For steady-state processes where materials do not accumulate within the system, the above equation can be simplified as

$$\sum G_i = \sum G_O \tag{2}$$

Accounting benchmark: When conducting material accounting, the corresponding accounting benchmark must be selected as the basis for calculation. In this design, the production cycle of a batch of operations is used as the benchmark for material accounting.

PD-1 Antibody: The production operation of PD-1 antibodies is a daily batch. For a given production scale, the annual production days of the product are calculated based on the annual and daily production of the product. Then, the required feed amount for one day of operation is calculated based on the total yield of the product, and material balance is carried out based on this. The relationship between the annual output, daily output, and annual production day of a product is:

$$Daily\ production = \frac{Annual\ output}{Annual\ production\ date} \tag{3}$$

The annual output in the formula is determined by the design task, and the annual production day depends on the specific production situation.

Protein products: The production process of protein products involves a batch every three days, which means the production cycle for the same batch is three days. For a given production scale, the batch production cycle (three days) is used as the basis for calculation. The batch production of the product is calculated based on the annual output and number of production batches. Then, the required feeding amount for a batch of operations is calculated based on the total yield of the product, and material balance is performed based on this. The relationship between the annual output, batch output, and annual production batches of a product is:

$$Batch\ yield = \frac{Annual\ output}{Annual\ production\ batches} \tag{4}$$

The annual output in the formula is determined by the design task, and the number of annual production batches depends on the specific production situation.

Basic information of accounting: 300 working days per year, 8 hours per shift; Production shift: 3 shifts/day for freeze-drying and pressing plugs, and 2 shifts/day for others; Production method: intermittent production; Product design and production capacity: 15 million PD-1 antibodies per year; 2 million protein products per year; Product specifications: PD-1 antibody 10 mL/bottle; 5 mL/bottle of protein products; Quality standard: Meets the requirements of the enterprise standard, with a protein concentration of 10 mg/mL;

Loss rate or yield: see Table 8.

Outer packaging size and form: see Table 9

Raw material content: see Table 10 and Table 11

Table 8 Summary of Loss Rate or Yield

name	percentage/%
Filling and capping semi-finished product qualification rate	99.4
Lamp inspection pass rate	95
Loss rate of lamp inspection and labeling operations	0.1
Outsourcing sampling rate	0.05

Table 9 Summary Table of Outer Packaging Dimensions and Forms

Number	name	Packaging size(mm×mm×mm)	Packaging form
1	Small box	70(L)×53(W)×24(H)	1 piece/small box
2	Middle box	129(L)×58(W)×146(H)	10 small/medium boxes
3	carton	304(L)×206(W)×310(H)	20 boxes/box

Table 10 Table of raw material content for each PD-1 antibody finished product

Number	component	Content (mg/tube)
1	PD-1 antibody protein	100
2	sucrose	400
3	Tween 80	2.0

Table 11 Table of Raw Material Content for Each Protein Product Finished Product

Number	component	Content (mg/tube)
1	Protein products Protein	50
2	sucrose	200
3	Tween 80	1.0

2.3.2. Material balance diagram

After the material balance calculation, the material balance block diagram of PD-1 antibody is shown in Figure 3:

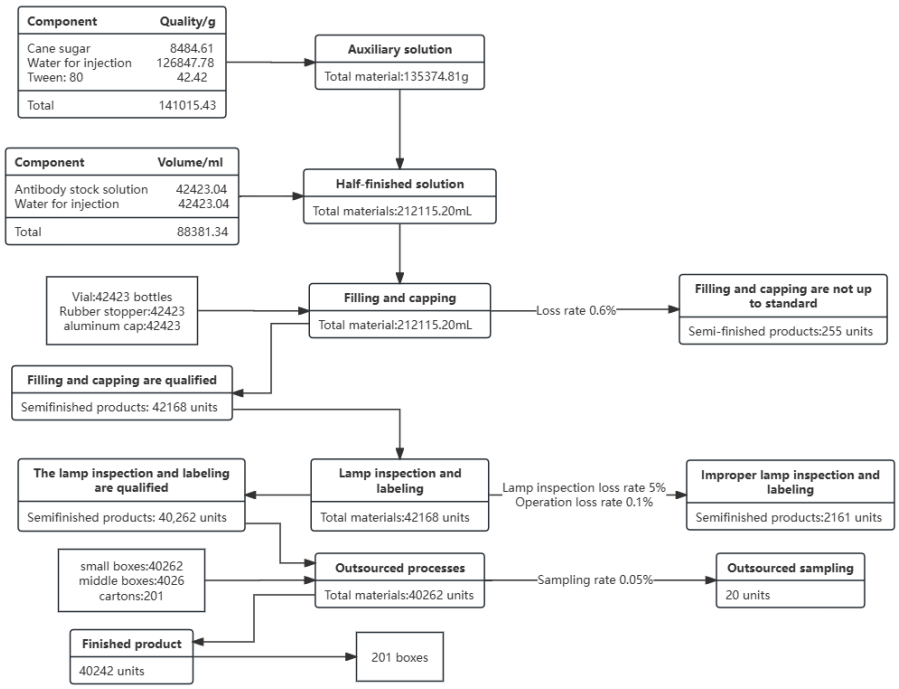

Figure 3 Material Balance Block Diagram of PD-1 Antibody (Calculated by Batch Production)

After the material balance calculation, the material balance block diagram of Protein Products is shown in Figure 4:

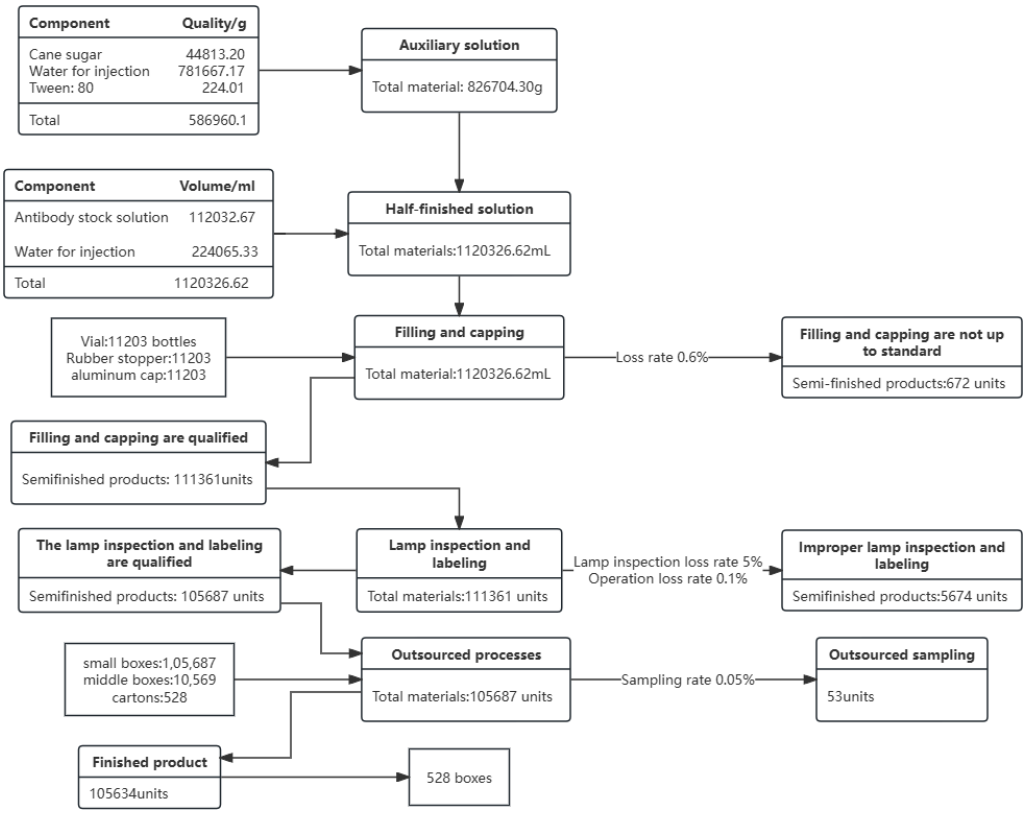

Figure 4 Material Balance Block Diagram of Protein Products (Calculated by Batch Yield)

2.4. Energy balance calculation

2.4.1. Accounting basis and benchmark

Overview: Energy balance is mainly based on the first law of thermodynamics to determine the heat load of equipment or devices [6]. Based on the size of the heat load, the properties of materials, and process requirements, the type, quantity, and main process dimensions of heat transfer equipment can be further determined.

The basic theory of energy balance: The heat balance equation of heat transfer equipment is:

$$Q1 + Q2 + Q3 = Q4 + Q5 + Q6 \tag{5}$$

In the formula:

Q_1 —The heat brought into the equipment by materials, kJ;

Q_2 —The heat or cooling capacity transferred from a heating agent or coolant to the equipment and the materials being processed, kJ;

Q_3 —The thermal effect of the process, kJ;

Q_4 —The heat carried out by the material from the equipment, kJ;

Q_5 —The amount of heat or cold consumed by heating or cooling equipment, kJ;

Q_6 —The heat dissipated by the equipment into the environment, kJ。

2.4.2. The specific process of heat balance calculation

For the convenience of calculation, the reference temperature for calculation is room temperature of 25 ℃.

Solution preparation: The average molar specific heat at constant pressure of the relevant materials is shown in Table 12.

Table 12 Summary of Average Constant Pressure Specific Heat Data

material	Average specific heat at constant pressure kJ·kg-1·℃-1
sucrose(L)	0.3
H2O	4.18

After material balance, the heat configuration of PD-1 antibody is shown in Table 13:

Table 13 Heat balance table for PD-1 antibody preparation

	entry name	Heat(kJ)		entry name	Heat(kJ)
input	Material brought in	-210057.54	output	Material carried out	210057.54
	Supplementary heating	0			
	Process thermal effect	0		heating equipment Or equipment scattering lose	0
	total	-210057.54		total	210057.54

After material balance, the heat configuration of Protein Products is shown in Table 14:

Table 14 Protein Products Preparation Heat Balance Table

	entry name	Heat(kJ)		entry name	Heat(kJ)
input	Material brought in	-35352.35	output	Material carried out	35352.35
	Supplementary heating	0			
	Process thermal effect	0		heating equipment Or equipment scattering lose	0
	total	-35352.35		total	35352.35

Energy balance calculation for other processes: Since the rubber plug treatment, filling, capping, lamp inspection, labeling, and outsourcing processes do not involve material changes, energy balance calculation is not considered.

3. Results

3.1. Workshop layout

Overview of Workshop Layout Design: Workshop layout design is an important part of pharmaceutical engineering design [7]. The rationality of workshop layout is not only closely related to construction, installation, and construction investment, but also closely related to the production, management, safety, and economic benefits of the workshop after completion. Therefore, the workshop layout design should be carefully and meticulously considered according to the design procedure. This workshop design involves the process design of the CDMO sterile formulation workshop for biological products. The production process is simple and there are no flammable or explosive chemicals. The workshop belongs to Class C workshop. The focus of this design is on how to reasonably arrange various functional areas and equipment to meet GMP requirements, as well as to ensure safety and economic rationality as much as possible, while also meeting various requirements from construction, installation to production and management [8]. Therefore, on the premise of meeting relevant laws, regulations, and production requirements, this design combines production characteristics and follows the principles of "safety first, economic practicality, and green environmental protection" to design the workshop layout plan.

Before conducting workshop design, the following design tasks should be completed to provide the following basic design data for this step, including process flow design, material balance, energy balance, and process equipment selection:

(1) Process flow diagrams with different depths, such as process flow diagrams with control points in the preliminary design stage and process flow diagrams with control points in the construction stage.

Process flow diagram with control points for the dosing process is shown in Figure 5

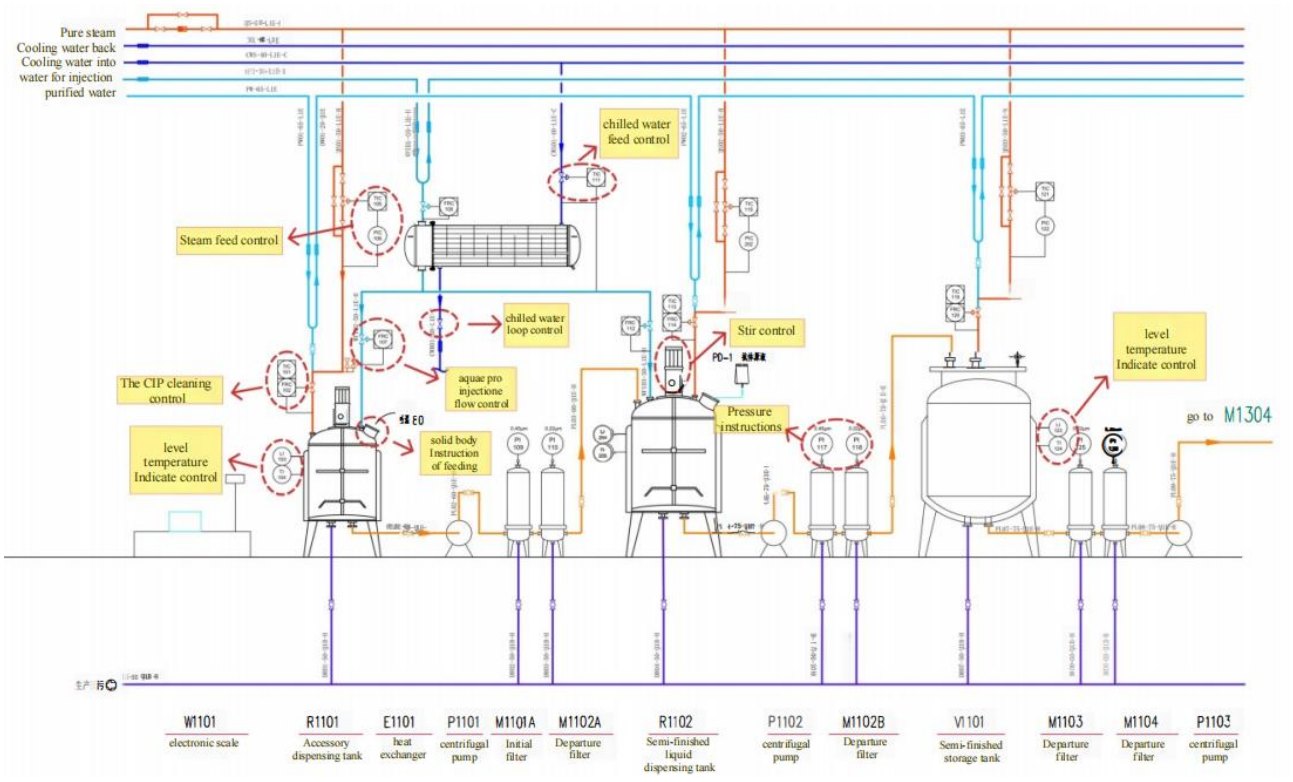

Figure 5 Process flow diagram with control points for the dosing process

The process flow chart of the two ingredients and stock solution mixture is shown in Figure 6 and Figure 7.

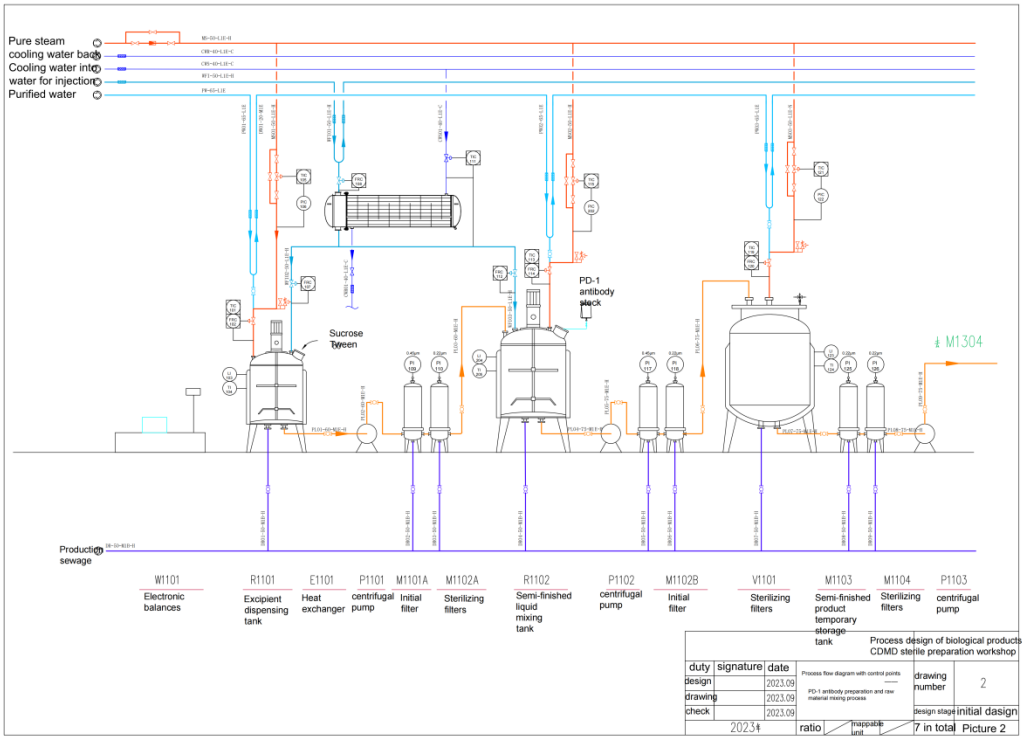

Figure 6 PD-1 antibody preparation and raw material mixing process

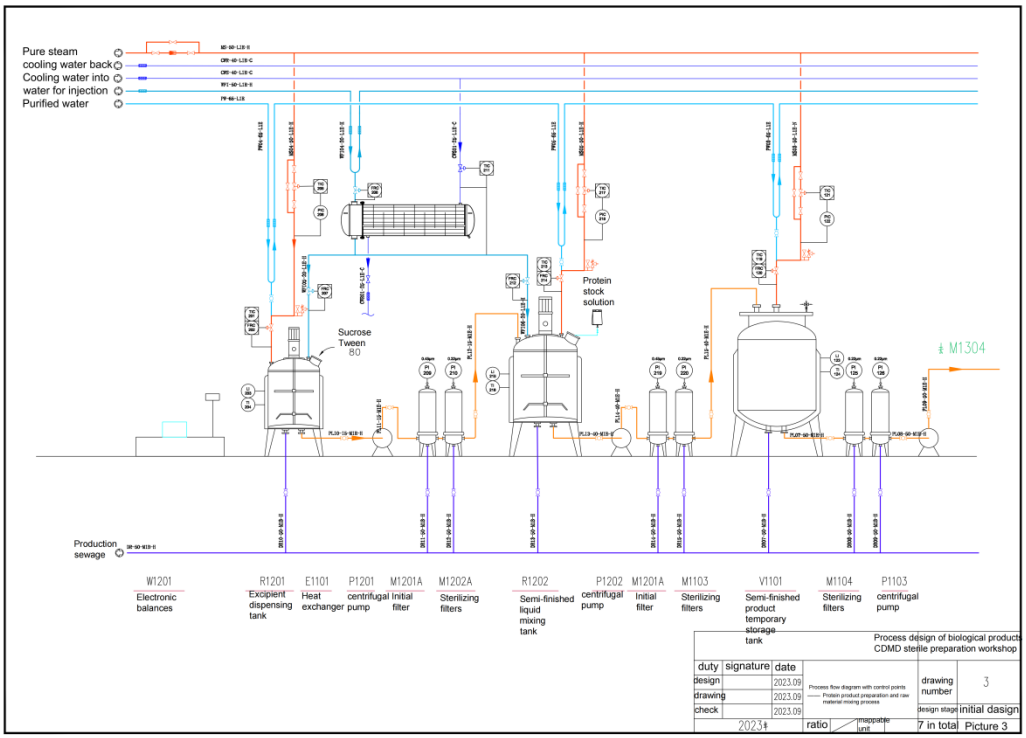

Figure 7 Protein products preparation and raw material mixing process

(2) Calculation data and results of material balance and energy balance, such as the quantity, composition, and properties of biological product raw materials, injection water, and auxiliary material solutions; Losses during filling, capping, and other processes.

(3) The selection and design results of process equipment, namely the equipment list, such as equipment model, external dimensions, weight, production capacity, operating conditions, etc., are shown in the workshop equipment layout diagram in the following figure.

The layout of workshop equipment is shown in Figure 8.

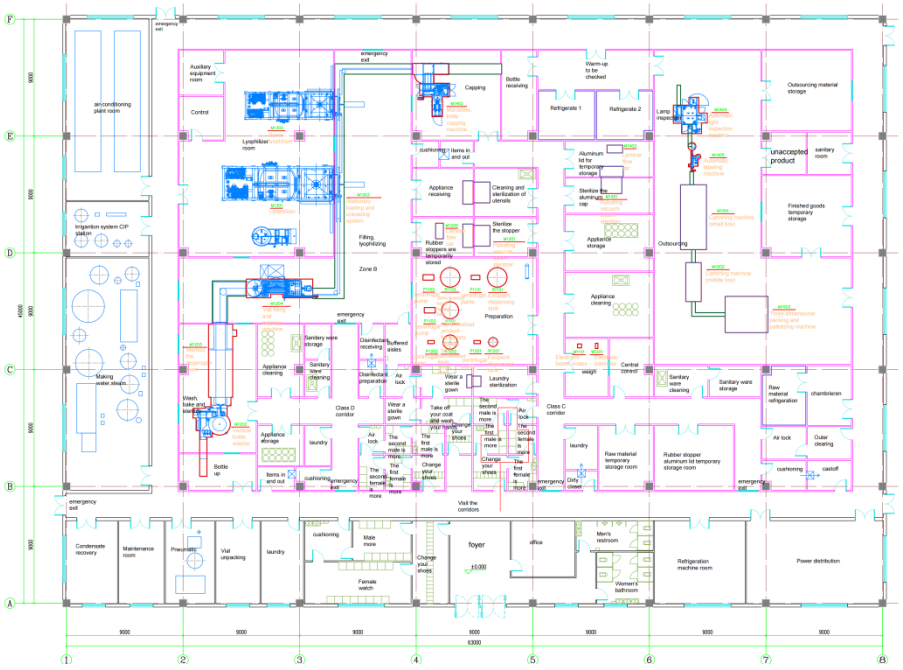

Figure 8 Workshop flow of people and logistics flow map

(4) The overall layout diagram of the factory area, including the connection between the workshop and other workshops and living facilities, as well as the distribution of people and logistics within the factory area are shown in the floor plan of workshop equipment.workshop equipment layout diagram in the following figure 9;

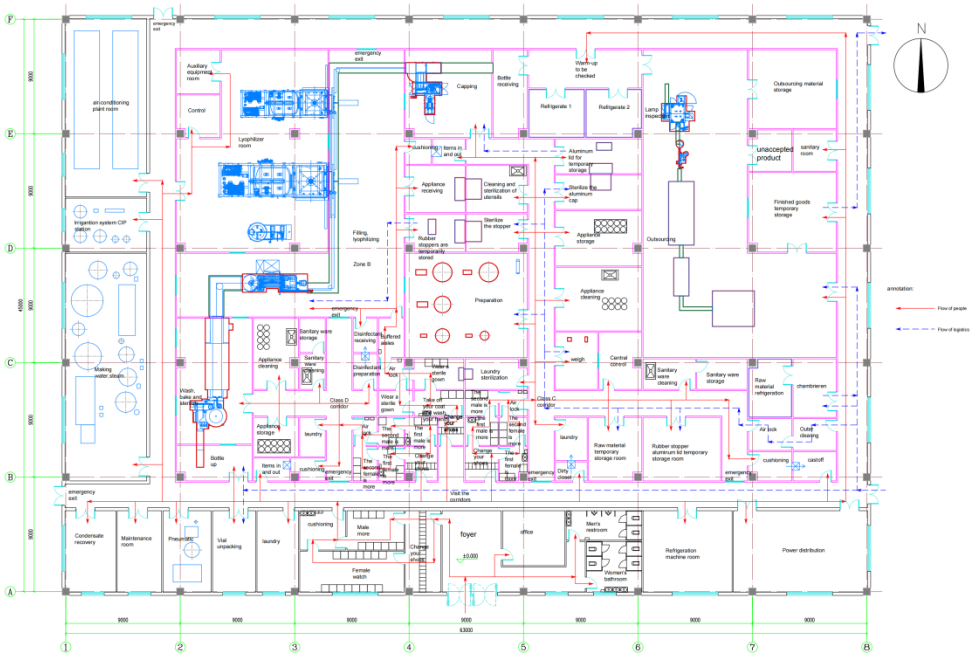

Figure 9 Floor plan of workshop equipment

(4) Other relevant information, including the staffing and personnel composition of the workshop, the situation of public utilities such as water, electricity, and steam, and the situation of the factory building.

3.2. Process pipeline calculation and selection

Pipeline selection: pipeline calculation basis

Pipeline calculation formula:$d = \sqrt{\frac{4Vs}{\pi u}}$

In the formula d: Pipeline inner diameter, mm

Vs: Volume flow rate of medium inside the pipe, m^3/s

u: Flow velocity inside the pipe, m/s

Usually, after the completion of pipe diameter design, rounding is carried out, and commonly used specifications and models of pipes are selected to reduce equipment costs.

3.3. Design of workshop automatic control system

Table 15 Main Control Points of Liquid Preparation Process

Control project	Main control points	Main Control Function Description
Equipment inspection control	Inspection indicator light Alarm indicator light	Prompt staff for inspection Prompt staff that there is an issue with the equipment, and it is necessary to To be repaired
Feeding control	Feeding indicator light Injection water feed valve flowmeter	Prompt staff to add materials Control injection water feed Measurement of injection water intake
Mixing control	Mixing button Speed adjustment button Mixing completion prompt light	Control blade stirring Control the stirring rate Prompt staff to proceed to the next step
Discharge control	Discharge valve Pump rear discharge valve	Control valve discharge Control valve discharge
Sterilization and filtration	Sterilization filter inlet valve Sterilization filter outlet valve Pressure control valve	Control valve feeding Control valve discharge Adjust pressure and control the driving force of operation
temperature control	Flow recording control instrument Steam regulating valve Flow recording control instrument Chilled water regulating valve Flow recording control instrument Liquid level indicator control instrument Temperature indicator control instrument Pressure indicator control instrument	Control hot water flow rate Control steam addition Control steam flow rate Control the addition of chilled water Control the flow rate of injection water Detecting liquid level and providing feedback on operating conditions Detect temperature and provide feedback on operating conditions Detect pressure and provide feedback on operating conditions

4. Conclusions

The process design of the sterile preparation workshop is a key link to ensure the quality and safety of drugs [9]. By establishing a sound aseptic preparation production and quality control strategy, contamination control strategy and sterility assurance system, the risk of contamination in the production process can be effectively reduced and the sterility and safety of the product can be ensured. In our research, we found that the layout of the aseptic preparation hall has a significant impact on production efficiency and product quality. The right layout ensures a smooth production process, reduces the risk of cross-contamination, and increases productivity. Therefore, in the process design process, it is necessary to fully consider factors such as the production environment, process flow and drug characteristics to formulate the best floor plan.

In summary, the process design of the CDMO sterile preparation workshop is a complex and important task. Through the establishment of a sound process design and quality control system, the safety and effectiveness of sterile preparations can be ensured, and people's health can be escorted. At the same time, we also need to constantly pay attention to the development of new technologies and methods to promote the progress and development of aseptic preparation production technology.

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