Targeted Preventive Maintenance of Pharmaceutical Equipment

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Abstract: To study effective management mode for preventive maintenance of equipment in pharmaceutical enterprises. Different pharmaceutical equipment has different importance in the producing process, so maintenance to each equipment should be different. A targeted maintenance requires to classify equipment and its components. To this aim, with help of assessment tools such as System Impact Assessment (SIA), Component Criticality Assessment (CCA) and decision-making grip, the specific targeted maintenance plan can be made and then implement it. Check the effect and feed back the problems. According to assess result of SIA & CCA, and decision-making grip, Pharmaceutical equipment can be classified into key equipment, important equipment and insignificant equipment. Components of equipment can be divided into two levels, critical and non-critical. For critical components of key equipment, comprehensive maintenance is needed. Maintenance of non-critical parts of key equipment and critical parts of important equipment should be paid great attention to. As for non-critical parts of important equipment and insignificant equipment, daily maintenance is enough. Such maintenance plan makes a distinction between the important equipment and the lesser ones. Through targeted management, preventive maintenance effect can be improved.

Keywords: Pharmaceutical Equipment, Preventive Maintenance, Decision-Making Grip, GMP

1. Introduction

Pharmaceutical equipment is the material basis of drug production. It is an key element influencing business efficiency and drug quality. A single "Breakdown Maintenance" mode cannot meet the drug quality requirements. [1] The revised version of "Good Manufacturing Practice"(GMP) in China has clearly proposed that equipment preventive maintenance plan and procedures must be formulated. United States’s cGMP also has some regulations about maintenance, such as "Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements". [2] Both two GMPs all emphasize the idea of "prevention first". Relatively weak equipment management consciousness, meanwhile, a large number of equipment in pharmaceutical enteredprised, especially API production enterprises with insufficient personnel and low professional competence have lead preventive maintenance to become a mere formality in many enterprises. [3] To this end, the author puts forward a new preventive maintenance mode. Based on PDCA cycle, with the help of assessment tools like System Impact Assessment (SIA), Component Criticality Assessment (CCA) and decision-making grip, the equipment and components can be classified to formulate a hierarchical management mode.

2. Theoretical Basis of Targeted Maintenance Management

One enterprise usually has dozens or even hundreds of devices, each of which plays a different role in the production process. Some of these equipments are frequently used, while others are used occasionally with less importance. They also operate in different ways, some with high reliability and others may with frequent breakdowns. At present, most
pharmaceutical companies do not carry out targeted equipment maintenance according to actual situation of each equipment, which results in insufficient maintenance or over-maintenance. Therefore, it is necessary to distinguish the equipment and carry out targeted maintenance.

2.1. Based on Equipment Importance

Generally, the larger the enterprise scale, the more equipment it has. Large and medium-sized enterprises usually have a large number of equipment. Different equipment plays a different role in the process of production, so the maintenance method should be different. When developing the maintenance strategy of each equipment, the importance of equipment should be classified first.

In addition to the production equipment, the pharmaceutical enterprise also involves utilities (such as HVAC) and auxiliary equipment (such as vacuum pump). Obviously, the importance of different equipment is different in the process of drug production. They can be divided into key equipment, important equipment and insignificant equipment through SIA. According to the general process of SIA (figure 1), when evaluating one equipment, answer No.1~No.7 questions in table 1. If there is one or more “Yes”, this equipment is seen as a key equipment. Otherwise, answer questions No.8~No.9, as long as there is one “yes”, the equipment is an important equipment. If all the questions in table 1 are answered “no”, a common equipment shall be defined. Table 2 is an example of equipment classification in API enterprises.

Figure 1. Flow chart of SIA.

2.2. Based on Statistical Results of Equipment Failure Information

| Table 1. Question list of SIA. |
|---|
| **No.** | **Questions** |
| 1 | Whether the equipment is directly exposed to the product |
| 2 | Whether the equipment provides auxiliary materials, Whether it is used for producing (or direct contact) some components, raw materials or solvents that are in contact with the process |
| 3 | Whether the equipment is used for cleaning or sterilization |
| 4 | Whether the equipment is used to protect the product character, such as product safety, concentration, quality, etc. |
| 5 | Whether the equipment generates data for receiving or rejecting the product and whether it is used to evaluate the disposition of the product |
| 6 | Whether the equipment affects the process control system linked to product safety, characteristic and concentration. |
| 7 | Whether the equipment is used for controlling, monitoring and alarming important environmental conditions. |
| 8 | Whether the equipment provides utilities or some function for a critical equipment. |
| 9 | Whether the equipment affects the performance of a key equipment. |

Table 2. Equipment classifications in API enterprises.

| System description | SIA assessment results | Equipment classification |
|---|---|---|
| Reactor | YNNYNYN | Key equipment |
| Centrifuge | YNNNYYN | Key equipment |
| Vacuum dryer | YNNNNY | Key equipment |
| Pulverizer | YNNNNY | Key equipment |
| Vacuum pump | NNNNNNYY | Important equipment |
| Nitrogen production equipment | NYNNNN | Key equipment |
| Cooling water system | NNNNNNNY | Important equipment |
| HVAC system | NYYNNNY | Key equipment |
| Purified water system | NYYNNNN | Key equipment |
| Elevator system | NNNNNNNN | Insignificant equipment |
| Fire fighting equipment | NNNNNNNN | Insignificant equipment |

Note: Some equipment has different uses in different enterprises such as nitrogen generating equipment, so the evaluation may vary in this way. This table is just for reference.

According to historical operation data of each equipment,
some equipment with the same characteristics can be picked out by some specific ways. Then targeted maintenance can be implemented to these devices with the same traits. The decision-making grid is one of the tools that can be used to distinguish different sets of devices. It takes the decision variable failure frequency as ordinate axis and failure time as abscissa axis, and then quantify them based on the statistic failure data. Choose a certain quantized interval to rank the two decision variables and then form the grid (figure 2). [6] In this grid, each squares represents a collection of devices with the same characteristics. Different equipment will fall into a grid area after decision. Equipment in the same area can be seen as the same kind.

The following method can be used in decision variable quantification: for each device, extracted the data related to decision variables from historical database. Accumulate the failure time of each device. Respectively sort the equipment failure frequency and the cumulative failure time in descending order. After sorted, accumulate the parameter values from big to small until the cumulative value is more than 80% of the sum of all parameter values. [7] Record the devices and their corresponding parameter value. For example, based on the failure data in table 3, a decision-making grid (figure 3) can be established using the method described above. The 3 levels of failure time can be set as "low"-(0, 20), "middle"-(20, 40), "high"-(40, 60) and 3 levels of failure frequency can be set as "low"-(0, 10), "middle"-(10, 20), "high"-(20, 30). As showed in figure 3, the equipment closer to the lower right corner have a worse reliability, and those closer to the top left corner has a better reliability. As a result, those equipment at the bottom right corner can be seen key or important device which need to be paid more attention in the maintenance.

3. Targeted Maintenance Plan

The equipment maintenance plan at least includes the maintenance object, maintenance method, maintenance cycle and other aspects. Maintenance methods include daily maintenance, spot check, cycled recondition and irregular improvement, etc. Daily maintenance is mainly carried out by the operator, including cleaning and lubrication before or after equipment operation; Spot check is a triple check mechanism formed by operators, administrators and maintainers. [1] Through fixed-point inspections, clearly know equipment technical status and find hidden danger timely. The analysis of periodic data is the basis of cycled recondition; The cycled recondition can be divided into minor repairs and overhaul, which is operated by professional maintainers aimed for renewing equipment state and eliminating the hidden trouble; Irregular partial improvement can be understood as performance improvements. maintenance personnel, and management personnel usually participate in it.
The maintenance cycle is mainly focused on cycled recondition, and many scholars have studied it. The maintenance period of traditional cycled recondition is always the same, which tends to increase maintenance costs and equipment performance destory. [9] According to the equipment failure rule (early failure period, accidental failure period and wearing malfunction period)[10], the maintenance period of equipment should be adjusted in real time according to the working age. Enterprises should determine the best minor repair or overhaul cycle of each device under lowest cost or maximum availability principle[11], according to the specific situation of equipment. Generally, the maintenance period of key equipment should be shorter than that of non-critical parts. "Condition-based maintenance" will be the future development tendency. [9]

| No. | Questions                                                                 |
|-----|---------------------------------------------------------------------------|
| 1   | Whether the component is used to control a key process parameter.         |
| 2   | Whether the normal operation or control, failure or alarm of the component has a direct impact on the quality of the product. |
| 3   | Whether the information generated by the component is recorded as part of the batch record, batch release data, or other GMP related files. |
| 4   | Whether the component is in direct contact with the product, product ingredient or internal packaging material of the product |
| 5   | Whether the component is used to control the key process parameters affecting product quality |
| 6   | Whether the component is used to create or maintain a system critical state |

Table 4. Question list of CCA.

Table 5. Component classification of purified water system.

| Components             | Description                                      | Assessment results | Criticality |
|------------------------|--------------------------------------------------|--------------------|-------------|
| Raw water tank         | Store raw water                                 | NNNNNN             | N           |
| Liquid level sensor    | Monitor the liquid level in the raw water tank   | NNNNNN             | N           |
| Multi-media filter     | Remove solid particles from raw water           | NNNNNN             | N           |
| Raw water pump         | Water supply                                    | NNNNNN             | N           |
| Pressure gauge         | Monitor multi-media filter inlet pressure       | NNNNNN             | N           |
| Activated carbon filter| Remove residual chlorine and organic matter from raw water | NNNNNN             | N           |
| Pressure gauge         | Monitor activated carbon filter inlet pressure  | NNNNNN             | N           |
| Softener               | Water softening                                 | NNNNNN             | N           |
| Flowmeter              | Monitor the saltwater flow of softener          | NNNNNN             | N           |
| Pressure gauge         | Monitor the inlet pressure of softener          | NNNNNN             | N           |
| Security filter        | Water inlet filtration of RO unit              | NNNNNN             | N           |
| RO membrane            | Remove ions from water                          | NYNNYN             | Y           |
| Pressure gauge         | Show operation pressure of RO unit.             | NYNNYN             | Y           |
| Heat exchanger         | Used for disinfection for RO and EDI units      | NYNNYN             | Y           |
| High pressure pump     | Blower pump for RO and EDI units                | NYNNYN             | Y           |
| pH probe               | Control the pH of inlet in RO unit              | NYNNYN             | Y           |
| Conductivity sensor    | Monitor the conductivity of RO outflow          | NYNNYN             | Y           |
| Flowmeter              | Monitor the water flow in RO unit               | NYNNYN             | Y           |
| Pressure gauge         | Monitor the operation pressure of EDI unit      | NYNNYN             | Y           |
| Conductivity sensor    | Monitor the conductivity of EDI outflow         | NYNNYN             | Y           |
| Flowmeter              | Monitor the water flow in RO unit               | NYNNYN             | Y           |
| Cleaning tank          | Store cleaning water                            | NNNNNN             | N           |
| Cleaning pump          | Cleaning water cycle                            | NNNNNN             | N           |
| Pressure gauge         | Monitor pressure of cleaning                    | NNNNNN             | N           |
| PLC control system     | Control unit of water producing                | NYYNNY             | Y           |
| Purified water tank    | Store purified water                            | NYNNYN             | Y           |
| Sanitary pump          | Transport purified water                        | NYNNYN             | Y           |
| Ultraviolet sterilizer | Purified water sterilization                    | NYNNYN             | Y           |
| Distribution pipes and valves | Connect and control the outflow                  | NYNNYN             | Y           |

Table 6. Preventive maintenance plan of purified water system.

| Equipment             | Class | Component       | Criticality    | Maintenance plan |
|-----------------------|-------|-----------------|---------------|------------------|
|                       |       |                 |               | Daily maintenance | Spot check | Cycled recondition | Irregular improvement |
| Purified water system |       |                 |               |                  |            |                  |
|                       |       |                 |               |                  | Non-critical |                  |                  |
| Raw water tank        |       |                 |               |                  |            |                  |                  |
| Liquid level sensor   |       |                 |               |                  |            |                  |                  |
| Multi-media filter    |       |                 |               |                  |            |                  |                  |
| Raw water pump        |       |                 |               |                  |            |                  |                  |
| Pressure gauge        |       |                 |               |                  |            |                  |                  |
| RO membrane           |       |                 |               |                  |            |                  |                  |
| Pressure gauge        |       |                 |               |                  |            |                  |                  |
| Heat exchanger        |       |                 |               |                  |            |                  |                  |
| pH probe              |       |                 |               |                  |            |                  |                  |
| Conductivity sensor   |       |                 |               |                  |            |                  |                  |
| Flowmeter             |       |                 |               |                  |            |                  |                  |
| Cleaning tank         |       |                 |               |                  |            |                  |                  |
| Cleaning pump         |       |                 |               |                  |            |                  |                  |
| Pressure gauge        |       |                 |               |                  |            |                  |                  |
| PLC control system    |       |                 |               |                  |            |                  |                  |
| Purified water tank   |       |                 |               |                  |            |                  |                  |
| Sanitary pump         |       |                 |               |                  |            |                  |                  |
| Ultraviolet sterilizer|       |                 |               |                  |            |                  |                  |
| Distribution pipes and valves |       |                 |               |                  |            |                  |                  |
### Equipment 
| Class | Component | Criticality | Daily maintenance | Spot check | Cycled recondition | Irregular improvement |
|-------|-----------|-------------|-------------------|------------|--------------------|-----------------------|
| Flowmeter | √ | √ | √ | √ |
| PLC control system | √ | √ | √ | √ |

Note: “√” means that the maintenance mode in the corresponding column is needed, while “×” means not needed. The maintenance circle is not declared in this table because each enterprise should set up their own reasonable circle according to equipment condition and enterprise capability.

According to evaluation results of equipment and component, combined with different methods and maintenance cycle, equipments actually need different levels of maintenance. As showed in figure 4, the key components of key equipment is the emphasis, which need a comprehensive maintenance. Those key components of important equipment should also be focused on. Table 6 is a specific preventive maintenance plan based on the assessment results of purified water system.

![Figure 4. Chart of targeted preventive maintenance of pharmaceutical equipment.](image)

### 4. Implementation, Check and Action of Preventive Maintenance Plan

A reasonable plan is the premise to achieve the goal, and effective implementation is the realization step of the expected goal. According to the maintenance plan, the equipment department of pharmaceutical enterprises should develop the specific maintenance operating procedures for each equipment. Personnel is the principal part of the maintenance performing. Learning from idea of “Total Productive Maintenance (TPM)” [12], mobilize full participation to cultivate the consciousness of equipment management personnel, maintainer and equipment operator in equipment improvement and problem finding.

Checking phase is a connecting link between the preceding and the following. It is the feedback of the implementation effect. Enterprise can collect and analyze the equipment failure data every a month or a quarter and then timely give these information to equipment department and quality department to find maintenance effectiveness as well as the deviation in the execution. From this process, the successful experience or existing deficiencies will be found. The action period is the response to check results. It is a process of summarizing the analysis. At this stage, the enterprise should formulate written management system and operation procedures for equipment maintenance according to the quarterly or annually inspection results. For those failure to solve, Enterprise can put forward the improvement measures on this basis and then proceed to the next PDCA cycle until the problem is solved.

### 5. Conclusion

Equipment maintenance is a must work in pharmaceutical enterprises, and preventive maintenance management must rely on scientific methods. According to the characteristics of the pharmaceutical equipment and failure data, the pharmaceutical equipment are classified into different levels with different importance, so that a well-directed equipment maintenance system can be formed. Flexibly using it can effectively improve the efficiency and quality of equipment maintenance.

However, the application of the assessment tools such as SIA & CCA and the maintenance level is not always fixed. The enterprise should make the best maintenance plan related
to specific issues. Meanwhile, the results assessed by SIA and CCA tools can always affected by subjectivity, more attention should be paid to avoid.

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