

Characteristics of Chinese GMP

Comparison of Chinese GMP and ICH Q7

In recent years, the pharmaceutical manufacturers in China are legally obligated to implement GMP (good manufacturing practice), in order to assure the quality of pharmaceutical products. For the foreign pharmaceutical companies entering the Chinese market, it is important to be aware of the characteristics of Chinese GMP and the differences between Chinese GMP and the international GMP – ICH Q7 when materials sourcing.

The current Chinese GMP - Good Manufacturing Practice for Pharmaceutical Products was amended and issued as regulation by the State Foods and Drugs Administration (SFDA) of China in 1998. It includes 14 chapters and 88 articles, covering organization and personnel, building and facilities, equipment, materials, hygiene and sanitation, validation, documentation, production management, quality management, production distribution and recall, complaints and adverse reactions report, and self-inspections. In addition, it encompasses 6 appendices, which are supplementary provisions for the aseptic drugs, non-aseptic drugs, APIs, biological product, radioactive products as well as Chinese medicine.

Based on Chinese GMP, criterion for GMP Certification and Inspection was issued in draft form by SFDA in 2006. There are 268 inspection items in the criteria in total, including 115 critical items and 153 non-critical items. The SFDA requires all pharmaceutical companies to gain GMP certification for the production of pharmaceuticals (e.g., APIs, finished products), with the deadline of June of 2004 stipulated. GMP certification is based on assessment of on-site inspection results (see table 1) and is valid for 5 years. After the validity period has transpired, a full inspection will be conducted by SFDA to check whether the drugs manufacture still meets the GMP requirements.

Tab.1: Criteria for the GMP Certification and Inspection*

Deficiencies found during inspection		Results
Number of critical items	Percentage of non-critical items	
0	≤ 20%	Qualified for the GMP certification
0	21 - 40%	Corrective actions should be taken within 6 months and inspection will be done again
≤ 3	≤ 20%	
0	> 40%	Not qualified for the GMP certification
≤ 3	> 20%	
> 3		

* Source: SFDA - Criteria for the GMP Certification and Inspection

In order to guide the Chinese pharmaceutical companies to carry out validation activities, a book - Guide for the Validation of Drug Production was published by SFDA in 2003 in Chinese, which was written by experts from various major Chinese pharmaceutical companies. It focuses mainly on theories, methods, and procedures as well as examples of validation, including validation of analytical methods, cleaning validation as well as validation of computerised systems. However, it should be stressed that this book is only a technical reference book for the validation of drugs production and is not legally required by SFDA.

This article focuses mainly on the comparison of Chinese GMP and ICH Q7, covering mainly the aspects of GMP starting point, personnel, quality management, buildings and facilities, materials management, production management, validation, and documentation.

Scope and GMP starting point

The ICH Q7 applies only to the manufacture of APIs for use in human drug (medicinal) products. In comparison, Chinese GMP is applicable to the manufacture of both finished products and active pharmaceutical ingredients.

An API starting material is defined and GMP starting point is specified in the ICH Q7 guideline.

In Chinese GMP, explicit definitions with regard to starting material and GMP starting point are not given. The only requirement is that the batch production records of APIs should be started at the latest from the refinement of crude product, which could be similar to the GMP starting point.

According to the ICH Q7: less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps). In comparison, Chinese GMP focuses mainly on the last production process steps from the crystallization, which are required to be executed in clean rooms.

Personnel

The ICH Q7 requires that there should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the production of intermediates and APIs. In Chinese GMP, there are more detailed requirements on the education of the responsible persons of company management, production management, and quality management. Those persons should have at a minimum a college degree of medicine, pharmaceuticals or related sciences. Training for personnel engaged in production and quality control of drugs is needed according to Chinese GMP, but there is no requirement on the periodical assessment of the effectiveness of training, although training examination is required.

Concerning the personnel hygiene, Chinese GMP requires additionally that health files of drug production personnel be established. For production personnel with direct contact with drugs, a physical examination should be at least annually conducted. In general, Chinese GMP focuses more on personnel hygiene in clean rooms.

Quality Management

According to ICH Q7, there should be an effective system for managing quality which should encompass the organizational structure, procedures, processes and resources, and necessary activities to ensure that products will meet the intended specifications for quality and purity. For this purpose, the responsibilities of the quality unit and responsibility for production activities are specified, and internal audits and product quality reviews are required. Moreover, in this quality management system, the quality unit (QU) must be independent from the production unit, fulfilling both quality assurance (QA) and quality control (QC) responsibilities.

In Chinese GMP, there is a quality management department which is responsible for quality control and testing of drugs. The quality management department should be led directly by the responsible management of the company. The responsible persons of the quality management department and the production management department should be independent of each other. Generally, the quality management department of Chinese GMP has limited responsibilities in comparison with the ICH Q7, focusing mainly on the activities related to product quality testing / analysis.

ICH Q7 requires that a product quality review to verify the consistency of process should be annually conducted and adequate corrective actions should be taken (see 2.50). In comparison, a similar requirement such as product quality review cannot be found in Chinese GMP.

Buildings and Facilities

According to Chinese GMP, pharmaceutical companies should be located in a clean environment, e.g., the location/site with less industrial pollution. The general layout of the production, administration, living, and ancillary areas should be appropriately arranged. Whether buildings are appropriately located in accordance with the production process flow

and the required air cleanliness classes, is considered to be one of the critical items during the SFDA's on-site inspection for GMP certification. In comparison, similar requirements are not described in the ICH Q7.

In Chinese GMP, it is not explicitly described that defined areas or other control systems for some activities (e.g., sampling, quarantine, laboratory operations, etc.) are to be considered during the design and construction of buildings and facilities.

There are adequate requirements for clean rooms in Chinese GMP. However, for the classification of air cleanliness grade, there are differences between Chinese GMP and international GMP. For example, the air cleanliness class of 300,000 in Chinese GMP is an unknown class for foreign countries (see Tab. 2).

Tab. 2: The classification of clean rooms – Chinese GMP*

Grade of air cleanliness	Maximal permitted number of particles /m ³		Maximal permitted number of microorganisms	
	≥ 0.5 μm	≥ 5 μm	Air sample (cfu/m ³)	Settle plates (cfu/plate)
100	3,500	0	5	1
10,000	350,000	2,000	100	3
100,000	3,500,000	20,000	500	10
300,000	10,500,000	60,000	-	15

* Source: The Annex of the Chinese GMP – General Principle

According to Chinese GMP, the last production steps of APIs (e.g., refinements, drying, packaging) should be conducted in clean rooms of not lower than class 300,000. For APIs with legal microbiological control requirements, they should be processed in clean rooms of class 10,000 (even in class 100 if necessary). In contrast, such kinds of requirement are not described in the ICH Q7.

Material Management

According to Chinese GMP, the management systems for purchase, storage, dispatching, and use of materials used for production should be established. However, there is no explicit requirement on e.g.:

- Changing the source of supply of critical raw materials should be treated according to change control;
- Materials stored in fiber drums, bags, or boxes should be stored off the floor and suitably spaced to permit cleaning and inspection;
- Sampling should be conducted at defined locations;
- Materials should be re-evaluated to determine their suitability for use;
- Full analysis should be conducted on at least three batches before reducing in-house testing.

Production Management

In ICH Q7, there are very detailed requirements on production and in-process controls (see Section 8). In Chinese GMP there are mainly four kinds of production management documents, e.g., master formula, job position instruction, standard operating procedure (SOP), and batch production records. However, the operational requirements for process and in-process control are only mentioned in the master formula and batch production records without detailed contents.

In ICH Q7, there are clear definitions and requirements to guide rejection, reprocessing, reworking, and recovery during the drugs production. In comparison, requirements on such activities are not prescribed in Chinese GMP. Moreover, operational procedures for deviation, change control, and out-of-specification (OOS) are also absent in Chinese GMP.

Validation

Risk analysis is nowadays highly recommended during the validation of drug production even if not directly outlined within the international GMP (ICH, US, EU). Before starting validation, a comprehensive risk analysis is conducted to define the APIs in terms of critical product attributes, to identify process parameters that could affect the critical quality attributes of the APIs, and to determine the range for each critical process parameter expected to be used during routine manufacturing and process control. However, there is no such recommendation on risk analysis or equivalent measures for validation in Chinese GMP.

In Chinese GMP, the requirements on validation are very briefly described. Design qualification (DQ), cleaning validation, validation of analytical methods, and validation of computerised systems are not officially required, although those validation activities are described in the SFDA's technical book - Guide for the Validation of Drug Production.

The Chinese GMP stipulates that re-validation should be conducted at defined intervals or after any significant changes that may affect the product quality, e.g., changes of production process, quality control method, critical raw material and excipient, and critical equipment. But detailed requirements on change control procedures cannot be found in Chinese GMP. It should be mentioned that a full re-validation is also required by Chinese GMP when the GMP-certificate validity period expires. In contrast, according to the ICH Q7, whether to execute re-validation should depend on the results of the periodic reviews of validated systems and the product quality reviews.

Documentation

According to ICH Q7, validation documents, e.g., all specifications, master production instructions, all procedures impacting products quality, validation protocols and validation reports should be approved by the Quality Unit (QU). In Chinese GMP, there are requirements on the drafting, revising, reviewing, approving, withdrawing, distributing and retaining of

validation documents, but it is not mentioned that important validation documents should be independently approved by quality management department. According to the SFDA's book, validation documents should be jointly approved by the manager of quality management department and the responsible vice-manager of company. For process validation, any critical changes to validation protocols should be jointly approved by the manager of quality management department and the manager of production management department.

In Chinese GMP, the requirements on the contents of documentation are not explicitly described, e.g., product quality control documents, master production instruction and batch production records. Furthermore, there is no detailed requirement on e.g., records of raw materials, intermediates, API labelling and packaging materials, laboratory control records, and batch production record review.

Summary

In general, Chinese GMP covers most of the important aspects of pharmaceuticals production, with even some of the provisions being comparable to international GMP. Nevertheless, the most obvious differences between Chinese GMP and ICH Q7 can be summarized as follows:

- ∅ The responsibilities of the quality management department are limited and not comparable to the responsibilities of the quality unit described in ICH Q7;
- ∅ Validation documents are not independently approved by the responsible persons of the quality management department;
- ∅ The definition of the GMP starting point is not required by Chinese GMP;
- ∅ There is no recommendation on risk analysis or equivalent procedures to identify the critical parameters/attributes;
- ∅ Chinese GMP focuses mainly on the last production steps of APIs (e.g., crystallization, drying, blending, packaging), which are required to be performed in clean rooms of the class 300.000 or even better;
- ∅ Re-validation does not depend on the results of periodic reviews of validated systems and product quality reviews;

- Ø There is no requirement on the periodic assessment of the effectiveness of training;
- Ø Design qualification, cleaning validation, validation of analytical methods, and validation of computerized system are not legally required by Chinese GMP, although they are described in the SFDA's technical book;
- Ø Some particular procedures are absent or not described in detail, e.g., deviations, change control, out-of-specification (OOS), reprocessing, reworking, recovery, etc..



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