He et al., Afr J Tradit Complement Altern Med. (2015) 12(4):56-64
http://dx.doi.org/10.4314/ajtcam.v12i4.9

IMPLEMENTATION STATUS AND BARRIERS OF GOOD MANUFACTURING PRACTICE (GMP) FOR CHINESE PATENT MEDICINE

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Abstract

Background: Safety, quality and effectiveness of Chinese patent medicine (CPM) are highly relevant to the manufacturing process. However, the level of manufacturing practice (GMP) for CPM as implemented in China is less reported in literatures. Therefore, the aim of this paper was to reveal the implementation status of GMP for CPM in China, in terms of implementation principle, implementation content, industrial impacts, and implementation barriers from both macro and micro aspects.
Methods: A comprehensive analysis was carried out with archival data and field work at CPM manufacturers.
Results: Both implementation principle and content of GMP for CPM in China indicated a transformation from provision-oriented to human-oriented, leaving more flexible operation space to CPM manufacturers. However, poor manufacturing practices may still exist because the implementation of GMP in China is not strict enough to eliminate all the unqualified CPM manufacturers from market. Moreover, compared with international WHO GMP, there are barriers for implementing GMP for CPM, including main deficiencies in quality control management, cost of GMP renovation projects, lack of education and training, and lack of expertise.
Conclusion: This paper found that the implementation of GMP for CPM still faced many barriers though GMP had generated some positive impacts on CPM manufacturing. Removal of implementation barriers could be considered, including strengthening personnel competence, improving the quality management system and enhancing the international communication with advanced GMP regulators.

Keywords: good manufacturing practice, GMP, Chinese patent medicine, traditional Chinese medicine, quality risk management

Introduction

The use of traditional Chinese medicine (TCM) is becoming popular around the world (Ge et al., 2014). TCM not only includes herbal plants, but also includes the herbal medicine preparation and formulas well known as Chinese patent medicine (CPM). With the rising trend of using natural medicine, CPM has received great attention given its medicinal advantages, like unique curative function or less toxic and side effect (Luo et al., 2000). Hence, China is determined to build a modernization system of CPM to not only enlarge domestic market but open the international market (Lai et al., 2012; Ma et al., 2014; Zhang, 2002). However, one of the largest obstacles for TCM internationalization lies in the safety issue of CPM (Au et al., 2000; Ernst, 2002).

The safety and efficacy of herbal medicine are critically determined by quality (WHO, 2007). Quality risk such as misidentification of herbal ingredients, substitutions, heavy metal contaminations and adulterations are reported consistently, related cases of severe and even fatal poisonings caused by CPM have also been noticed (Chan et al., 1995; Fischman, 2000; Kang-Yum and Oransky, 1992).

Proper quality control of the manufacturing process should be necessary to minimize the risk (Pach et al., 2003). Therefore, good manufacturing practice (GMP) remains one of the most important tools to guarantee that the manufacturing process was carried out in right ways and under serious supervision, quality control measures are well adapted, and final CPM products are of high quality to protect the public health (Calixto, 2000).

GMP regulation in China was first introduced in 1995, and has experienced several revisions (Wang and Sun, 2009). Two main revised GMP standards keep regulating the manufacturing process of CPM, including the 1998 old GMP (short for "Good Manufacturing Practice for Pharmaceutical Products (*Amended in 1998) SDA Order #9*") and the 2010 new GMP (short for "Good Manufacturing Practice for Pharmaceutical Products (*Amended in 2010) SDA Order #79*"). Early researches from the perspective of regulators have been carried out to find out the evolutional revision of GMP contents in specific clauses, like the change in air cleanliness class or the distribution requirement (Hu, 2012).

However, as a practically operable tool, the implementation of GMP depends on the realistic adoption of CPM manufacturers that have to get GMP certifications in the actual production period before marketing (Li and Sun, 2005; Wang and Li, 2015).

To explore the quality assurance issues of CPM, it's meaningful to study the implementation of GMP standards based on actual manufacturers' perspectives.

Previous researches about GMP management in manufacturers have pointed out some disadvantages in the GMP certification and inspection system. After passing the certification of old GMP in 2004, some qualified manufacturers have become tired of keeping strict execution standards with what the GMP documents' required persistently (Hu, 2006).

In China, a large number of standard operating procedures (SOPs) still remain vacant and chaos in most of TCM manufacturers (Pan et al., 2005). In the implementation process of GMP, investment in small and medium-sized state-owned manufacturers' renovation also became big obstacle (Fu, 2002). In addition, GMP inspection was disjointed from market surveillance, and pre-approval inspection was introduced late after 2006 (State Food and Drug Administration Center for Certification, 2009).

In general, the actual implementation situation of GMP for CPM remains less studied yet and requires further explorations.

Thus, this paper aims to reveal the implementation status of GMP for CPM in China, in terms of implementation principle, implementation content, implementation impact, and implementation barriers from macro and micro aspects, hoping to provide references for future GMP

http://dx.doi.org/10.4314/ajtcam.v12i4.9

certification and development of CPM. Moreover, this comprehensive review is also expected to provide reference for the development and implementation of GMP for other traditional and alternative medicine all over the world.

Review Method

To realize comprehensive analysis about the GMP implementation for CPM, materials from multiple sources were collected and analyzed for this study. Firstly, information collection and analysis from online database, government websites, national statistics, and authoritative papers were carried out to obtain publicly available information about the macroscopic implementation situation of GMP for CPM. In particular, materials from China Food and Drug Administration (www.cfda.gov.cn) were systematically collected and analyzed to report the GMP implementation at macro level.

Secondly, first-hand materials at selected manufacturers were collected. A semi-structured protocol has been designed according to the 1998 GMP and the 2010 GMP to get concrete feedbacks from CPM manufacturers about the microscopic implementation status of GMP. Two leading TCM manufacturers in China were targeted to collect information about the implementation of GMP for CPM. In addition, one western medicine enterprise was also studied to provide comparative information about GMP implementation in China. In the three sample manufacturers, interviews with the support of semi-structured protocool were carried out directly with persons who are responsible for GMP implementation to get their opinion towards the design and implementation of GMP for CPM or western medicine. The basic information of the sample manufacturers is summarized in Table 1.

Table 1: Basic information of the sample manufacturers

	Guangzhou Baiyunshan Phamaceuticals General Factory (BYS)	Tianda Holdings Limited (Zhuhai) (Tianda)	Regenex Pharmaceuticals Limited (Regenex)
The major categories of enterprise production	Chinese patent medicine	Chinese patent medicine	Western medicine
Company scale	Large state-owned enterprise	Medium-sized private manufacturers	Medium-sized private manufacturers
The participants in interviews	Director of GMP Office	Technician of Quality Management Department	Manager of Production Department
When to start GMP management	1999	2010	2004
When to pass the 1998 GMP certification	2003	2010	2008
Whether pass the 2010 GMP certification or not	Most of the products have passed	No	Yes

Macroscopic Implementation Status of the 1998 GMP for CPM

The 1998 GMP was still in use today as norms for quality management of drugs. Some CPM factories still only owned manufacture certifications of the 1998 GMP. In China, the implementation of the 1998 GMP followed the secondary GMP certification system for drugs. National certification process was for high risk injection and biological products; provincial certification process was for non-sterile products, including TCM preparations.

The implementation background of the 1998 GMP could be concluded as rapid growth of CPM industry, high level of industrial concentration and a time when big state-owned manufacturers accounted for a large proportion of CPM sales. And the most important problem that time was that there exited so many low-level CPM manufacturers, the foundation of TCM research and development (R&D) were relatively low so that TCM products weren't with a high technical content, industrial competitiveness were too weak to get involved in international pharmaceutical market. These problems would be solved following the guidelines of national policies and technological innovation, by the means of GMP certification to guarantee the quality. So, the 1998 GMP for drugs was introduced under the support from Ministry of Health and the need of the country's pharmaceutical markets. Soon, the GMP regulation was promoted in various TCM manufacturing manufacturers, and was not difficult to implement in the initial time.

A series of internal management departments has been modified or built to ensure the implementation of the drugs GMP, including National Health and Family Planning Commission, Ministry of Health, SFDA, State Administration of Traditional Chinese Medicine, China Association of Traditional Chinese Medicine and so on. Each department performed its own function and SFDA was mainly responsible for the management of GMP for CPM. Department of TCMs and Ethno-Medicines Supervision in SFDA took charge of the protocol, supervision and implementation of TCM GMP. Provincial FDAs had their responsibility to take care of the supervision and inspection of CPM GMP in the provinces.

The quality censorship of the 1998 GMP mainly involved: (1) Focus on examination of drugs' manufacturers with bad behavior record and unqualified sampling results, confirm follow-up inspection requirements towards those key manufacturers; (2) Timely inspection into potential instable manufacturers; (3) Build the random drug testing system called "test flight" for an unexpected inspection without inform the manufacturers. The government agencies' constitution and the inspection institutions showed much firmer enforcement of the GMP rules. In the achievement of the 1998 GMP, it's easy to find that the rules have integrated the TCM industry at some extent by cutting down finished products of poor quality. The number of CPM manufacturers was decreased to 1,016 till March 2004, any manufacturers without the 1998 GMP certification were asked to close down. However, from the ensemble performance of CPM industry, the production yield and industrial output value has been increased in a stable speed, with only a little fluctuation (see Figure 1 and Figure 2).

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Macroscopic Implementation Status of the 2010 GMP for CPM

The new GMP guideline for drugs was formally put into action on 1 March, 2011. The 2010 GMP had 14 chapters, 313 items, increased obviously by the content of the 1998 GMP. More detailed and precise items have been adjusted especially in the aspects of management, standards of premises and equipment, risk control and software management.

The main revised content in new GMP can be concluded as: (1) Strength the quality control of traditional Chinese medicinal materials and decoction pieces, the control of extraction process and the management requirements of storage; (2) Requirements on the whole quality control projects of traditional Chinese medicinal materials and preparations; (3) Requirements on the control of solvent recovery in the process of extraction; and (4) Special regulations about the chapters referring to personnel, premises and equipment, materials, documents, and production control, based on the characteristics of CPM. Moreover, axenic medicine manufacturers were required to achieve the GMP certification before 31 December, 2013, other manufacture corporate must finish the certification before the end of 2015.

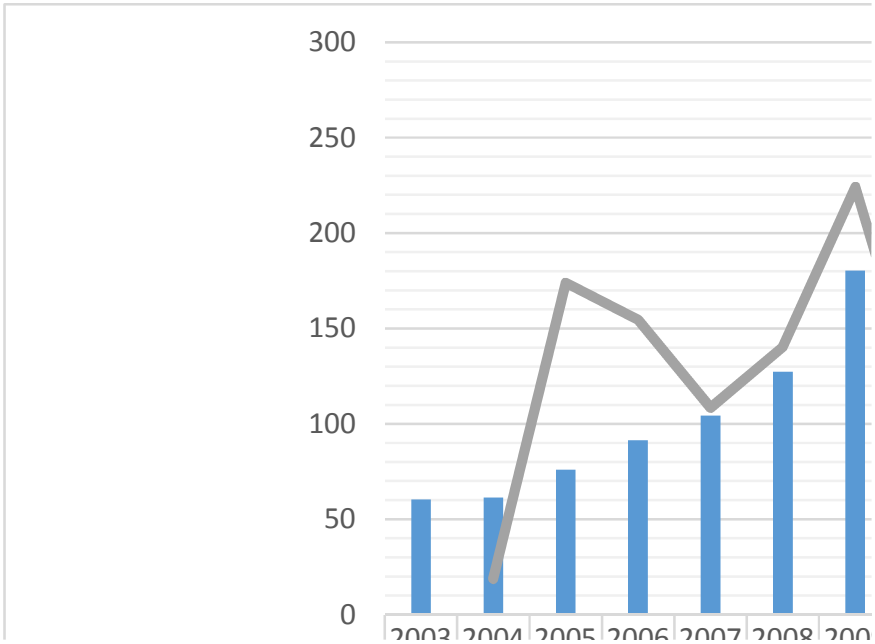

Figure 1: The production and its growing rate of CPM in China from 2003 to the first half year of 2011

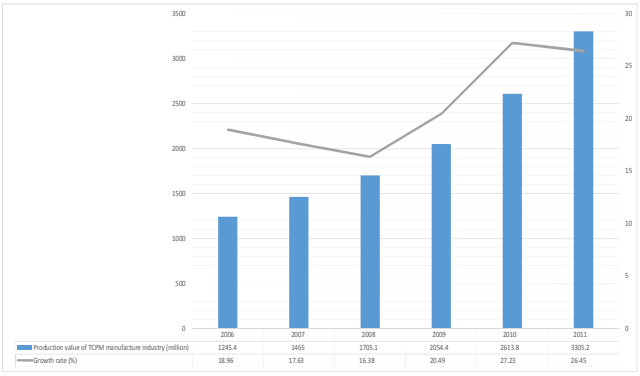

Figure 2: The production output value and its growing rate of CPM manufacture industry in China (2006-2011)

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It seemed that the implementation of the new GMP has made the GMP certification process of CPM transform from provision-oriented to human-oriented; the evaluation standard becomes stricter, but with more flexible and advanced operation methods for CPM manufacturers (see Table 2). In the past, provisions were the only standard to test the qualification of manufacturers in the field inspection, which made the inspection easier as the manufacturers have studied the provisions roundly and became familiar with the thoughts of inspectors. Now, the new GMP enhanced an updated management theory emphasized the importance of software and personnel. Also, the principle of quality risk management (QRM), quality control (QC) and quality assurance (QA) have been highlighted in the new GMP. Till now, the manufacturers haven't integrated the GMP into various parts of QRM completely and flexibly, as they didn't totally understand each component in QRM and how to use it, especially in the aspects of change control, error treatment, corrective and preventive action. Additionally, because of the requirements of "humanity" in the new GMP, administration personnel with quality management knowledge became a key factor in the implementation process. The recognition of inspectors' qualifications, the quality of manufacturing workers, or the specialization of qualified person (QP) was requiring to improve. All the process were mean to ensure the certification of GMP and further guarantee the risk controllability and quality traceability of final products.

Till now, no more than half of CPM manufacturers have obtained the new GMP certification. The total number of CPM manufacturers has decreased at some extent, but the whole manufacturing sector was in a stable growth according to the data of 2011 (see Table 3). The performance might indicate that small manufacturers were forced to shut down with difficulty to pass the new GMP, and large manufacturers develop better and fulfill the market on the basis of the company strength to easily pass the new GMP standard.

Table 2: Comparison of evaluation standard between the 1998 and the 2010 GMP

The 1998 GMP			The 2010 GMP
Items			If no defects were found, then pass the GMP certification.
Serious defects	General defects	Decision outcome	
0	≤20%	Pass the GMP certification	If no serious defects were found, and the defects ≤10, manufacturers would get the GMP certification after rectification with the verification of local inspection department.
0	21%~40%	Follow-up inspection within 6 months' rectification	
≤3	》20%	Fail the GMP certification	
>3			

Table 3: Scale merit of CPM manufacturing industry (2007-2011)

	Number of manufacturers	Employees	Total assets	Total assets growth rate	Total liabilities	Total liabilities growth rate
2007.11	1,350	359,409	1,846.93	9.04	850.99	8.04
2008.11	1,408	364,692	1,976.53	8.06	893.46	4.35
2009.11	1,480	375,735	2,168.03	12.48	956.08	9.53
2010.11	1,540	401,797	2,589.76	16.95	1,150.91	14.45
2011.12	1,328	426,444	3,105.81	24.14	1,245.27	21.46

Micro Implementation of GMP for CPM

Micro Implementation Principle of GMP: The manufacturers generally acknowledged that firstly they were just trying to meet the requirements of government.

Because the enactment of the 1998 GMP required that manufacturers were allowed to enter the drugs market only after a paper of GMP certification, the highest priority of pharmaceutical manufacturers was to pass the GMP inspection as soon as possible.

When the 2010 GMP has been issued, the CPM manufacturers indicated that the implementation of GMP was still restricted in the fulfillment of institutions, though the requirements for technical and management level have been improved.

The manufacturers indicated that compared to the 1998 GMP with clear clause and easy procedure, the 2010 GMP blurred relatively in clauses and the difficulty of content has increased.

More guidance was added in the 2010 GMP to make the manufacturers operate flexibly, while operating step-by-step following the clauses in the 1998 GMP.

The new GMP would help manufacturers to take more care of personnel quality, as well as guarantee the production quality. It can be summarized that the implementation principles of GMP transformed from provision-oriented to human-oriented, implying more flexible and more adaptable.

Micro Implementation Content of GMP*:* In the aspect of content, three sample manufacturers all have implemented basic GMP requirements according to the general provisions. The main implementation content is summarized in Table 4.

They all had core personnel to satisfy the need of production and management, private manufacturers were facing with relatively high personnel mobility especially at the grassroots level.

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Moreover, three sample manufacturers had special training department and appropriate training course for personnel, the training content also contained related necessary knowledge confirmed with the requirement of the new GMP, including legal training, GMP training, responsibilities, skills and SOP training. Premises and equipment have been updated.

The new GMP enhanced the design layout requirements about production area, warehouse rea, quality control area and supplementary area separately.

Most of their investments in GMP have been put into the premises and equipment transformation, some CPM processing plant were directly newly built and replenished with new advanced devices.

QRM was all required in the implementation of GMP in the three manufacturers, to meet with the new GMP.

There are also some differences in implementation. To consider the raw materials in CPM manufacturers, state-owned large manufacturers afforded to build their own GAP bases and pretreatment plant, so that they could ensure the controllability of material sources by themselves besides a few materials came from manufacturers. However, private medium-sized manufacturers got their raw materials mostly from the manufacturers and distributors.

Table 4: GMP content results

	Guangzhou Baiyunshan Phamaceuticals General Factory (BYS)	Tianda Holdings Limited (Zhuhai) (Tianda)	Regenex Pharmaceuticals Limited (Regenex)
Difficulty of implementation of GMP	Acceptable after increasing input	Acceptable after increasing input	No influence under current economic condition
Personnel			
Personnel allocation	Stable to meet the needs of production and management	Stable basically in core person and basically meet the needs of production and management	Stable basically in core person and basically meet the needs of production and management
Qualified person	Yes	Yes	Yes
Provision for responsibilities	Clear with document requirements in personnel	Clear with document requirements in personnel	Clear with document requirements in personnel
Personnel training	Yes (HR is responsible for the training)	Yes (HR is responsible for the training)	Yes (Special department for training)
Training content	Legal training GMP training Responsibilities Skills SOP training	Legal training GMP training Responsibilities Skills SOP training	Legal training GMP training Responsibilities Skills SOP training
Premises and equipment			
Equipment upgrading	Yes	Yes	Yes
Premises upgrading	Yes	Yes	Yes
Production			
Purchasing for materials	Some purchased from manufactures and others by itself	Most purchased from distributors and a few from manufactures	All purchased from manufactures
Quality Audit of suppliers	All materials should be audited	All	All
Materials sample	Sampling test in each batch	Sampling test in each batch	Sampling test in each batch
Documentation			
Batch dossier for drugs	Yes	Yes	Yes
Management of batch dossier of drugs	Quality management department	Quality management department	Quality management department
Quality control system			
The progress in QRM	Risk identification Risk assessment Risk control Risk communication Risk review	Risk identification Risk assessment Risk control Risk communication Risk review	Risk identification Risk assessment Risk control Risk communication Risk review

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Micro Implementation Impact of GMP

The industrial impact of GMP implementation could be analyzed in different aspects, including the influence on drugs' quality, drugs' passing rate and the brand effect. The performance about passing rate of CPM manufacturers was not sufficient to show the achievement of the new GMP in the current stage, as the approval deadline would last to the end of 2015. The manufacturers mentioned the benefit for the company brand from implementing GMP meanwhile the new GMP certification was regarded as one of important evaluation index in the public bidding of Essential Medicine List. However, despite of the improvement in manufacturing line, feedbacks of drugs' quality didn't make significantly progress after the implementation of GMP for CPM.

The manager from the sample manufacturers mentioned: "It's a chance to prove the capability of enterprise to get the new GMP in the first time, we have consensus that only large CPM manufacturers with economic strength can take the lead in passing the new GMP, it's another evidence to prove that the TCM market is still occupied by large manufacturers with relatively high quality manufacturing line, though little fluctuations were perceived in the market". Large manufacturers showed advantages than others in the first stage of the implementation of GMP.

Relationship with inspection departments and upstream suppliers were also considered. The manufacturers tended to own a close connection with government in the implementation of GMP. The provincial government and supervision department organized regular training class for quality persons, and also suggested some good guidance and opinions for the reform in the GMP department, in order to improve the management of corporate and support the manufacturers get through the new GMP. The relationship with government could be concluded as harmony, while the inspection towards GMP became more stringent. Once a year's general reexamination was carried out by the supervision departments, in detail, it's once a year general investigation in regional council, and yearly selective examination in city council. Usually, there were follow-up inspections after the second year of GMP certification and test flight in every year. On the other hand, the manufacturers also tended to a close connection with upstream suppliers as well. The quality of raw materials was taken so seriously that the quality of suppliers should be ensured. The manufacturers set up special departments and responsible person for the suppliers' audition and quality feedbacks ever since the establishment of production department. They also required relatively strict in the supplier audit. Moreover, the manufacturers' managers mentioned: "The relationship between suppliers and manufacturers can benefit each other. Because the GMP requirements for suppliers are relatively weak, they often need the results of manufacturers' audit to verify their own products, and try to improve the quality of raw materials."

At last, for the future acceptance period of the GMP certification, the manufacturers thought that the implementation force should be enhanced to shut down unqualified manufacture manufacturers in the end of 2015. The case manufacturers all thought that the developing trend of GMP content would be closer to the mainstream of international GMP standard, especially the WHO GMP. In the management of quality control system, more €experience from overseas should be necessary, so that the quality of final products would be regulated more normatively than the current implementation level.

Main Implementation Barriers

The implementation barriers were also clearly identified (see Table 5). Firstly, two main barriers were identified by case manufacturers: difficulty in implementing GMP and difficulty in management layers. Through the interview about the most difficult items in GMP implementation, large CPM enterprise regarded the development of personnel quality as the most difficult. No matter the training for current employees or the recruit for new GMP staff should be emphasized in the work. In details, the personnel training process in drug manufacturing manufacturers were regarded as empty and formulaic, even some business executives or GMP department heads weren't pharmaceutical technical personnel or owned corresponding technical titles, resulted in unprofessional training for operating personnel.

Table 5: Barriers to effective GMP implementation identified by CPM manufacturers

	Guangzhou Baiyunshan Phamaceuticals General Factory (BYS)	Tianda Holdings Limited (Zhuhai) (Tianda)	Regenex Pharmaceuticals Limited (Regenex)
Most difficult items in GMP implementation	Personnel	Control of quality of suppliers Cost management	QRM
More worthy of attention items in GMP implementation	Quality of raw materials and QRM	Quality of raw materials	Personnel QRM Distributors
Management difficulty in GMP implementation	Increase of quality of management layers	Cost management and personnel training	Increase of quality of management layers, especially about QRM

On the other hand, cost and quality assurance of TCM materials became the difficulty of small-medium CPM manufacturers. They regarded incoming materials control, supplier assessment and balance of cost as key obstacles in the GMP implementation process. Besides, western medicine manufacturers thought the QRM as difficulty and emphasis together, they mentioned: "Because the county doesn't require a fixed model about the QRM in pharmaceutical manufacturers rather than the requirements of exploration for suitable mode, it's difficult for the domestic manufacturers to embed the risk assessment mode of thought. Most of these domestic manufacturers have never contacted with the concept of risk management. It's still in the initial stage of the implementation of QRM in China."

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Secondly, the three case manufacturers all admitted that cost would increase during the implementation of GMP, with an affordable change. Concerned with the management layer, they indicated that "The new GMP has a stricter and more direct requirement for the capability and quality of management layer". They mentioned in detail that: "Managers should enhance their abilities and cognitions in the assessment of risk deviation, the judgment of risk control, etc. They are also required to make a decision through lots of document investigation and case analysis instead of making decisions so easily like before."

Besides, the items those worth paying the most attention in GMP implementation showed different in the three case manufacturers. Two CPM manufacturers focused on quality of raw materials, including accessory and packaging materials. It's another barrier that some suppliers couldn't obey GMP standards; they were so small-scale and unstable that the supplier audit became more difficult for CPM manufacturers. As for the western medicine manufacturer, personnel and QRM were in first place simultaneously and they made it each other possible.

Discussion

Implementation Status of GMP for CPM and its Implications

From the view of manufacturers, multiple resource materials were analyzed in this paper through macro and micro aspects to study the implementation situation of CPM GMP in China. It's obvious that the content of the 2010 GMP compared to the 1998 GMP has transformed from provision-oriented to human-oriented. Provisions about the management and supervision of drugs' quality has been enhanced as the principle of GMP tended to pay more attention to QRM, such as the items about accuracy of qualitative and quantitative methods, the quality control standards were adjusted (Zhang et al., 2012). The implementation of CPM GMP should consider the characteristic of TCM to pay more attention to the process control in extraction and storage because of the special medicinal nature of traditional patent medicine differing from the western medicines (Tan, 2008). Through the analysis of macroscopic information and the interviews with CPM manufacturers, it's obvious that there are two key points in the GMP implementation process: cultivating professional quality management staffs and adaptation of QRM. Although government departments constantly emphasized the importance of QRM, few manufacturers could fully grasp the concept of QRM. It's extremely important to develop specialized personnel with advanced knowledge and technology about the whole risk control system.

Concerned with the industrial implementation impact, the new GMP kept strict censorship following the 1998 GMP, and far more deepened the implementation operations requirements in the detailed provisions. However, manufacturers still doubted if the implementation of the new GMP could actually benefit the CPM market. Beyond that, CPM manufacturers generally admitted that it could help improve the quality of CPM products, and further control the quality of Chinese medicinal materials from the source under the cooperated implementation of both GMP and GAP. Besides, the response of CPM manufacturers did not present much difficulty in passing the new GMP, and they accepted the GMP inspection as a chance to introduce advanced management system and to enhance the enterprise's capability.

The results also indicated that GMP implementation required major investment in upgrading manufacturing facilities and this had implications for local producers. Cost problems have shut down lots of small CPM manufacturers in China, especially the manufacturers producing Chinese medicine decoction pieces. Large manufacturers might be satisfied with the results because their strength would be expanded by merger and acquisition. But for the local producers without strong fund to implement GMP, they need support to search solutions for them. So, future research would be useful to look from the manufacturers' perspective, especially the small and medium CPM manufacturers, at the cost of compliance with GMP and how it's reflected in price, also at the cost to introduce quality control system, the training of staff for implementation of these new system and even the fees investing in premises transformation.

Main Barriers of GMP for CPM and its Implications

The unique medicinal nature of TCM has ensured the importance of the quality of raw materials. CPM manufacturers had fine traditions in supplier audit to guarantee the materials' quality so that the Chinese medicine raw materials have taken up more than eighty percent of the total TCM export sales (Beijing Business Today, 2014). Large manufacturers with own GAP bases could control the quality of supplier more easily, and its only barrier for small and medium sized CPM manufacturers to consider the supplier audit and the cost management on GMP renovation projects.

Furthermore, QRM was challenged in the new GMP implementation system, and became the main barriers together with talent reserves and personnel training. Compared with the international GMP regulations, like the WHO GMP or PIC/S, the QRM promoting in China was still in the first stage (He et al., 2015). Many CPM manufacturers have only built up basic quality control system based on the basic requirements to get the GMP certification. CPM manufacturers in China had defects in basic hardware of the quality control system, so that most of the risk assessment tools could not come into use. For instance, the general tool of QRM was question-profile method, fault tree analysis was only used in major and difficult project in China, and the use of failure mode effects and criticality analysis or Markov analysis et al., were rarely found in the quality control departments (Liu et al., 2007).

Modernization of GMP in China is a very essential step in bringing CPM to the standardized international level. The WHO GMP has become main reference of drugs' GMP in China since 1998, and the 2010 GMP in China has adopted the sanitation and hygiene grading standard of the contents in the WHO GMP (Li et al., 2014). Similar contents didn't reflect the same implementation effect as mentioned before. Compared with the WHO GMP, the barriers of GMP for CPM in China have been revealed more obviously. While the quality of raw materials was regarded as barriers in implementing GMP, the WHO GMP has specified many requirements for quality control of starting materials, including correct identification of species of medicinal plants, special storage and special sanitation and cleaning methods for various materials. Moreover, the QRM system in WHO is more effectively implemented than GMP in China. WHO inspections were scheduled on a risk basis, taking into account all known factors that could affect the risk on quality, safety and efficacy, including results from previous WHO inspections, results from inspections by other national regulators, and the recalls or complaints since last inspection, etc. (Huang et al., 2013; WHO, 2011). In fact, the implementation of GMP for herbal medicines showed a significant increase from 2001 when no countries or jurisdictions in the region reported applying GMP for TCM products; there are now nine countries and jurisdictions with active GMP in 2010. However, just like the GMP for CPM in China, there were still a lot of poor manufacturing practices out there in WHO, in the Global Survey questionnaire conducted in 2001, Member States of WHO identified the main barriers regarding GMP issues for herbal medicines – lack of education and training and lack of expertise.

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In general, no matter the main barriers recognized by CPM manufacturers or the gap between GMP in China with international mainstream GMP, removal of these barriers should consider personnel training, QRM systems and the international communication. It should be noticed that the success of a QRM system depends on educating and training management and employees in the importance of their role in producing safe drugs (Hrudey et al., 2006). It's the government's responsibility to help settle the QRM system into CPM manufacturers, and make the QRM dynamic, iterative and responsive to change. As implementation performance of WHO GMP indicated a trend for global harmonization, it's necessary to strengthen international communication and learn from the advanced technical or administrative theory from mainstream GMP standards to remove barriers (Choudhary and Sekhon, 2011).

Conclusion

Using macro materials and field work with CPM manufacturers, this paper showed that the implementation of the new GMP for CPM had transformed from provision-oriented to human-oriented, which meant more flexible operations and relatively doubtful inspections. Quality of raw materials and QRM were regarded as key points and also became barriers in the implementation of GMP for CPM in China. Another barrier recognized by small and medium sized manufacturers was the cost management when implementing GMP renovation system. To improve the GMP for CPM, regulators and manufacturers should take actions including strengthening personnel competence, improving the quality management system and enhancing the international communication with advanced GMP regulators.

These experiences of GMP for CPM also provide some meaningful implications for GMP implementation in other nations that want to upgrade their traditional medicine. First, an evolutionary strategy could be adopted to strengthen the implement of GMP and avoid industrial quality disorder from radical GMP requirements. Secondly, the related practices of chemical and biopharmaceutical GMP could be referred and incorporated into GMP for traditional medicine after adjusting to the characteristics of traditional medicine. Thirdly, manufacturers as key implementer of GMP must pay much attention on training all of their employees and empowering professional GMP management staffs. With continuous improvement of GMP hardware, the manufacturers of traditional medicine need to give more value on human in implementing GMP.

Acknowledgements

This work was supported by the Research Fund of University of Macau (MYRG160 (Y1-L2)-ICMS11-HH; MYRG2015-00072-ICMS-QRCM).

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