Design of the Quality System for Pharmaceutical Commissioned Production under MAH System

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Abstract

Objective To ensure the quality and safety of drugs in the whole cycle of pharmaceutical commissioned production under the drug marketing authorization holder (MAH) system, and to establish a perfect quality management system for it. **Methods** Literature review was used to study the factors that influenced the quality management system of pharmaceutical commissioned production because the implementation of MAH system in China was late, and the experience accumulated by pharmaceutical industry was not enough. **Results and Conclusion** Based on the MAH system, it is of great significance to establish the quality management system for pharmaceutical commissioned production.

Keywords: MAH; marketing authorization holder; quality management system

1 Overview

The drug marketing authorization holder (MAH) system came into effect in China late, which brought an opportunity for the development of pharmaceutical commissioned production [1]. This system has shown great advantages in research and development and production capacity, which has good prospects after being popularized throughout the country. However, the quality system of pharmaceutical commissioned production is not perfect under MAH system, which include drug research and development, technology transfer and production services. Therefore, we should establish a good, effective and more comprehensive quality management of drug production by designing the quality management system of contract manufacturing for drugs under MAH system.

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2 Resume of MAH main responsibilities

The drug marketing authorization holder (MAH) usually refers to drug research and development institutions or company with technology and credentials which hold a drug approval license. Meanwhile, MAHs shall also be liable for the quality during the life-cycle of the drug [2].

2.1 Establish and improve a sound quality assurance system

A system of drug quality assurance shall be established and improved. The holder and the authorized party should conduct work on research, manufacturing and management and sign a series of agreements including entrustment agreement and

quality agreement. Between quality management system of the MAHs and the authorized party, the connection should be effective and both sides should establish a quality assurance management system that can cover the whole life cycle of a drug from research to production to withdrawal from the market. Besides, the whole process shall comply with the drug management regulations, drug manufacturing, management and a series of regulatory requirements.

2.2 Assess authorized manufacturing capabilities

Inspection should be conducted on the authorized enterprises, mainly focusing on the workshop, test conditions, manufacturing technology and facilities and production quality management level. In addition, the authorized enterprise needs to meet the requirements of drug quality management and compliant with GMP.

2.3 Supervision of the contract manufacturing of drugs

Supervision and guidance should be provided for drug by the commissioned enterprise, and the corresponding measures (such as selecting personnel with experience in drug production and quality management to conduct spot supervision of the quality management of the commissioned production enterprise) should be taken as well. Supervise The commissioned production enterprises should be supervised to ensure that the prescription and process of drugs comply with national standards and standards made by relevant regulatory authorities. Besides, the production of drugs is completed under such standards. Lastly, the drugs must meet the expected use and registration requirements.

2.4 Carry out medicinal products to be listed on the market by law

We should formulate the rules and procedures for medicinal products to be listed on the market.

2.5 Conduct comprehensive and systematic quality review of relevant parties

We should regularly review the quality management system of the entrusted enterprise to guarantee that the facilities, workshop environment, production equipment, cleaning methods, and manufacturing process always meet the standards.

2.6 Establish drug traceability systems

We should establish drug traceability systems and provide traceability information according to regulatory requirements that can guarantee that every production step and information of drugs will be traced back.

2.7 Annual report

An annual report system should be established to report the information to the drug administrative department(s) about the drug production and the distribution, the post-marketing studies, and the risk management in accordance with the regulations before April 30th.

2.8 Continuously carry out post drug marketing management

MAH shall formulate drug post-marketing risk management plans to collect and analyze the information of the listed drugs to confirm the safety, efficacy and controllability of the drugs throughout their entire lifecycle, which will strengthen continuous management of drugs [3].

3 Problems in the quality system for pharmaceutical commissioned production under the MAH system

3.1 Failure to establish an effective quality communication mechanism

Most pharmaceutical commissioned enterprises

will undertake the entrusted business of multiple MAHs at the same time, and each MAH enterprise has different specific quality requirements. Currently, most pharmaceutical commissioned enterprises have not established a complete quality information transmission mechanism, and cannot translate the agreement into the content of the enterprise's quality management process within the enterprise. When the commissioned enterprise encounters abnormal situations that affect the quality of drugs during the manufacturing process, it may not be able to inform MAH for risk assessment promptly, which may result in potential quality problems not being identified and prevented earlier. Therefore, it is necessary to establish an effective quality communication mechanism with MAH.

3.2 Failure to establish a sound transfer system of technology in pharmaceutical manufacturing

The transfer of pharmaceutical technology is the reproduction of known knowledge and experience at the research and manufacturing stages, with the aim of facilitating the transfer of pharmaceutical processes between different manufacturing departments and sites, and achieving seamless integration of drug manufacturing. Currently, some multinational pharmaceutical companies have explored technology transfer models and project management systems that meet statutory requirements. However, some domestic pharmaceutical enterprises have incomplete systems for pharmaceutical technology transfer.

3.3 Failure to establish a sound management system for drug manufacturing quality

Most traditional pharmaceutical enterprises establish their quality systems based on GMP requirements [4], but GMP's provisions focus on commercial manufacturing process and involve less quality requirements on drug research and development. Under the MAH system, some MAHs are research and development institutions that do not carry out drug process validation, commercial manufacturing, and post marketing risks, resulting in an imperfect MAH manufacturing quality system. The characteristics of research and development activities connected to commercial manufacturing models have not been contemplated, which affects the normal progress of pharmaceutical activities throughout the entire process.

4 Quality system construction

The MAH system was established officially in China with the revision of the "Drug Administration Law" in 2019. Accordingly, the MAHs need to guarantee the safety of the entire pharmaceutical life-cycle from manufacturing to delisting by law. In addition, the establishment of a quality system should still comply with GMP to minimize adverse effects in drug manufacturing, including contamination, confusion, and errors. It is also necessary to make a plan to develop a set of CCS related controlling measures for microorganisms such as infections under the premise of ensuring drug performance and quality, which can guarantee the safety, effectiveness, and reliability of drugs [4].

The construction of the quality system based on the MAH system includes several aspects such as human resources, facilities, materials, methods, and environment.

4.1 Human resources

4.1.1 Personnel allocation and requirements

Enterprises should employ a certain number of staff who must possess corresponding skills, education, certificates, work experience, and training. The responsibilities of each department need to be clearly defined. Personnel related to drug manufacturing quality should be trained, and operation procedures should be established for staff.

Enterprises need to guarantee the health condition of their employees. Personnel related to

drug manufacturing quality should undergo at least one physical examination per year. Besides, employee health records should be established. Rules and regulations should be set up for staff. For example, employees with infectious diseases or exposed wounds on their bodies should not contact with the drugs directly.

4.1.2 Training

Pharmaceutical enterprises shall establish training systems and appoint department heads or specialized personnel to take charge of the training work. The responsible person needs to specify training plans and protocols, and experienced manufacturing quality management personnel have to review the training plans and keep training records. Before taking over the work, personnel involved in drug manufacturing and quality control should be trained to meet the job requirements. During training, trainees are required to sign on the training record, and those who have not arrived should specify the reason for their absence. After the training, the trainees need to be assessed.

4.2 Facilities

4.2.1 Facilities and equipment

The factory environment and equipment should meet the requirements of the national drug standards, and the formulated production technology and registered drug specifications need to be reviewed and approved by the drug regulatory department. The commissioned enterprise has to consider factors such as the characteristics, processes, and conditions of the entrusted drug production. Then, it can determine whether the enterprise's premises, facilities and equipment can be shared if multiple products. Finally it should conduct a feasibility analysis report. The facilities, equipment, and test instruments of the enterprise should be confirmed, and the approved processes, operating SOPs, and test methods should be validated. Regular confirmation is required. The commissioned enterprise needs to make a plan for drug manufacturing, and confirmation and validation of the production should be carried out according to the predetermined plan and recorded.

4.2.2 Validation of facilities and air conditioning systems

Pharmaceutical enterprises should reasonably design the space, including logistics and pedestrian flow design, and select appropriate decoration materials. Then, they can determine user requirement specifications (URS) based on Good Manufacturing Practice (GMP) and HVAC system, and confirm environmental parameters that affect product quality. Installation qualification includes ensuring that the equipment and required systems are operated according to the design drawings, installation drawings, and relevant quality requirements. Besides, it must confirm that the installed equipment complies with regulations and has been reviewed and approved. Operational qualification includes all systems such as HVAC system and purification system, should be verified after installation. After starting the air conditioning system, pharmaceutical enterprises must confirm that each unit operates in accordance with the design requirements and the performance requirements of the instrument. Performance qualification includes confirming the performance of the clean room meet the requirements of GMP for the environment after starting the air conditioning purification system. Besides, pharmaceutical enterprises should make detailed environmental monitoring methods and determine the key parameters and acceptance limits.

Lastly, pharmaceutical enterprises must list the partition diagram of the air conditioning processing unit and the layout of the system's air supply, return, and exhaust (completion drawings).

4.3 Materials

4.3.1 Management of suppliers

The quality management department of the

enterprise should conduct qualification and compliance audits, quality assessments, and on-site audits of material suppliers. Material management uses level management to conduct risk assessment based on the impact of materials on product quality. The material levels can be divided into primary and non-primary.

The quality management department shall establish a list for qualified material suppliers after evaluation, including material names, specifications, material codes, quality standards, etc. The supplier list is sent to the material management department of the enterprise, and the material information should be updated in real time. Regular re-evaluation includes the yearly re-qualification evaluation. The on-site audit cycle needs to be determined according to the situation.

4.3.2 Management of materials

Material acceptance confirmation includes ensuring that all procedures for material procurement are complete, such as quality specifications and procurement contracts. Besides, it should simultaneously confirm whether the supplier is qualified [5]. Material stock-in refers to the storage procedures are processed after the materials arrive and pass the acceptance examinations. The materials are sent to the waiting area of the warehouse for further inspection. If the materials are not qualified, they need to be sent to the unqualified area of the warehouse. QA conducts audits and quality evaluations of materials as required, and the qualified person should make a conclusion on whether they can be released. Approved materials shall be stored in the qualified area and marked accordingly.

The principle of material release between the commissioning and the authorized party means that the holder and the authorized party should clarify the responsible parties for the procurement, acceptance, inspection, and other aspects of drug manufacturing materials, and have to make an agreement. The responsible party in the agreement needs to ensure that all manufacturing materials meet quality standards, and all materials must be inspected and qualified before they can be used for production. If the quality standards change during the manufacturing process, the authorized party and the commissioning party need to make corresponding changes to the content of the quality agreement. After completing the material inspection, one party needs to make copies of the inspection report and material release form and give them to the other party. The other party needs to conduct a re-inspection of the materials to ensure their quality.

4.4 Method

4.4.1 Management of recall

Enterprises should establish a system to determine the reliability of recall. A dedicated department should be established for recall work. With a dedicated person in charge, the recall department should be an independent entity. The recall should be able to be initiated at any time and implemented quickly. Drugs that need to be recalled due to the safety hazards shall be reported to the Drug Administration within the given time. The person in charge of product recall needs to have a grasp of the shipment and delivery of drugs, and be able to check the shipment records of drugs in the first time. The entire process of recall needs to be recorded and a report needs to be generated. The report includes the shipment quantity and recall quantity, all of which need to be explained. Regular system evaluations of the recall system should be conducted. The holder shall establish requirements for the recall of the entrusted party's products.

4.4.2 On site supervision and management

As to the job responsibilities related to commissioned production, new product technology transfer, and mass commercial production, cross functional relationships and job vacancies between organizational structures may lead to buck passing [6]. Establishing a communication mechanism can make various decisions of the enterprise to be implemented

effectively [7].

All responsible persons, quality authorized personnel, and key position operators should effectively fulfill their job responsibilities. They must be familiar with the legal and regulatory requirements necessary for production and quality management in this enterprise, and apply them proficiently. Besides, they should be familiar with the responsibilities of this position and the necessary documents, systems, such as the cleaning operation of key equipment in the clean area. The division of labor of the quality authorized person is clear and there is no overlap in job responsibilities. The temporary transfer of authorization has been approved by the legal representative or person in charge of the enterprise, which has been specified in writing.

The development and implementation of documents should meet the requirements. The design of batch production record should comply with regulations and the production data must have traceability.

The operation is in accordance with the process requirements. The quality between batches of drugs is stable. The manufacturing equipment and inspection instruments have been validated or confirmed in accordance with GMP, and continuously maintained in validate. The inspection method has been validated by methodology and the validation process meets the requirements. The inspectors should have the corresponding capabilities to ensure the reliability and accuracy of the data, and the audit trail must meet the requirements. The defects identified during the quality review and self-inspection of enterprise products should be continuously rectified. The risk control measures for recalling and destroying drugs are continuously implemented. If there is a significant change, the holder shall conduct sampling inspections on at least three consecutive batches of finished products after the change is approved. The relevant requirements should be specified in the quality agreement.

The bad credit records should be paid attention to, such as two batches of products that fail the random inspection in the past year, the supervisory conclusions that do not meet the requirements of GMP within the past three years, and serious violations of drug regulatory laws or dishonest records of key personnel in the past five years. On-site assessments, technical level and quality management of the entrusted party should be conducted.

4.4.3 CCS control principles

The sources of pollution risks include residues, confusion, machine transfer and airborne.

The responsible parties for pollution risk management include MAHs and the pharmaceutical production enterprise. When adding new products in shared facilities, commissioners and the commissioned pharmaceutical production enterprise should update the collinearity strategies of the product in the first time. Besides, they should make emergency planning management for possible new and cross contamination. Holders and commissioned production enterprises should closely monitor technological progress and updated regulatory requirements, review and evaluate collinearity strategies, identify new risk points in time, develop appropriate risk control measures, reduce collinearity risks, and keep pollution and cross pollution under control.

Pollution control is the core of GMP management. GMP aims to minimize a series of risks such as errors and confusion in the manufacturing process of drugs. EMA has made new revisions, which include the concept of pollution control strategies and require pharmaceutical enterprises to provide pollution control strategy documents. The PIC/S GMP Appendix 2, which came into effect in 2022, explicitly requests a written pollution control strategy.

Three characteristics of pollution control strategies are forward-looking, systematic, and dynamic.

Four components of pollution control strategy are the foundation of CCS, scientific knowledge, quality risk management, and quality culture.

Pollution control measures include personnel training, sanitation and clothes changing, process design, equipment design for cleaning and hygiene,

facility and shared system design, and management of suppliers, materials, consumables, and containers. Verification and monitoring of measures include continuous personnel qualification confirmation, process confirmation and lifecycle management, verification and confirmation of analytical methods, confirmation and reconfirmation of facilities and equipment, verification and continuous confirmation of shared systems, personnel management, material management, process control, shared systems, pest control, and environmental control. Management and communication include trend management, survey process, continuous improvement, communication evaluation, protocol management, change control, risk management, quality control, and comprehensive coordination.

4.5 Environments

Co-production of drugs refers to the production of multiple drugs on a shared production line, including shared premises, facilities, and equipment, but excluding shared quality control laboratories, warehouses, sampling rooms, and other auxiliary facilities and instruments.

If there are no clear provisions in laws, regulations, rules, and national standards, the MAHs and the drug manufacturing enterprise need to comprehensively consider factors such as the property process of the drug, characteristics, uses, and production equipment. At the same time, the feasibility of co-production of multiple products should be evaluated to form a risk report. The holder is primarily responsible for the feasibility and controllability of co-production, and shall provide the commissioned pharmaceutical production enterprise with pharmacological and toxicological information or health-based exposure limits, review and approve the co-production risk assessment report, and regularly inspect the risk control strategy of co-production.

The lifecycle of drug co-production strategy covers four stages such as drug research and development, technology transfer, drug manufacturing, and marketing.

The cleaning validation lifecycle consists of three stages such as cleaning process design and development, cleaning process validation, and continuous cleaning process confirmation. During the drug production stage, consideration should be given to whether contamination may occur between co-production, and corresponding control measures should be developed for possible contamination. And it is necessary to regularly inspect the collinearity and verify the formulated response measures to avoid pollution.

5 Case analysis

5.1 Basic information of YL company's quality management system

YL company was established in 2008 and officially started operation in 2011. It mainly engaged in MAH, drug manufacturing and research and development. The company has multiple dosage forms such as active pharmaceutical ingredients, injections and tablets, which has strong research and development capabilities and complete infrastructure equipment. After years of development, the company has established a good reputation in the industry and its products cover multiple provinces and cities in China.

5.2 Analysis of quality management system operation issues in YL company

The original quality system of YL company was mainly based on GMP (Good Manufacturing Practice) standards, including basic quality management and operational processes. However, with the gradual implementation of the MAH (Marketing Authorization Holder) system, companies have realized that the existing quality system cannot meet the regulatory requirements and market demands under the new situation.

The main characteristics of the original quality system include quality control centered on the production process, but it does not have systematic

communication mechanisms for the entrusting and entrusted parties. This model leads to information asymmetry between the entrusting and entrusted parties, making it difficult to detect and resolve potential quality issues in time.

The original system did not have a delegated product release system. After the production of the drugs, the delegated and entrusted should have a systematic release process. Otherwise, it may lead to unclear responsibilities and the product flowing into the market can have some risks.

In summary, when facing new requirements under the MAH system, pharmaceutical enterprises urgently need to improve their existing quality system to guarantee stable product quality and enhance their competitiveness and reputation in the industry.

6 Improvement effect of YL company's quality management system

6.1 Establishment and implementation of product release system

The basic framework of the product release system should cover multiple key elements to guarantee the safety and effectiveness of drugs during the commissioned production process.

6.1.1 Key control points for commissioned product release

Material inspection can ensure that all materials is strictly inspected before use and meet release requirements.

Production process monitoring means to carry out real time monitoring of key links in the manufacturing process to ensure compliance and stability of manufacturing processes and conditions.

Finished product inspection refers to the finished product must be strictly inspected to confirm that it meets the predetermined quality standards.

Finished product release means the finished products must be released by the entrusting party before entering the market for sale.

6.1.2 Recording and traceability mechanism

Detailed records must be established for each product release, including inspection results, release signatures, audit opinions, etc. These records will provide a basis for future quality traceability and auditing, ensuring that all released products are traceable.

6.1.3 Training and responsibilities

For the implementation of the release system, it is necessary to provide systematic training to relevant personnel to fully understand the importance of the system. At the same time, it is vital to clarify the responsibilities of each position and ensure that all employees can fulfill their duties during the release process.

By establishing the above basic framework, the product release system will effectively enhance the quality control of pharmaceutical commissioned production, ensuring the compliance and safety of drugs in the market.

6.2 Specific operation guideline for entrusted product release

Product commercial release refers to the authorized release by the principal.

6.2.1 Trustee's requirements

After the entrusted party completes the factory release, copies or originals of the batch production records and batch inspection records shall be submitted to the holder for final review.

6.2.2 Principal release review

Holders should review the release procedures developed by the entrusted production enterprise, clarify the market release standards for drugs, review the inspection results and documents of drugs. Besides, they should check whether the inspection

results comply with national drug standard based on the copies or originals of batch production and inspection records, release certificates, and on-site monitoring QA feedback on the production situation and deviation records of products., Meanwhile, they have to verify the drug production process complies with GMP, the production process and raw materials, excipients and packaging materials comply with legal requirements, and confirm that their quality meets the requirements.

6.2.3 Market release

The quality authorized person of the entrusting party shall make a decision on whether to release the product for market based on the audit results. The product can only be released for market after being signed by the quality authorized person who is ultimately responsible for the release of the product. He should provide a product release certificate stamped with the official seal of the quality department, and transmit it to the entrusted party by photo, email, or other means.

6.2.4 Product transportation

Based on the holder's listing release certificate, the trustee shall transport the products to the designated location in accordance with the quality requirements or the trustee's warehouse. The entire process must ensure the storage condition of drugs and traceability of data.

Through the above steps, the release process of drugs is ensured to be scientific and rigorous, which can effectively guarantee the quality and safety of drugs. At the same time, companies should regularly review and optimize this process to adapt to constantly changing market and regulatory requirements.

6.3 Establishment of communication mechanism

The communication mechanism plays a crucial role in the quality system of pharmaceutical commissioned production. The communication mechanism needs to clarify the following key objectives.

It can ensure real-time transmission of information between the entrusting party and the entrusted party and reduce delays and distortions during the information transmission process.

A two-way feedback mechanism is established to enable all parties to provide timely feedback and propose improvement suggestions.

It can improve the efficiency of team collaboration and promote communication and cooperation between the entrusting party and the entrusted party.

By setting these goals, communication mechanism can effectively support the quality system of pharmaceutical commissioned production and promote the smooth progress of the overall process.

6.4 Implementation of internal communication channels

6.4.1 Significance of communication

The communication strategy of the entrusting party and the entrusted party should focus on efficiency, transparency and collaboration, ensuring timely sharing of information and efficient execution of decisions among all parties in the process of pharmaceutical commissioned production. Firstly, establishing a regular communication mechanism is crucial. Monthly or quarterly communication meetings should be held and the entrusting party and the entrusted party can be invited to participate in the discussion of manufacturing progress, quality issues and market feedback. This regular interaction can not only solve problems in time, but also enhance trust and cooperation among all parties.

6.4.2 Communication platform

Modern information technology tools should be utilized to enhance communication efficiency. A dedicated online platform can be established for all parties to share documents, data, and real-

time information. Through this method, the entrusting party and the entrusted party can view the production status, quality inspection results, and other relevant information at any time, reducing the lag in information transmission. In addition, instant messaging tools can be used to establish a rapid response mechanism in case of unexpected issues.

6.4.3 Clear responsibility

Communication responsibilities and role assignments should be clearly defined. A designated contact person should be entrusted to ensure that responsible parties can be quickly identified in daily communication, which can reduce information omissions and misunderstandings. At the same time, the communication effectiveness of partners should be regularly evaluated, and communication processes should be optimized through feedback mechanisms to ensure the accuracy and effectiveness of information transmission.

6.4.4 Mechanism of feedback

A transparent feedback mechanism should be established. Both the entrusting party and the entrusted party are encouraged to provide opinions and suggestions. Besides, the feedback collected in time should be summarized and handled. In this way, communication strategies can be continuously optimized, overall cooperation efficiency can be improved, and the quality and safety of pharmaceutical commissioned production can be guaranteed.

7 Conclusion

In August 2019, the newly revised Drug Administration Law was approved, mainly clarifying the MAH system from legal aspects, which also marked the official implementation of MAH system in China. However, MAH system still faces many challenges, such as the unclear quality management system related to pharmaceutical commissioned production. This article designs a quality management system for pharmaceutical commissioned production under MAH system, which is an important guarantee to effectively assume responsibility for drug quality in the drug life cycle.

This article systematically and comprehensively designs and studies the commissioned production quality management system, making the system more specific and detailed, with strong reference and operability. The establishment and improvement of the commissioned production quality management system is of great significance in ensuring drug quality and medication safety, filling the gap in the comprehensive refinement of the entrustment production quality management system research under MAH system, and enhancing the experience in production management system in China.

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