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Research Article

Production process and quality control in Caspian Tamin Pharmaceutical Company

Mohammad Torkashvand, Atefeh Hasanzadeh*

Fouman Faculty of Engineering, College of Engineering, University of Tehran, Tehran, Iran

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✉:A. Hasanzadeh
hasanzadeh.a@ut.ac.ir

ABSTRACT

Caspian Tamin Pharmaceutical Company strives to produce and process injectable and non-injectable pharmaceutical products, including ampoules, ointments, gel creams, suppositories, and oral solutions in the form of syrups. Have high sensitivity) is also done carefully. Therefore, the higher the experiences and knowledge of the relevant personnel and the accuracy of the device and its efficiency (producing more product and better quality, in less time, leads to a more favorable production result). All processes in this factory are following GMP and WHO rules. The goal of Caspian Tamin Pharmaceutical Company is to produce pharmaceutical products with a focus on injectable products to promote community health. On the other hand, Caspian Tamin Pharmaceutical Company aims to supply and provide a large number of low-volume injectable drugs. These and other details have been studied in detail in this paper.

Keywords: Process, Production, Control, Pharmaceutical Company

1. Introduction

Caspian Tamin Pharmaceutical Company was established in 1983 to produce pharmaceutical products focusing on injectable products. All processes in this factory are based on GMP principles. The products of this company were initially only different types of ampoules and during the past years, the company has tried to increase the number of products and their variety. In 2001, the production of semi-solid forms (creams, ointments, gels, and suppositories), oral solutions, and syrups was launched along with ampoules. The company currently offers more than 100 pharmaceutical products.

Caspian Supply Group drugs are:

1) Ampoule classification:

- Analgesics and anti-inflammatory drugs
- Anti-myasthenia gravis and muscle relaxants
- Hypnotic drugs, Samad Parkinson antidepressant, anticonvulsant, anti-anxiety and anti-psychosis
- Hormonal drugs
- Antihistamines and bronchodilators
- Cardiovascular drugs, electrolytes
- Corticosteroid drugs
- Local and general anesthetics
- Antibiotics
- Gastrointestinal drugs
- Dietary supplements and vitamins
- Athenagonal drugs

2) Classification of suppositories:

- Analgesics and anti-inflammatory drugs
- Gastrointestinal drugs

3) Classification of syrup and oral solution:

- Antihistamines and bronchodilators
- Dietary supplements and vitamins

4) Categories of creams, ointments, and gels:

- Analgesics and anti-inflammatory drugs
- Gastrointestinal drugs
- Dietary supplements and vitamins
- Dermatological drugs
- Antibiotics

Other products of the Company include vials and syringes ready for injection.

5) Classification of vials:

- Cardiovascular drugs, electrolytes

2. Experimental

2.1. Quality Assurance and Control Unit

The existing drug quality management system in Caspian Tacin Pharmaceutical Company is based on models proposed by reputable organizations such as The International Conference of Harmonization (ICH) in the form of ICH Q10 guidelines and Pharmaceutical Inspection operation scheme PIC / s. The company has also used other quality management systems such as ISO 9000 series (quality management system) and ISO 14000 series of the environmental management system and ISO 18000 occupational health and industrial safety management). The company has recently established ISO 17025 (laboratory quality

management) to strengthen its quality area in the field of quality control and calibration laboratories.

2.2. Production Unit

Caspian currently manufactures more than 100 pharmaceutical products in major therapeutic fields, such as cardiovascular, infectious, analgesic, gastrointestinal, general anesthesia, hormonal, sex hormones, bone balance, and vitamins. The main goal of Caspian Supply Pharmaceutical Company is to provide a wide range of low-volume injectable drugs. It is also developing activities to produce liquid and semi-solid medicines, including creams, ointments, gels, suppositories, as well as oral solutions and syrups.

2.3. Research and Development Unit (R&D)

The company's research unit is responsible for designing and developing new drug formulations as well as improving the quality of current products by using the most up-to-date pharmaceutical resources and advanced device facilities.

2.4. Activities of the research unit

- ✓ Studying simple initial and product analysis methods as well as designing analysis methods if needed
- ✓ Pre-formulation and formulation levels
- ✓ Providing the information needed to add new products to the drug list
- ✓ Compiling a comprehensive drug file and submitting it to receive a drug production license
- ✓ Product analysis and stability tests (at this stage, if necessary, the analysis method is validated.)
- ✓ Formulation of new products to strengthen the company's product portfolio

✓ Modifying the current product formulation of the company to improve the quality of products

The production of this factory is divided into two phases: phase 1, which is the place of manufacturing restorative drugs, and phase 2, which is the place of manufacturing non-injectable drugs (liquid and semi-solid). Given that the existence of safe water following international standards is required for the manufacture of injectable drugs, this issue causes pharmaceutical companies to pay more attention to the water industry and make their efforts to produce water with a degree of day by day. Higher purity, higher efficiency while operating at a lower cost.

2.5. Water supply

Water used in the pharmaceutical industry must have microbial and chemical properties to be approved by pharmaceutical standards and can be used in production processes. One of the most important indicators of medicinal water quality is the amount of microbial and biological agents. Therefore, choosing an effective disinfection method is one of the most basic principles in designing a pharmaceutical water treatment [1].

In pure water production systems, water can be stored at temperatures above 70 °C or less than 10 ° C; However, keeping water at room temperature can increase the likelihood of microbial contamination of water. Under these conditions, the use of disinfectants to control or reduce the microbial load of water is essential. Some cases, such as chlorine, nitrogen, and hydrogen peroxide, are most used due to their safety and lack of undesirable changes in water [2]. The effect of three disinfectants of chlorine, ozone, and hydrogen peroxide with a concentration of l ppm on the five microorganism's index Pseudomonas aeruginosa, staphylococcus aureus, candida Albicans. Aspergillus Niger and E.coli Microbial suspensions were exposed to disinfectants under the same conditions. Finally, ozone was selected and

identified as the best disinfectant by reducing more than Log 5 of bacterial agents and Log 1 of yeast. Then the reduction in the number of microorganisms shows the effectiveness of disinfectants [3].

WIFI (water for injection according to US Pharmacopoeia (USP) standards) is water used to make pharmaceuticals and injectable products that require endotoxin levels to be controlled. Sometimes this water is used to wash equipment or sets. In contact with injectable products, the minimum quality of injectable water sources for injectable drinking water is based on the definitions of US, European and Japanese pharmacopeias and with the necessary definitions by the World Health Organization (WHO) [4].

Undergoes the necessary pre-treatment, the water used in the Caspian Company's water is the well and the process or pre-treatment includes:

1. Chlorination to kill germs
2. Clarifier: using pack materials (complex) that absorb iron and manganese in water, then use a double-walled tank to settle the material after sticking to the complex and snook tank for storage
3. the Sand source (sand filter): composed of several layers of silica to absorb excess iron and manganese (silica has a higher absorption power than iron and manganese.
4. Carbon filter: removes organic matter, fats, hydrocarbons, and even chlorine. At this stage, the sample of water entering the carbon source turns yellow by adding a few drops of chlorine solution, which indicates the presence of chlorine in the water. To ensure the removal of chlorine in the carbonated effluent, a sample of the effluent is taken and a few drops of chlorine solution are added to it, which is usually not discolored in the water and is a sign of chlorine removal because otherwise, the carbon source does not work properly.

In the next step, it enters the reverse osmosis system (RO = reverse osmosis) or additional purification and disinfection systems such as ultrafiltration (UF), MIX BED RESIN and ozone system, ultraviolet (UV) light, diesel, and EDI to supply the water required by the pharmaceutical industry (WIFI) following USP standards, the effluent must have all the chemical properties of pure water plus the properties of bacterial endotoxins [5].

It should be noted that the deionized column, which is the main part of the RO device, is the first product of hydroponics, i.e. pure water p.w. It is used to make syrups, suppositories, wash ampoules, wash factory equipment and even prepare distilled water.

Pure water enters the distillation water machine, which is made of five distillation columns, using PIC control systems, and finally flows to the storage and storage tank of distilled water by opening the special valve for distilled water. In the distilled water storage tank, storage is done by circulating pump or using wind vapor between 86-96 C° .

Pure water is circulated by the pump 24 hours a day after passing through the UV device. The use of UV devices is for water stability, ultraviolet light causes sterilization of microbial particles and thus can prevent the growth and proliferation of pathogens.

Out of circuit P.W only in cases of disinfection. The whole water supply system operates according to the instructions of SOP and disinfection operations are performed according to the schedule. According to the predetermined schedule, daily, weekly and monthly, the sites specified in the hydropower unit are sampled and controlled by the microbiology unit, and also by the quality control unit, the chemical properties of pure and distilled water are controlled daily. Quality control laboratory approval, the manufacturing process continues to progress.

2.6. Good Manufacturing Practice (GMP)

GMP ensures that products are continuously manufactured and controlled following quality standards, appropriate for the intended use, and following the sales market license or product requirements. GMP is associated with both production and quality control and has requirement [6]. main objectives of GMP are:

1. Improve product quality.
2. Ensure product performance.
3. Reduce waste
4. Avoid potential production hazards

2.7. Types of pollution

1. Contaminants in the pharmaceutical industry can be divided into three types: particulate, microbial, and contact or cross-contamination [7]
2. Particulates: Pollution from airborne particles is called particulate pollution and its sources are dust, dirt, paper, and metal [8]
3. Microorganisms: Infection caused by microorganisms is called microbial infection and its sources are bacteria, yeasts, and fungi [9]
4. Cross Contamination: Cross-contamination occurs when a clean body comes in contact with a dirty body and the infection is transferred from a dirty body to a clean body [10].

2.8. Cleanroom

A cleanroom is a room where the concentration of airborne particles and microbial load is controlled and it is constructed and used in such a way that the production of airborne particles is minimized and affective factors such as temperature, humidity, pressure are in it.

Be controlled as needed)). The airflow directed into the clean rooms is filtered and filtered by a special device, and also the indoor air is constantly rotated and refined by air particles cleaning devices with HEPA or ULPA filters (HEPA). ULPA) are eliminated [11].

2.9. Cleanroom classification

Each stage of production, including weighing, sampling, manufacturing, filtering, filling, sealing, and final packaging, must be in separate spaces with different degrees of cleanliness and with a minimum number of employees. Therefore, it is not possible to perform several steps in a clean hall that has clean air. In sterile wards, according to Table 1, 4 types of cleanrooms are usually used.

Table 1 - Classification of cleanrooms

Room position	European classification	English classification
Sterile (Aseptic)	Class A	Class 100 without staff
Sterile (Aseptic)	Class B	Class 100 with staff
Clean Room	Class C	Class 10.00
Clean Room	Class D	Class 100,000

- These conditions may be without work (At Rest) or in working conditions (Operation)

- CNC are rooms that do not have a clean class but have filtered and controlled air (such as changing rooms and cartons).

Characteristics of cleanroom clothes

Clothing Material: Clothing should be of a material that does not release particles, can be cleaned and cleaned, has no electric charge and does not absorb microorganisms, is resistant to chemicals, and can be autoclaved for clean rooms with class A. Fabrics with a close and

compact texture have the advantage of effectively filtering out and controlling particles and particles with bacteria emitted from the individual [12].

Clothing model: one-size-fits-all clothing for men and women, without pockets and belts, adjustable (elastic) and with a zipper on the front of the clothing, which can be made of steel or non-metal, the sleeves are loose and have wrist and pull sleeves.

Shoe type: non-slip footrest with rubber sole and washable.

Hats and masks: The cap is made of clothing that completely covers the head and has a mask.

Requirements for clothing required for each grade of a cleanroom in terms of cleanliness include:

Grade D: Hair and beard should be covered. Protective clothing and appropriate footwear (slippers) or top should be worn.

Grade C: Hair and beard covered. A one-piece or two-piece dress, blouse, and pants that are pleated and closed at the wrists and have a long collar should be used with appropriate shoes or shoes. This type of clothing should not scatter any lint or particles.

Grade A /B: The hat should completely cover the hair, beard, and mustache. The hat should go all the way to the collar and neck. Use a face mask to prevent particles from falling from the face. Appropriate sterile plastic or rubber gloves that do not contain powder should also be worn on sterile or disinfected shoes. The bottom of the pants should go into the shoe and the sleeves should be tucked into the gloves. Protective clothing should not release any fibers with the particle and prevent the release of particles separated from the body.

Fig. 1- Proper cover of cleanroom

Items that are not allowed to enter a cleanroom

As a general rule, anything that is not needed in a cleanroom should not be cleaned like a room.

- Items that should not enter the cleanroom are:
- Food, beverages, sweets
- Foodstuffs in cans or bottles
- Tobacco
- Newspapers, magazines, books, and paper napkins
- Pencil and pencil eraser

How to disinfect construction rooms

Disinfectants have toxic effects because they are designed to kill germs and can have side effects on human cells. [13]. Some disinfectants cause asthma (eg, chlorine bleach/sodium hypochlorite, quaternary ammonium compounds). Some play a role in cancer (eg, orthophenylphenol). Some disinfectants have been found (e.g., bleach, chlorine, pine oil, and

thymol) or pose environmental hazards, such as silver and quaternary ammonium chloride compounds: alcohol, chlorine, and its compounds, formaldehyde, glutaraldehyde. , Hydrogen peroxide (hydrogen peroxide) Peracetic acid, Combination of peracetic acid and hydrogen peroxide of iodides, ortho-phthalaldehyde (OPA), Phenol, Quaternary ammonium compounds [14].

Phase 1: Injectable drugs

1. Observing proper coverage and personal hygiene
2. Cleaning the environment according to the instructions (sop)
3. Coordination with the department supervisor in doing the work
4. Technical control of equipment and coordination with technical agents.
5. Accuracy, obsession, and vigilance when doing work.
6. Full coordination with the control representative during production and performing defined tasks in its presence.
7. Thorough washing of tanks (manufacturing containers), holders, and hoses for filtration and filling, filtering, and autoclave (for sterilizing medical and laboratory instruments at high pressure and temperature and using water vapor) their process according to the instructions.
8. Drain the water of autoclaved tanks
9. Control the volume of dewatering and volume of the product based on the batch sheet
10. Transfer of raw materials from the weighing part to the structure.
11. Proper position of raw materials and their non-interference.

12. Receiving yellow card (under testing) and green card approval (agreement for use) for manufacturing and filtration and filling card approval from the control representative during production.
13. Product manufacturing and filtration under the supervision of the control agent during production.
14. Absolute presence of the operator during product filtration.
15. Check the tank after filtration for leakage of nitrogen gas solution.
16. Open the solution of the lines according to the coordination made by the filling supervisor with the union representative.
17. Intermittent inspection of tanks when filling and controlling nitrogen gas pressure on them.
18. Accurate recording of events and work performed for each product batch in the manufacturing reporter and the forms available in the unit and the daily logbook.
19. Weekly unit disinfection according to instructions
20. Inspect electricity, water, gas, and steam tanks containing the product before leaving the unit.
21. Cleaning the construction line after finishing the construction according to the instructions.

Weighing raw materials

Import of raw materials to the warehouse - »Specification by the warehouse representative -» Sampling of raw materials by the representative of the laboratory and attaching a yellow sheet (under testing) - » Microbial and chemical inspection.

If approved, the card approval (Approved for use) and otherwise the red confirmation sheet (Rejected) will be attached to the initial simple. (Raw materials are checked when entering the warehouse. The yellow leaf is examined. They remain in quarantine until the laboratory issues a card approval after examining the microbial and chemical samples. If allowed, the raw materials can be used. Therefore, all the materials used have yellow and card approvals, which is a sign that the laboratory has checked and approved them.

Packaging :After manufacturing and approval of the product by the laboratory, the product enters the packaging section, which in phase 1 (injection medicine manufacturing section), this section includes three stages: washing, filling, and coding**.**

Washing: After receiving the ampoule pumice from the warehouse, they are entered by the operator, the pumice is washed in 10 steps. These 10 stages are divided into two parts. 6 stages: The nozzles send the air into the puddles by pressing from the bottom up, and the 4 phases go into the water by the device at the bottom of the puddles. All the steps are done in one cycle. It is done in such a way that after placing the shells in the device, the nozzles send pure water into the shells by pressure, then the air goes into the shells by pressure to dry them, the next step is similar to the first step with The difference is that distilled water enters the puddles, the last step is spent drying the puddles with air. Finally, the puddles are completely sterilized in the washing machine by steam and grease**.**

Filling: It should be noted that the filling part of the ampoule is a closed area and completely sterile, and the special operator must use hats, gloves, full-length clothes, slippers, and all items that do not cause any manual intervention to prevent the product from being sterile. The filling machine has 8 nozzles, which means that 8 ampoules are produced each time. Before the pockets are filled with the injected solution, nitrogen gas is poured into the puddles, then the solution is injected into the puddles, and nitrogen gas is injected into them again to keep the solution stable. Eventually, the shell is closed by city gas and oxygen**.**

Coding: In this part, the ampoules are carefully examined by the relevant operator, these examinations are related to the appearance of the ampoule, its volume, the absence of particles in the ampoule, which if viewed, will be separate from other products and part of the waste**.**

After packaging, samples are sent to the laboratory for chemical and microbial analysis. Then, if the product is an autoclave, it should be transferred to an autoclave to be at a temperature of 121 ° C for 1 hour and 15 minutes, from which time 15 minutes will be spent sterilizing the ampoule. The products are then transferred to the quarantine section. After obtaining permission for packaging by the particle control device, they are approached. This device shines on the shells of the ampoule. If the node breaks after passing through the ampoule, it means that there is a particle in the ampoule, and the device separates the ampoule from the other ampoules**.**

After controlling the particle, the blister machine forms a PVC sheet and molds it so that the ampoules can be placed inside it. The ampoules are manually transferred to the Rondo machine and the machine automatically inserts them into their molds. The Linx machine prepares the labeling and the laser machine (video jet printer) records the product specifications on the boxes. The packaging is done either by hand or with the machine,

finally, after packaging the products, they have to be quarantined for a while until the sales license is issued by the quality control laboratory**.**

Phase 2: liquids and semi-solids

Semi-solid filling:

After receiving the batch sheet, it is done through the warehouse representative to the production manager of the product manufacturing process, the order of which has been announced. To make the product, a green sheet must be obtained from the person in charge of production, who represents the laboratory, during the production process (which includes all the manufacturing steps, including weighing, manufacturing, filling, and packaging). The production manager does the work related to this important**.**

After the necessary preparations in the warehouse, the raw materials are weighed according to the batch list under the supervision of the production representative and during production and are recorded in the relevant sheet. The production manager weighs the raw materials for the second time, which is called the re-weighing process. After re-weighing, the raw materials are transferred to the production department for production. The material is then made according to its sop (recipe) by the manufacturing operations**.**

In the filling section, the products are filled according to the instructions and with the relevant devices. During filling, the representative must send samples to the laboratory for necessary tests during production. In other words, some of each product is sent as a chemical sample, some as a microbial sample, and at the end of the work, some bulk samples are sent to the laboratory**.**

Filling fluids :First, the filling device must be rinsed with deionized water, the water sample must be delivered to the laboratory, and a water health permit must be obtained. After

obtaining the license, the first test the device with 6 to 12 bottles of syrup to adjust the timing of the device, but this number of glasses depends on the number of nozzles of the device, in which case the device is 6 nozzles. The purpose of this inspection is to ensure that all glass is filled with the relevant nozzles accurately**.**

During production, the representative is responsible for placing empty glasses with the number of nozzles in the filling machine every hour, so that after filling, he writes the weight of the filled glass and measures the consumption volume according to the desired syrup density**.** After filling, the products are quarantined in the warehouse to get the license from the laboratory for packaging. If a license is obtained, the products will be ready for packaging**.**

According to the batch sheet, the items used in the packaging are sent to the warehouse by the quality assurance representative. In the packaging section, the product specifications are recorded on the boxes and are prepared for packaging by hand or machine along with a brochure**.**

Quality Assurance Lab: Analyzes are performed according to USP instructions. In the laboratory, according to the SOP, they check the number of active ingredients in the product or anything important to the laboratory and the USP.

All steps are performed in the laboratory as in other parts of the Caspian plant according to the SOP. Also, to issue a green card approval, all available items must be filled in for microbial and chemical testing and registered in the available software. Finally, if all the steps are approved, a green card approval will be sent to the relevant department.

3. Discussion

The formulation of pharmaceutical forms has undergone extensive changes in the past decades due to the pre-compaction of fast machines and now super-machines with automatic weight control systems as well as the possibility of access to active pharmaceutical ingredients that have direct compressibility [15].

4. Conclusion

All processes in this factory are following GMP and WHO rules. The goal of Caspian Tamin Pharmaceutical Company is to produce pharmaceutical products with a focus on injectable products to promote community health. On the other hand, Caspian Tamin Pharmaceutical Company aims to supply and provide a large number of low-volume injectable drugs.

This company is one of the largest and most successful manufacturers of low-volume injectable drugs in Iran. Caspian Tamin Pharmaceutical Company is one of the most important pioneers of hospital drugs in the domestic market.

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