

Comparison of the EC-GMP Guide Part I with the SFDA-GMP Guideline for Chinese companies

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Summary

Contractual agreements between Chinese and European – or German – companies in the pharmaceutical field are targeted at procuring active pharmaceutical ingredients or even finished pharmaceuticals from China – or at their partial manufacture in China.

In these circumstances, regulations stipulate that the on-site capacity of the contractual partner should be checked and, in almost all cases, an audit carried out for this purpose. In order to understand and also to be able to evaluate regulatory implementation with reference to GMP on site and to guarantee better comparability between Europe and China, it is helpful, if not necessary, to be aware of the GMP requirements in the country concerned.

Although the regulations of the People's Republic of China are currently being revised, this paper presents a comparison of both

currently valid GMP guidelines, those of the European Union and those of the People's Republic of China, with reference to the requirements for finished pharmaceuticals.

The Chinese GMP Guideline establishes a good basis for guaranteeing quality and safety in the manufacture and control of pharmaceuticals. For a comprehensive implementation of the regulatory requirements of the EU-GMP Guide, Chinese producers need to add the missing requirements to the Chinese Guideline.

Summary

Contract manufacturing of pharmaceutical products such as Active Pharmaceutical Ingredients and Finished Pharmaceuticals - or manufacturing steps thereof - will be performed very often in the Federal Republic of China, initiated

by European or German companies. It is a legal obligation to perform an audit at the site of contract.

The work executed at the Chinese company has to be performed according to the European GMP Guideline. To understand and to assess the differences between the European GMP requirements and those from the SFDA GMP, it is beneficial to have knowledge about the content, the implementation and the understanding of both, the guidelines of Europe and those of China.

The following publication compares the requirements of the SFDA GMP and the EC GMP Guideline Part I for Finished Pharmaceuticals.

The requirements of the Chinese GMP Guideline for the manufacturing and quality control of the finished pharmaceuticals will lead only basically to an acceptable quality standard. To adhere finally to the EC GMP Guideline the Chinese companies must attend the missing parts.

1. Introduction

Globalisation and increasing cost pressure from healthcare systems are forcing numerous pharmaceutical companies to switch to sourcing from low-wage

countries. Both German and European pharmaceutical companies are finding Chinese contractors to be increasingly cost-effective manufacturers or suppliers. In addition to the

procurement of active pharmaceutical ingredients - or in occasional instances even finished pharmaceuticals - increased manufacturing is also encountered in the exclusive subcontract agreement.

Some 80% of all active pharmaceutical ingredients used in European pharmaceuticals are now produced in India or China. Both Indian and Chinese pharmaceutical companies are attempting, sometimes very aggressively, to offer production capacity also for finished pharmaceuticals. While a succession of Chinese manufacturers are now exporting their finished pharmaceuticals to Europe, there is a significant difference as far as the USA is concerned. To date, the US FDA has not yet approved a Chinese company in connection with finished pharmaceuticals in order for a finished pharmaceutical to be exported to the USA. In view of this, as much significance should be given to qualitative aspects as to economic interests when purchasing pharmaceutical products from third countries. After all, at the end of the value-added chain is a product which has a direct influence on peoples' health.

For these reasons it is helpful to be aware of the official GMP requirements for Chinese pharmaceutical manufacturers and to compare their contents with the European requirements. Only by precise knowledge of the respective rules and regulations, is it possible to assess more accurately the quality of a manufactured product in the shape of a pharmaceutical or an active pharmaceutical ingredient.

Since an on-site audit is essential in almost all cases, a further point is relevant. In order for the production and quality control processes on site in China to be understood and compared with the European guidelines, there is also a decisive advantage in knowing the local official guidelines for external contractors.

In recent years, new regulations and guidelines have been issued by the Chinese government (State Food and Drug Administration, SFDA), which regulate the GMP standards for the manufacture and control of pharmaceutical products [1-5].

These also include a guide which specifies the relevant basic rules and standards for GMP-compliant manufacture and quality control. It differs from the European guide essentially in the fact that it is equally valid for the manufacture and control both of finished pharmaceuticals and of APIs (see Article 2).

2. Legal framework of the Chinese GMP Guide

In China, Article 9 of the Drug Administration Law of the People's Republic of China calls for the application of Good Manufacturing Practice in the manufacture of pharmaceuticals. The law comprises a total of 10 chapters and has been in force in its current version since December 2001. The GMP rules are also described in the Good Manufacturing Practice for Pharmaceuticals Guideline. Here, as already mentioned, there is hardly any distinction made in principle between active pharmaceutical ingredients and finished pharmaceuticals.

The difficulty in assessing the GMP level partly lies in the fact that proof of manufacture according to GMP guidelines in the Chinese GMP system is based on independent and not international rules, which are furthermore not published in English by the SFDA [6]. This of course makes it difficult for most Europeans to access these guidelines. The differences become even more obvious upon inspection of factories in China.

A new Chinese contractor (a manufacturer of active pharmaceutical ingredients or pharmaceuticals) receives a GMP certificate valid for five years after successful inspection by the SFDA (the basis of all inspections by the Chinese authorities is the SFDA-GMP Guideline).

The deadline for all Chinese manufacturers for such a GMP certification was in June 2004. Since

then, Chinese pharmaceutical manufacturers who do not have such a certificate are no longer permitted to produce for the local market – the law however does not prevent production for export to other countries!

The CPhI, one of the most important international pharmaceutical events, which was held last year in Milan, was attended by numerous Chinese chemical plants which supplied active pharmaceutical ingredients produced in China to European countries. This is difficult to comprehend since many manufacturers do not even fulfil the local standard of the SFDA and also are not subject to monitoring by health authorities [7].

3. Comparison of the regulations

3.1 Comparison with ICH Q7

As already indicated, the Chinese GMP Guide is valid and applicable to both finished pharmaceuticals and active pharmaceutical ingredients.

The differences between the SFDA-GMP Guideline and the EC-GMP Guideline part II for API have already been explained in detail in various papers [8, 9]; they will receive no further consideration therefore in this study.

The papers quoted, together with the comparisons shown here (see Table 2) between the two systems of rules (SFDA-GMP and EC-GMP Part I), constitute a good basis for efficiently carrying out on-site inspections and recognising similarities as well as evaluating differences.

Table 1 compares the contents of the ICH Q7, the SFDA-GMP Guideline and the EC-GMP Guideline part 1.

This brief table gives a summary of how the headings of chapters of the Chinese GMP Guideline in some cases overlap in the two systems of rules while in other cases there is no correlation. Basically it can be said however

Tab. 1: Comparison between the separate chapters of the ICH Q7, SFDA GMP and EC-GMP Guideline Part 1 systems of rules. The headings can also be found in the SFDA GMP (in accordance with [8]).

ICH Q7	SFDA GMP	EU-GMP Guideline
1 Introduction	2 General Provisions	1 Quality Mangement
2 Quality Management	3 Organisation and Personnel	2 Personnel
3 Personnel	4 Buildings & Facilities	3 Premises and Equipment
4 Buildings & Facilities	5 Equipment	4 Documentation
5 Process Equipment	6 Material Management	5 Production
6 Documentation & Records	7 Hygiene	6 Quality Control
7 Material Management	8 Validation	7 Contract Manufacturer and Analysis
8 Production & In-Process Controls	9 Documentation	8 Complaints and Product Recall
9 Packaging and Labelling	10 Production Management	9 Self-inspection
10 Storage and Distribution	11 Quality Management	
11 Laboratory Controls	12 Distribution & Recall	
12 Validation	13 Complaint & Adverse Drug Reaction Report	
13 Change Control	14 Self-Inspection	
14 Rejection and Reuse of Material	Supplementary Articles	
15 Complaints & Recalls		
16 Contract Manufacturers		
17 Agents, Brokers, Traders...		
18 APIs manufactured by Cell Cultures/Fermentation		
19 APIs for Clinical Trials		
20 Glossary		

that the structure and contents of the Chinese GMP Guideline cover all the necessary topics which are required for governing the safety and quality of pharmaceutical products.

3.2 Comparison with the EU-GMP Guide Part I

The purpose of the comparison in Table 2 is to list both the differences and the similarities between the SFDA-GMP Guideline and the EU-GMP Guide Part I for finished pharmaceuticals.

The SFDA-GMP Guideline was taken as the target, and analogies drawn with the EC-GMP Guide Part I.

The details of the EC-GMP Guideline Part I were always only compared with the requirements of the Chinese GMP with corresponding contents. There is therefore the possibility that similar sounding chapters are not present while other chapters are.

It should also be added that the SFDA-GMP Guideline includes six further appendices, in addition to the

general requirements for pharmaceutical products.

They contain detailed requirements regarding:

- Aseptic Drugs
- Non-Aseptic Drugs
- Active Pharmaceutical Ingredients
- Biological Products
- Radioactive Products
- Chinese Medicine

In order to make sure that Table 2 remains clear, no further consideration is given to the appendices.

4. Comparison matrix

A note should be prefixed to the comparison matrix (Table 2) to the effect that the list does not represent an exhaustive comparison. In many cases, analogies can be found throughout the two texts, which are only apparent after a full reading of the SFDA-GMP Guideline. They have not been compiled here in detail.

5. Special differences between the two guidelines

In order to explain the degree of differentiation in more detail, some characteristic comparisons should be taken from Table 2.

5.1 Quality management system

The main differences are that the SFDA-GMP Guideline in the points listed below makes no further reference to compliance with the corresponding European requirements of a working quality management system:

- No mention of a risk analysis
- Quality control is not mentioned in the GMP Guide
- Personal hygiene is only mentioned as a secondary matter
- An ongoing stability check is not stipulated in more detail
- The Product Quality Review is not mentioned
- Computer systems and their validation are not mentioned
- Validations of processes and quality control methods are not mentioned (although they are mentioned in the SFDA's Technical Book [7])

5.2 Quality control

When considering the inspection of a pharmaceutical, it should be specifically emphasised that no unit is named to carry out the function of checking a pharmaceutical and of monitoring during production, such as environmental monitoring. Quality control as such is not mentioned in the respective systems of law or the underlying requirements.

Chapter 3 "Building and Facilities" does in fact mention a "Testing Lab". As in the European GMP requirement, it talks of a physical separation of this "Testing Lab" from production. This could presumably indicate quality control.

Tab. 2: Comparison matrix.

EU-GMP Part I	Chinese GMP Guideline	Remarks
Chapter 5 Production	Chapter 9 Production Management	
	Article 66. Master production instruction, position operation procedure, or standard operation procedure (SOP) should not be changed randomly. Where appropriate, written procedures should be followed for revising and approval of document.	The basic requirements are laid down in Chapter 4, Documentation, of the EU GMP Part I.
5.8 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits. 5.15 Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.	Article 67. Material balance should be confirmed for the quantity of each batch. Investigation should be performed if there is critical deviation. It can be released only after confirming that there is no potential effect on product quality based on reasonable explanation.	
4.17 During processing, the following information should be recorded at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person responsible for the processing operations: ...	Article 68. Entries in batch production record should be clear, actual and intact and signed by operator as well as checker. Record should remain tidy and should not be damaged or corrected randomly. Corrections to entries should be signed and leave the original entry still readable. Batch production record should be preserved as archive according to batch number until one year after expiry date. For drugs without specified shelf life, batch production record should be preserved for at least 3 years.	The retention time of the documentation is described in the German decree AMWHV.
	Article 69. A "batch" is defined as follows: a specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. Batch number should be assigned for each batch of pharmaceuticals.	The definition of "Batch" is mentioned in the Glossar of the EU-GMP Part I: A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.
5.19 Cross-contamination should be avoided by appropriate technical or organisational measures, for example: a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning; b) providing appropriate air-locks and air extraction; c) minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air; d) keeping protective clothing inside areas where products with special risk of cross contamination are processed; e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross contamination; f) using "closed systems" of production; g) testing for residues and use of cleaning status labels on equipment. 5.9 Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross contamination.	Article 70. In order to prevent contamination and mix-up, the following measures should be taken: 1. The fact that there is no carry-over from previous production should be confirmed. 2. Precaution should be taken to prevent dust. 3. Production operation of different product, different specification should not be conducted in the same area at the same time. When several packaging lines are working at the same time, quarantine or effective measures should be taken to prevent contamination and mix-up. 4. Cross contamination from gas, steam, spray or organism derived from material and product during manufacturing should be prevented. 5. Product or material name, batch number, and quantity etc. should be indicated on each operation room, equipment and container. 6. Selected medicinal plant should be cleaned with mobile water. Used water should not be used for other medicinal plant. Medicinal plant with different characteristic should not be washed at the same time. Cleaned and processed medicinal plant should not be dried in open air. Sterilization of medicinal plant and intermediate should not alter the efficacy or quality as appropriate. Medicinal plant powder directly as ingredient should subject micro-organism test before introducing.	How to avoid mix-ups it is also described in the chapter dealing with packaging, quality control, and production of the EU GMP Part I.
	Article 71. Appropriate process water should be employed according to master production instruction. Process water should meet predetermined specification. Process water should be tested regularly and the test should be documented. Test cycle should be specified based on validation report.	

Tab. 2 - continued

EU-GMP Part I	Chinese GMP Guideline	Remarks
Chapter 5 Production	Chapter 9 Production Management	
<p>4.18 The following information should be entered at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person(s) responsible for the packaging operations:</p> <ol style="list-style-type: none"> the name of the product; the date(s) and times of the packaging operations; the name of the responsible person carrying out the packaging operation; the initials of the operators of the different significant steps; records of checks for identity and conformity with the packaging instructions including the results of in-process controls; details of the packaging operations carried out, including references to equipment and the packaging lines used; whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting; notes on any special problems or unusual events including details, with signed authorization for any deviation from the Manufacturing Formula and Processing Instructions; the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation. 	<p>Article 72. Batch package record should be available. Content of batch package record should include:</p> <ol style="list-style-type: none"> name, batch number and specification of product for packaging, label, instruction and qualified certificate bearing batch number, received quantity of product for packaging and package material, signature of the person who distribute, receive, and check for above mentioned material, quantity of packaged material, cleaning record for previous package activity (copy) and cleaning record for current package activity, inspection result after finishing package operation, and signature of the inspector, signature of production responsible person. 	
	<p>Article 73. Cleaning activity should be performed after each manufacturing process by operation personnel and documented. Cleaning record should include manufacturing stage, product name, batch number, cleaning date, inspection item and result, signature of responsible person and checker. Cleaning record should be incorporated into batch production record.</p>	<p>These requirements can be found in the chapter 3, 4, and 5 of the EU GMP Part I.</p>

The Chinese GMP system of rules stipulates a “Quality Unit” which engages in the tasks of quality control, as in the GMP Guide Part II:

1. Make decision on the release or reject of material and intermediate.
2. Review batch production record before distribution and make decision on the release of final product.

Other stipulations as specified in detail in Chapter 6 of the EC-GMP Guide are given no further consideration.

The Drug Administration Law of the People’s Republic of China, which can be equated with the German AMG (Pharmaceutical Act) and provides for the implementation of the GMP Guide, contains the following chapters:

- I General Provisions
- II Control over Drug Manufacturers
- III Control over Drug Distributors
- IV Control over Pharmaceuticals in Medical Institutions
- V Control over Drugs
- VI Control over Drug Packaging
- VII Control over Drug Pricing and Advertising
- VIII Inspection of Drugs
- IX Legal Liabilities
- X Supplementary Provisions

A more specific reference to quality control can be found in Chapter II under Articles 8 and 12 (Fig. 1).

Further details and specific stipulations for tasks and responsibilities as found in

Chapter 6 of the EC-GMP Guide are not mentioned.

All other parts of the law which are described under the heading of “Control over...” focus on control by the Chinese State over pharmaceutical contractors and their marketing of pharmaceuticals.

5.3 Clean room requirements

An important appendix to the Chinese GMP Guide should also be briefly outlined. In the classification of clean rooms, only a limited analogy is made to the European GMP Guide Part I, Appendix 1.

Article 8
 A drug manufacturer to be established shall meet the following requirements: (1) having legally qualified pharmaceutical and engineering professionals, and the necessary technical workers;
 (2) having the premises, facilities, and hygienic environment required for drug manufacturing;
 (3) having the institutions and personnel capable of quality control and testing for drugs to be produced and the necessary instruments and equipment; and
 (4) having rules and regulations to ensure the quality of drugs.

Article 12
 Drug manufacturers shall perform quality tests of the drugs produced; no drugs that do not meet the national drug standards or that are not produced according to the processing procedures for the prepared slices of Chinese crude drugs formulated by the drug regulatory department of the people's government of the province, autonomous region, or municipality directly under the Central Government may be released.

Fig.1: Reference to quality control in Chapter II, Article 8 and 12 of the Drug Administration Law of the People's Republic of China, as translated [8].

Tab. 3: Requirements regarding environmental monitoring (from [7]).

Grade of air cleanliness	Maximum permitted number of particles / m ³		Maximum permitted number of microorganisms	
	ε 0.5 μm	ε 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

Tab. 4: Requirements of the EC-GMP Guideline regarding environmental monitoring (from [12]).

Grade of air cleanliness	Maximum permitted number of particles / m ³		Maximum permitted number of microorganisms	
	ε 0.5 μm	ε 5 μm	Air sample (cfu/m ³)	Settle plates (cfu/plate)
A	3,500	1	< 1	1
B	/	/	/	/
C	350,000	2,000	100	50
D	3,500.00	20,000	200	100

If you consider the clean room classification along with the hygiene requirements, it appears that, in addition to the absence of clean room Class B, another clean room class is given which, from the writer's point of view, can be taken as proof of the production of API.

Furthermore, in the consideration of microbial contamination and the number of particles, no further explanation is given as to whether the limits for clean rooms apply when in operation or when not.

In the opinion of the writer, the values shown would apply when not in operation and are therefore, it would seem, comparable with those of the FDA (Tab. 3, 4).

In connection with the following topic of personal hygiene, the Chinese GMP does not contain any requirements for microbiological inspection of staff, particularly as regards hands.

There is also no requirement for checking microbiological contamination using contact plates.

5.4 Personal Hygiene

For the production of pharmaceuticals and in particular products with special hygienic and microbiological requirements, such as e.g. sterile products, the European GMP Guide particularly emphasises conduct in the clean room and the associated training of staff.

Consultation of the corresponding Chinese GMP system of rules shows no sign of a correspondingly clear emphasis on hygienic requirements, knowledge and appropriate behaviour of staff in this connection.

Possible references or specifications can be found throughout the other chapters of the Chinese GMP requirements.

Audits are handicapped in that there are no precise requirements with regard to training or clothes and general conduct. The qualifications and level of training of staff can be questioned and evaluated only according to the product and situation.

5.5 Documentation

On the whole, identical requirements regarding contents and specifications for documentation are imposed in the two guidelines.

However, two interesting points need to be emphasised.

Firstly, the Chinese GMP rules detail the design and structure of regulations with specifications which are not to be found in the European requirements. Secondly, documents are directed to the quality management system which, according to the European specifications, should rather be attributed to quality control.

Here there is the idea again of a "quality unit" as required in the API rules and standards.

5.6 Marketing

The Chinese GMP rules have a special feature: there is a separate chapter on the marketing of pharmaceuticals, the explanation and specifications of which in Germany are only to be found in the Pharmaceuticals Act.

6. Current situation in China - revision of the guidelines

2007 was a very turbulent year for the SFDA. The former senior director, Zheng Xiaoyu, was executed for corruption in connection with falsified clinical studies [10]. More than 30 high-ranking SFDA members were also investigated. A regrouping within the SFDA was introduced under Shao Mingli, and a number of auditing procedures were initiated. The Pharmaceutical GMP Inspection Standards among others were subsequently revised, taking effect on 1.1.2008. The rules and standards underlying the stipulations for official inspections by the SFDA were expanded from originally 225 to 259 articles and the requirement for inspections of staff qualifications, production processes, quality control and validation documents was increased [11].

A revised draft version was also presented for the Good Manufacturing Guideline for Pharmaceuticals, which was extended from originally 88 to 343 articles (!) (for the first time the topic "Change Control" is also now taken up in the Chinese guidelines). When and in what final version this will actually be implemented is still unclear. However, there seems to be no intention to separate the guidelines according to separate GMP regulations for active pharmaceutical ingredients and finished pharmaceuticals. The complete adaptation of ICH Q7 for active pharmaceutical ingredients is therefore unlikely in the medium term.

7. Conclusion

The particular pharmaceutical contractor must satisfy himself about the implementation and the understanding of the relevant rules and standards in the individual companies and businesses in third countries before importing and using the product.

On closer examination of the SFDA-GMP Guideline however, the Chinese contractor complying with the rules and standards should be able to guarantee an acceptable quality of its products which corresponds to that of the European Union. Due to the huge number of Chinese production plants, estimated at 20,000, in the chemical and pharmaceutical sector, the careful selection and assessment of the quality level of the potential contractual partner has a fundamentally important role. Under no circumstances should this task be determined by economic aspects.

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Acknowledgement

The translation of the Good Manufacturing Guideline for Pharmaceuticals was kindly provided by the company Dolder AG. The translation from the Chinese was carried out by Shuqiao Zhang and Jason Ma (Dolder Shanghai), to whom we extend our thanks.

No liability is accepted for any mistakes in the English version.

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