Site Master File,

a competent regulatory document

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vorgelegt von

Susanne Rathmann aus

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Betreuer und 1. Referent: Dr. J. Hofer

Zweiter Referent: Dr. M. Baccouche

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1. Executive Summary

A Site Master File (SMF), also referred to as plant master file or site reference file, is prepared by the manufacturer and contains specific information about the quality management system in place, the production and/or quality control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of a pharmaceutical operation is carried out on the site, a Site Master File need only describe those operations, e.g. analysis, packaging, etc. Guidance on the preparation and set up is provided in the Pharmaceutical Inspection Co-Operation Scheme (PIC/S) Explanatory Notes for Industry on the Preparation of a Site Master File in the current version as of July 2004 (PE 008-2). PIC/S is a cooperative arrangement between health authorities whose purpose includes leading the international development, implementation, and maintenance of harmonised GMP standards and quality systems of world-wide pharmaceutical inspectorates.

The function of a Site Master File is to give the national regulatory authority inspector

- an introduction to the company and its activities,
- an indication that an appropriate quality system is in place,
- an information about the sites GMP compliance,
- and an indication that the site is “ready for inspection” prior to an inspection taking place.

Depending on national requirements a SMF is not required, can be either voluntary submitted or must be submitted to the competent authority.

The assessment of a SMF, if available, will be part of the inspection report. Therefore, the content should reflect brief, but comprehensive, current practice at the site. Preparation and maintenance of a SMF is a complex and even time consuming task, which requires co-ordination and resources. Based on the structure of a given company input from various departments is required. In this thesis two possible procedures for set up and maintenance of a Site Master File are introduced and a summary of possible advantages and disadvantages of both procedures is provided.

The question under which circumstances it is advisable for companies to prepare a SMF and under which circumstances it is advisable to better not to prepare a SMF is raised. As there are a lot of factors to take into account a decision analysis is performed. It is concluded that for global working companies there are more arguments for set up a SMF than against a SMF provided that a set up and maintenance strategy, laid down in a written procedure, is available.

The United Kingdom, Germany, the United States and Taiwan are selected as examples to illustrate different usage of a SMF in different regions.

2. Introduction

Good Manufacturing Practices (GMP) regulations require a quality approach to manufacturing, enabling companies to minimize or eliminate instances of contamination, mix-ups, and errors. This in turn, protects the consumer from purchasing a product which is not effective or even dangerous. Failure of firms to comply with GMP regulations can result in very serious consequences. Most countries will only accept import and sale of medicines that have been manufactured according to international recognized Good Manufacturing Practice standards [I2].

Dealing with GMP in the 21st century is still extremely cumbersome. GMP regulations and quality system expectations still differ between regions and countries. Although there is a need for pharmaceuticals companies to establish global supply chains and to work globally regulatory authorities still seems to work locally with respect to GMP [67].

Good Manufacturing Practices are in effect in several countries either implemented through national codes or drug laws, regulations (as in USA and Japan) or directives as in the European Union. Even if the national implementation differs the intent of authorities is the GMP to be strictly followed to consistently assure pharmaceutical product quality. That means for the regulatory authorities to approve efficacious and safe drugs of good pharmaceutical product quality as fast as possible, and to protect patients from unsafe or inefficacious drugs.

That means for the pharmaceutical companies that they can only be economically successful, when they produce products which are fit for their intended use, comply with the requirements of the marketing authorization and GMP and do not place patients at risks due to inadequate safety, quality or efficacy.

GMP-Inspections are on-site assessments of the compliance of manufacturers with the principles of GMP performed by officials (inspectors) of competent authorities. According to the definition of the WHO [72]: “Inspections are part of the overall drug quality assurance system. The objective of inspecting pharmaceutical manufacturing facilities is either to enforce Good Manufacturing Practice (GMP) compliance or to provide authorization for the manufacture of specific pharmaceutical products, usually in relation to an application for marketing authorization.”

Inspection and licensing of pharmaceutical manufacturing facilities are “a vital element of drug control” [72] to contribute to the protection of public health. Over the years the number of inspection per site has increased continuously. The challenge for industry is the different interpretation of the GMPs by all the inspectorates [67]. On the other hand the amount of time required for preparing, hosting and follow up of inspections is high for the manufacturing sites.

Especially the number of inspections from foreign Regulatory Health Authorities has increased dramatically. Figure 1 gives an overview about the number of inspections for one company site in between the years 2001 and 2006 [67].

A Site Master File is a tool to facilitate the inspection procedure when submitted to a regulatory authority prior to an inspection. The aim of a SMF is to demonstrate the company's compliance with GMP and giving a general overview about the facility and its operations.

Although it is not mandatory in the most countries to provide a SMF some pharmaceutical companies would prefer providing them to their competent authority on a voluntary base. Some countries will always request for a SMF some countries will not, this only depends on the national legal requirements. However, a SMF, if available, can assist and will be useful to the regulatory authority in planning and conducting of GMP inspections.

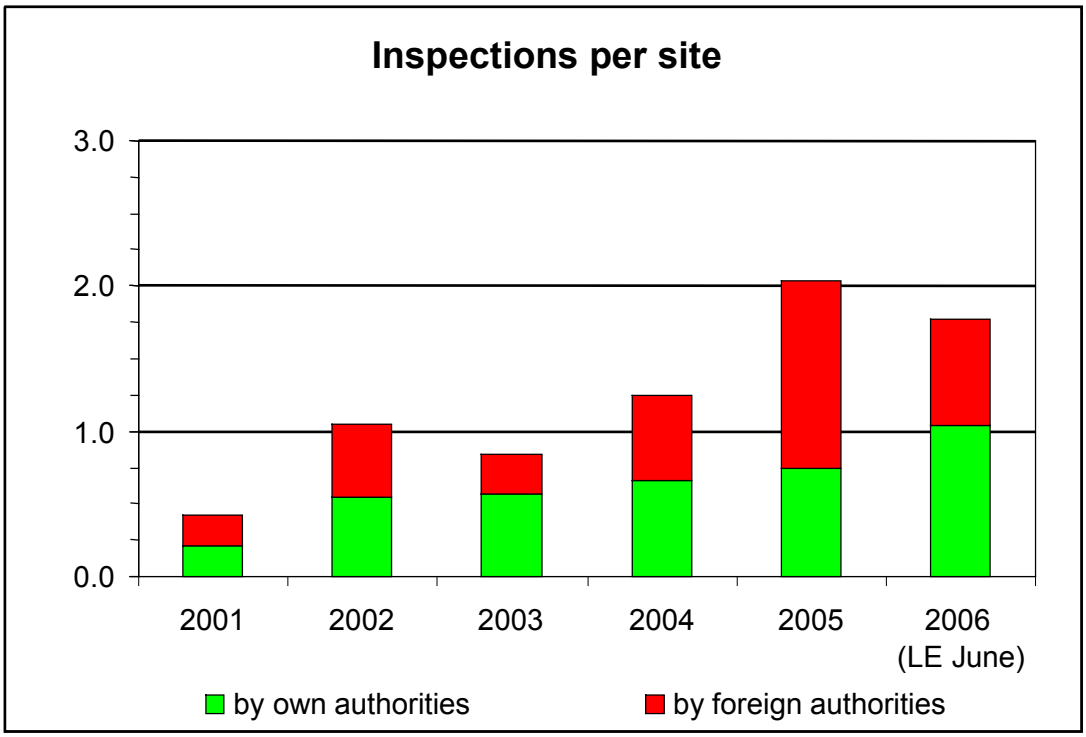


Figure 1: Number of inspections for one site between 2001 and June 2006 [67]

This master thesis examines the usefulness of a SMF and provides information about the background of GMP and the role of PIC/S. Furthermore it gives a definition of a SMF and introduces format and content. It is discussed under which circumstances a manufacturing site should consider to set up a SMF and under which circumstances it is better to not set up a SMF. A fictive decision analysis is performed to elucidate the decision making process. Finally a current overview about the use of a SMF in different regions (United Kingdom, Germany, United States and Taiwan) is provided.

3. Background GMP and PIC/S

3.1 Principle of GMP

Licensed pharmaceutical products (= products with a marketing authorization) should be manufactured only by licensed manufacturers (holders of a manufacturing authorization) whose activities are regularly inspected by competent national authorities [22].

Good manufacturing practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product. The main risks are: unexpected contamination of products, causing damage to health or even death; incorrect labels on containers, which could mean that patients receive the wrong medicine; insufficient or too much active ingredient, resulting in ineffective treatment or adverse effects. GMP covers all aspects of production; from the starting materials, premises and equipment to the training and personal hygiene of staff. Detailed, written procedures are essential for each process that could affect the quality of the finished product. There must be systems to provide documented proof that correct procedures are consistently followed at each step in the manufacturing process - every time a product is made.

The main GMP principle is the “principle of Quality assurance” which means:
“The holder of a manufacturing authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the marketing authorisation and do not place patients at risk due to inadequate safety, quality or efficacy. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality Assurance Incorporating Good Manufacturing Practice and Quality Control.
Good Manufacturing Practice (GMP) is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation or product specification” [6, 7].

In the late 1960s/early 1970s the WHO was the first international organisation who has established detailed guidelines for GMP. Many countries have established their own GMP requirements based on WHO GMP. Other countries have harmonized their requirements, for example in the Association of South-East Asian Nations (ASEAN), in the European Union (EU GMP) and through the Pharmaceutical Inspection Convention Scheme (PIC/S GMP).The PIC/S GMP Guide derived from the WHO Guide and was further developed in order to comply with stringent manufacturing and health requirements in PIC/S countries, to cover new areas (e.g. biologicals etc.). For a long time both guides remain equivalent but this is no longer the case, as the PIC/S GMP Guide has become more stringent than the WHO GMP Guide regarding e.g. sterile products (see table 1 for a comparison of the chapters of the PIC/S and the WHO GMP guides). In the late 1980s/early 1990s the PIC/S GMP Guide was adopted by the EU and further developed in close co-operation with PIC/S. Since that time, the EU and the PIC/S GMP Guide have been developed in parallel and whenever a change has been made to one, the other has been amended so that both Guides remains practically identical [14].

There is a slight difference in Annex 16, which has not been adopted by PIC/S and remains EU specific. Furthermore the expression “Qualified Person” does not exist under the PIC/S, it has been replaced by “authorised person” [7, 73]. (Regarding the structure of the EU GMP guide see Annex 5). However, PIC/S will strive to keep its GMP Guide equivalent in terms of GMP requirements with the EU GMP Guide and respectively equivalent to other GMP guides. Last up date of the PIC/S GMP guide was made in April 2007 because of a reorganisation of the PIC/S GMP Guide in Part I, Part II and Annexes with Incorporation of PE 007 (= ICH APIs guide Q7A) as Part II [63, 64].

The main problem of dealing with GMP is that GMP and quality system expectations still differ between regions and countries. It is often crucial that the wording in the guidelines or regulations left room for interpretation for both the regulatory authorities and the companies. On the other side there is always the need for the authorities to adapt GMP guidelines (regulations) on new technological and scientific standards. For example the EMEA Ad hoc GMP Inspection Service Group published in their work plan for 2007 [56] several planned amendments for the EU GMP guide e.g. an amendment to GMP introduction to reflect the implementation of ICH Q 9 (Quality Risk Management), an amendment to Chapter 1 to introduce quality risk management as part of the manufacturer’s quality assurance system, an amendment to Chapter 3 and 5 to finalise guidance on the need for dedicated self-contained facilities.

The same applies for the United States as for any other country as well. In August 2002 the FDA started a new initiative “pharmaceutical CGMPs for the 21st Century”. The intention was to integrate quality systems and risk management approaches into the existing programs with the goal of encouraging industry to adopt modern and innovative manufacturing technologies. This initiative was spurred by the fact that since 1978, when the last major revision of the CGMP regulation was published there have been many advances in manufacturing science and in the understanding of quality systems [46].

Furthermore the implementation of the ICH Q 9 guideline on quality risk management will change the GMP environment and need to be implemented into the GMP guidelines. In the EU it is currently under discussion to integrate this guideline into the EU GMP guideline [57].

The development of the ICH Q 10 guideline on pharmaceutical quality systems will have impact on the GMP environment and needs implementation in national guidelines and regulation as well once finally adopted. Adoption of Step 2 is expected in spring 2007 [58].

Table 1: Comparison Chapters SMF with EU/PIC/S GMP and WHO GMP for Medicinal Products

SMF	EU/PIC/S GMP	WHO GMP
Chapter 1: General Information	Chapter 1: Quality Management	Section 1: Quality Assurance (as described in quality manual)
Chapter 2: Personnel	Chapter 2: Personnel	Section 9: Organisation and personnel Section 10: Training Section 11 Personnel hygiene
Chapter 3: Premises and Equipment	Chapter 3: Premise and Equipment	Section 12: Premises Section 13: Equipment Section 3: Sanitation and hygiene Section 4: Validation
Chapter 4: Documentation	Chapter 4: Documentation	Section 15: Documentation
Chapter 5: Production	Chapter 5: Production	Section 16: Good practice in production Section 14: Materials
Chapter 6: Quality Control	Chapter 6: Quality Control	Section 17: Good practice in Quality Control
Chapter 7: Contract Manufacture and Analysis	Chapter 7: Contract Manufacture and Analysis	Section 7: Contract production and analysis
Chapter 8: Distribution, Complaints and Product Recall	Chapter 8: Complaints and Product Recall	Section 5: Complaints Section 6: Product Recalls
Chapter 9: Self Inspection	Chapter 9: Self-Inspections	Section 8: Self-inspection and quality audits

3.2 The role of PIC/S

The PIC/S is an informal arrangement between Regulatory Authorities, which exchange information on GMP inspections (including certificates) on a purely voluntary basis. PIC/S is the abbreviation and logo used to describe both the Pharmaceutical Inspection Convention (PIC) and the Pharmaceutical Inspection Co-operation Scheme (PIC Scheme) operating together in parallel.

PIC (Pharmaceutical Inspection Convention) was founded on 8 October 1970 by the Member States of the European Free Trade Association (EFTA) under the title “Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmaceutical Products. The main goal of the PIC Convention was to mutually recognise GMP inspections in order to facilitate the trade of pharmaceuticals. To understand the importance of PIC it is important to know that in those times national health authorities, including those from the EEC, were still exclusively competent for GMP inspections and little or no harmonisation had been made at the European level [14]. With the Treaty of Maastricht in 1992 the completion of the European Union was accelerated and on 2 November 1995 PIC Regulatory Authorities decided to establish a new co-operation instrument. This became necessary when it was realised that an incompatibility between PIC and European law did not permit individual EU countries that were members of PIC to sign agreements with other countries seeking to join PIC. Only the European Commission was permitted to sign agreements with countries outside Europe, and the Commission itself was not a member of PIC. Therefore, a less formal and more flexible cooperation scheme was developed to continue and enhance the work of PIC. Instead of being a legal treaty

between countries (i.e. like PIC), the PIC Scheme is a cooperative arrangement between health authorities [40].
PIC/S is a pioneer organisation in the field of harmonising inspection procedures worldwide and developed common standards in the field of Good Manufacturing Practice (GMP). PIC/S is currently a set of 30 Participating Authorities (PA) belonging to 29 countries. Additionally there are the following "Associated Partners" (previously called as "Observes" [66]): UNICEF, WHO and the EMEA (see Annex 3). In November 2006 PIC/S met for the first time with representatives of international industry and professional associations, i.e. EFPIA, FIP, IFPMA, ISPE and PDA [66].

The main goal of PIC/S is: "To lead the international development, implementation and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products and active pharmaceutical ingredients (API)". This is to be achieved by developing and promoting harmonised GMP standards and guidance documents; training competent authorities, in particular inspectors; assessing (and reassessing) inspectorates; and facilitating the co-operation and networking for competent authorities and international organisations [14].

The PIC/S has stringent rules regarding membership and expects new members to have an equivalent GMP inspection and Quality System in place. Regulatory Authority applying for PIC/S membership must use the PIC/S or EC GMP Guide before it can join PIC/S. The aim is to make PIC/S more of a global organisation rather than an European focussed one. Therefore, the focus is to expand membership.
PIC/S has also been a pioneer in developing a number of guidelines and guidance documents. So a Guide to Good Manufacturing Practice for Medicinal Products and special GMP Guides for example a GMP Guide for Blood Establishments has been published.

When searching for guidelines regarding set up and maintenance of a Site Master File the PIC/S publications are the state of the art and "current thinking documents" as PIC/S is the "think-tank" in respect to GMP [14]. The explanatory note for industry on the preparation on a Site Master File [3] is the main document which provides detailed guidance on set up and maintenance of a Site Master File. This guidance has been introduced as document: PH 4/93 in April 1993 [71]. The current version is PE 008-2 dated on 1 July 2004.

Furthermore PIC/S published guidance documents regarding "Site Master File for Plasma Warehouses" (PI 020-2) [12] and "Site Master File for Source Plasma Establishments" (PI 019-2) [13]. As these SMFs are specific for blood products and falling under a specific GMP guide (GMP guide for Blood Establishments) both SMFs are not discussed in this master thesis.

3.3 Regulatory Consequences

GMP guides and regulations left always some room for interpretation; therefore there is a need for harmonisation. The different interpretation of GMP by different inspectorates is a challenge for the industry. PIC/S will go ahead to work on global GMP harmonisation and to expand membership. Non-PIC/S authorities and organisations have a greater confidence in medicines manufactured in countries

where the Regulatory Authority is a PIC/S Participating Authority.

Consequences for the industry, when their relevant regulatory authority becomes a member of PIC/S are the following indirect benefits [14]:

- Reduced duplication of inspections.
- Cost savings.
- Export facilitation.
- Enhanced market access.

PIC/S effort to strengthen the cooperation with industry and professional association's is expected to improve the knowledge of inspectors and authorities with particular manufacturing process and new technologies and may lead to a more proactive cooperation.

4. Legal Framework EU/US/ROW

4.1 General Aspects

The following international guidance's applies (only legal requirements if locally adopted) [67]:

- Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (http://www.picscheme.org/indexnoflash.php).
- Norms, standards and guidelines for Quality Assurance: WHO (http://www.who.int/medicines/areas/quality_safety/quality_assurance/en/index.html).
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (www.ICH.org).

Providing a SMF to inspectors of competent authorities may be necessary in connection to:

- an application for a marketing authorization (or a renewal or variation);
- an application for a manufacturing licence;
- an application for importation of medicinal products;
- an application for a wholesalers licence (only if locally required);
- an application for a company registration (required mainly in Non-EU countries e.g. Gulf States: Jordan, United Arab Emirates);
- an application for a conformity certificate conforms to monograph of the Ph. Eur.

As a general rule manufacturers are advised to refer to national regulations whether it is mandatory for manufacturing of medicinal products, investigational medicinal products or active pharmaceutical ingredients to provide a SMF connected to the activities listed above.

4.2 EU: Inspections, GMP, Site Master File

Inspections

In the EU there is a common approach on inspections. Inspections performed by the national competent authorities are considered as equivalent and are on behalf of the whole Community. There is a common format for inspection reports, manufacturing authorisations and GMP certificates. National Authorities are responsible for issuing and supervising national authorisations, authorisation of clinical trials, authorisation and supervision of manufacturers, wholesale and importation in their territory.

The responsibility to perform inspections has the “Supervisory Authority” which is the Competent Authority of the Member State in which the product is either manufactured or imported, controlled and released for sale within the EU (Art. 18 of Regulation 726/2004) [34]. Art. 111 (5) of Directive 2001/83/EC require a GMP certificate to be issued to the manufacturer within 90 days of carrying out an inspection if manufacturer complies with GMP. Competent authorities have the power to carry out unannounced inspections (including inspections at the premises of marketing authorisation holders (Art. 111 of Directive 2001/83/EC, as amended by Directive 2004/27/EC). Authorities may also take samples of marketed products to test compliance with the authorised specifications. Currently national competent authorities routinely inspect all sites under their supervision no less frequently than once every three years.

Inspections are also performed in connection with the granting of a marketing authorisation by the Community (Pre-authorisation inspection) according Art. 8(2)/33(2)/19(3)/44(3) of Regulation (EC) 726/2004 or Art. 111(4) of Directive 2001/83/EC. Marketing authorisation applications or variations (to verify GMP status of manufacturer listed in the application) and a specific request arising out of the assessment of the Quality dossier (module 3) of application are triggers for such inspections. The EMEA has the co-ordinating role when a centralised product is involved. Where a manufacturing site is located in the EEA it is normally not necessary to request an inspection to confirm the GMP status as it is required by Directive 2003/94/EC to be regularly inspected by the relevant authorities. In case of a centralised procedure inspections usually take place in parallel with the “clock stop” period and will approximately be conducted within two months from the adoption of the inspection request. Inspectors finalise the reports and send to the EMEA inspections sector by day 180 at the latest, which circulate to the Rapporteur, Co-Rapporteur and CHMP.

Inspections are furthermore performed in connection with manufacturing authorisation according Art. 40 of Directive 2001/83/EC Art. 13 of Directive 2001/20/EC and Art. 4 of Directive 2003/94/EC. National competent authorities are obliged to ensure that all manufacturers of medicinal products (and investigational medicinal products), which included importers in their territories are subject to Manufacturing Authorisations. Certified release by a Qualified Person is mandatory in the EU. According to Art. 40 of Directive 2001/83 the manufacturer should have suitable and sufficient premises at his disposal. Manufacturers are obliged ”to give prior notice to their competent authority of any changes he may wish to make to any of the particulars supplied pursuant to Article 41”. Therefore it is necessary to up date the SMF if provided to a CA in the EU.

Inspections of manufacturers of the active substance are performed according to Art. 111(1) of Directive 2001/83/EC.

Inspections in third countries (non EU/EEA) are conducted when necessary e.g. when requested by the CHMP (Art. 19 of Regulation 726/2004). In case of inspections in third countries (non EU/EEA) the Supervisory Authority is responsible for supervision of manufacturer on behalf of the community. The Supervisory Authority is defined by the point at which the product enters the EU.
The existence of a Mutual Recognition Agreement (MRA) facilitates the exchange of inspection reports and reducing the need for foreign inspection. A MRA is the "appropriate arrangement" according to Art. 51 (2) of Directive 2001/83/EC made with the exporting country to ensure that the manufacturer of medicinal products applies GMP standards, which are "at least equivalent to those laid down in the Community". Fully operational MRAs are in place with Australia, Canada, Japan, New Zealand and Switzerland. The MRA with the United States is not in operation [34].

In the EU there are the following types of inspections [10]:

- **General GMP inspections** (also termed regular, periodic, planned or routine) should be carried out before a manufacturing authorization is granted. This kind of inspection may also be necessary for a significant variation of the manufacturing authorization and if there is a history of non-compliance.
- **Re-inspections** (also termed follow-up or reassessment) may be indicated to monitor the corrective actions required during the previous inspection.
- **Product- or process-related inspections** (also termed special or problem oriented) may be indicated to assess the adherence of the manufacturer to the marketing authorization dossier and the way the batch documentation is kept. It is also indicated when complaints and recalls may concern one product or group of products or processing procedures (e.g. sterilization, labelling, etc).

GMP

All medicinal products manufactured or imported into the Community, including medicinal products intended for export, must be manufactured in accordance with the legal requirements and guidelines relating to GMP. Compliance with these principles and guidelines is mandatory in the European Economic Area (EEA).

The legal basis for GMP for marketed products is provided in Title IV (manufacture and importation) and Title XI (supervision and sanctions) of Directive 2001/83/EC. This applies for all products authorised for marketing nationally, under the mutual recognition or decentralised procedures and for products authorised under the centralised procedure (Article 19 of Regulation (EC) No 726/2004 links to Directive 2001/83/EC).
The legal provisions relating to GMP were modified by Directive 2004/27/EC (amending Directive 2001/83/EC).

The legal basis for GMP for investigational medicinal products is Directive 2001/20/EC. In addition Directive 2005/28/EC details provisions relating to manufacture/import authorisations with respect to investigational medicinal products.

The GMP Directive for human medicines, Directive 2003/94/EC, details the principles and guidelines of GMP and is applicable to both marketed products and investigational medicinal products. The legal text is supplemented by guidance given in the Guide to Good Manufacturing Practice for Medicinal Products (Volume 4 of the rules governing medicinal products for human and veterinary use in the European Union) [6]. The Guide is presented in two parts: Part I covering basic requirements for medicinal products and Part II covering basic requirements for active substances and is identical with the ICH guideline for active pharmaceutical ingredients [4]. Annexes cover specific areas. The general structure of the EU GMP guide is provided in Annex 5.

The compilation of community procedures on inspections and exchange of information is maintained and published by the EMEA on behalf of the European Commission. It is a collection of GMP inspection related procedures and forms agreed by the GMP inspectorates of all the Member States to facilitate administrative collaboration, harmonisation and exchange of inspection-related information. Art. 3 of Directive 2003/94/EC require Member States to take account of these procedures.

At the date of accession the new Member States of the EU had to comply fully with all EU GMP requirements [34]. Table 2 summarises the main requirements relevant in the EU and provides as an example the implementation in Germany.

Table 2: Summary legal base in EU and in Germany

	Europe	**Germany**
Conformity with GMP	Dir 2001/83/EC Art. 46 (f) Dir 2003/93/EC Art. 4	§ 3 AMWHV
Compliance with Marketing Authorisation	Dir 2003/93/EC Art. 5	§ 13 (2) AMWHV
Manufacturing Authorisation (Licence) for MP	2001/83/EC Art. 40	§ 13 (1) AMG
Import of MP	2001/83/EC Art. 40	§ 72 (1) AMG
Wholesale of MP	2001/83/EC Art. 77	§ 52 a AMG
Quality Assurance System	Dir 2003/93 Art. 6	§ 3 AMWHV
Inspection Authorisation MP	Dir 2001/83/EC Art. 111 (5)	§ 25 (5) AMG pre-approval inspection

Manufacturers of the active substance and manufacturers of medicinal product are falling under different GMP and legal requirements in the EU. The differences are summarised in table 3. The different requirements must be reflected in the SMF as well and should be taken into account when preparing a SMF.
According to Art. 46 and 46a of Directive 2001/83/EC active substances must be manufactured in accordance with GMP, but a manufacturing licence for active substance manufacturers is not required. The batch release/ manufacturing site of the finished product has the responsibility to ensure and declare that their suppliers of the active substance comply with GMP requirements. Art. 46 of Directive 2001/83/EC apply also for “certain excipients”.

Directive 2004/27/EC provide for a database on manufacturing and import authorisations, GMP certificates and non-GMP compliance information, currently under development as the EudraGMP database [I19].

EudraGMP will contain information on all manufacturing and importation authorisations and GMP certificates issued by EEA competent authorities. It is expected that EudraGMP database will facilitate best use of resources and help to avoid duplication of inspections in particular in third countries.

Table 3: Comparison requirements for API and medicinal products in the EU

Requirement	Finished products	Active ingredients
Manufacturing Authorisation	Manufacturers should be authorised (Art. 40 Dir 2001/83) by CA of the Member States	Manufacturers not submitted to authorisation except in some member states and for certain activities (e.g. biological or sterile API)
Release	By "Qualified Person"	By specified authorised person
GMP	Principles laid down in Directive 2003/94	Principles not laid down in a Directive
	Requirements described in Part I of Volume 4 of the EU Rules Governing Medicinal Products	Requirements described in Part II of Volume 4 of the EU Rules Governing Medicinal Products
	Mandatory adherence to GMP (Art. 46 (f) Dir 2001/83)	Mandatory adherence to GMP (Art. 46 (f) + 46a Dir 2001/83) but under the responsibility of the Finished Product Manufacturer
Verification of GMP compliance	Shall be ensured by means of repeated inspections (Art. 111 Dir 2001/83 and Art. 3 Dir 2003/94), routinely every two to three years	Either by verification of the way the Finished Product manufacturer has ensured API's manufacturer compliance with GMP Or by inspection which may be carried out on a case-by-case basis with a risk-based approach (Art. 111 Dir 2001/83)
	CA issues manufacturing authorisation and GMP certificate (after each satisfactory inspection)	In case of satisfactory inspection, CA issues GMP certificate
	Inspection do not replace manufacturers obligations to comply with GMP	Inspection do not replace manufacturers obligations to comply with GMP
Global requirements	EU GMP requirements (Dir 2003/94 and Volume 4 of Rules governing Medicinal Products) specific to EU	ICH Q7A guideline. This guideline is implemented as Part II of Volume 4 of EU Rules
	Some technical differences with US-FDA and Japan MHLW	Same technical requirements PIC/S, US, Japan
	Products manufactured outside EU should be imported through a EU side authorised by its competent authority ("supervisory authority")	No further requirements if manufactured outside EU
	Testing in the importing site	Importation under the responsibility of the Finished Product manufacturer
MRAs with EU	Australia, New Zealand, Canada, Switzerland and Japan	Australia, New Zealand and Switzerland
Scope of GMP and manufacturing authorisation	Scope = any part of the manufacture of the medicinal product	Scope = only manufacture from the defined "starting material"
	Authorisation required for import, export only, total and partial manufacture, dividing up, packaging or presentation	Manufacture includes "total and partial manufacture, import, dividing up, packaging, presentation, repackaging and relabelling"

(modified after [29])

Site Master File

A SMF may be prepared to facilitate the inspection procedure. It is not required to submit a Site Master File to the EMEA [10, I9]. The EU Commission produces a draft guideline regarding a format for a European Site Master File in 1997 but this guideline was never adopted [9, 34]. Although the document has not been adopted it may be used as a guide regarding set up of a SMF in the EU.
Regarding GMP inspections during the assessment of a marketing authorisation application the following is mentioned on the EMEA homepage [I9]:
"It is helpful to have a site/plant master file for use in preparing and carrying out the inspection. The preferred format is that recommended by the Pharmaceutical Inspection Co-operation Scheme (PIC/PICS). The Applicant should supply this document directly to the Inspection Team as far in advance of the inspection as possible. The site/plant master file is however not required to be submitted to the EMEA".

Once the CPMP or CVMP has requested an inspection and the inspection team has been agreed the EMEA notifies the applicant that an inspection will take place. An example for a report to the CVMP was found in the EPAR of Fevaxyn Pentofel (a veterinary product) [I10]:

"The Committee expressed concerns relating to the production of the vaccine at the manufacturing site in Ireland. Specifically, information was requested on how to avoid the potential risk for cross contamination of the ventilation system between different campaign productions, and measures were required to ensure cleaning validation between campaign production. Documentation relative to all these points was made available in the Plant Master File for the manufacturing site; to the satisfaction of the CVMP".

If provided to the Competent Authority the assessment of a SMF will be part of the inspection report. "A report prepared for communication to another Member State or a community body (e.g. CPMP) should include the general information of the company which may be based on the information based on the information contained in an up-to-date Site Master File prepared by the company and agreed by the inspector."[10]. In the compilation of the community procedures it is also mentioned that the SMF may be added to the inspection report if considered necessary.

A SMF can also be required in connection with the verification of the GMP status of manufacturers in third countries [10]: "If necessary written questions arising from a review of this may need to be raised and the responses reviewed." If the last EEA inspection is more than five years ago a SMF is to be completed/updated within six months from the assessment date. If the last EEA inspection has been carried out between three and five years ago a SMF is to be updated with one year from the assessment date. Coloured printouts of water treatment, air handling and drawings should be attached in A3 or A2 format.

When performing joint audit programmes for EEA GMP inspectorates a Site Master File/Reference File (if available) may also be requested by the inspectors and copied to the observing audit team [61].

In the EU a SMF is considered as a helpful tool in order to support the inspection process, but it is not mandatory to have available a SMF.

4.3 US: Inspections, GMP, Site Master File

Inspections

Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) requires that new drugs be approved by FDA. The Federal Food, Drug and Cosmetic Act (FD&C) also provides that all imported drugs are required to meet the same standards as domestic products under 21 U.S.C. 381. Any product that is found in violation of FDA laws and regulations is subject to Refusal of Admission. Applicable Code of Federal Regulation is 21 CFR Part 1, Subpart E: Imports and Exports [51].

The FDA introduced a system-based approach when conducting an inspection [47]. In a drug establishment six (6) systems were identified for inspection. The Quality system and the five manufacturing systems: Production; Facilities and Equipment; Laboratory Control; Materials and Packaging and Labelling. It is important to understand this system because it reflects the subchapter structure of the CGMP regulation which is different from the EU, PIC/S or WHO GMP guideline (see Annex 6). In general there are the following types of inspection [78]:

- Periodic (biennial) comprehensive cGMP inspection.
- Pre-Approval Inspection (PAI).
- For cause inspection.

According to the Federal Food, Drug, and Cosmetic Act the FDA has to inspect domestic drug manufacturing establishments at least once every 2 years. But the FDA recognised that there are not enough FDA resources available to inspect every aspect of cGMP during every inspection visit [47]. Therefore since 2005, a risk-based inspection model for prioritizing drug manufacturing establishments for routine inspection applies. The full inspection option includes coverage of at least four of the systems, the abbreviated inspection option covers of at least two systems. However in both options the Quality System must be one of the systems to be selected for inspection. At the end of the inspection the so called “form FDA 483 Inspectional Observations” is presented and discussed. Form 483 is intended to inform the manufacturer’s management in writing about significant objectionable conditions, relating to products and/or processes, or other violations of the FD&C Act and related Acts, which were observed during the inspection. An inspection report (here called “Establishment Inspection Report” = EIR) is written by the FDA inspector and send to the manufacturing site. Results of inspections are classified as: NAI (No Action Indicated), VAI (Voluntary Action Indicated) or OAI (Official Action Indicated).

An inspection report that documents that one or more of the six systems is/are out of control is classified as “OAI”. A system is considered as out of control based on GMP deficiencies which suggest a lack of assurance of quality [78]. In this case the FDA may issue a “Warning Letter” to address that an action for the site is required. Warning letters are posted on the FDA web page [I21]. Sites have 15 days response time to a warning letter. Failure to correct the violations listed in a warning letter may result in FDA regulatory action without further notice for example to injunction, seizure or prosecution.

Foreign companies are not obliged to comply with the US regulations except for the commitments in applications filed with the FDA and/or the import of their products in the US. Imported products are required to meet the same standards as domestic products under 21 U.S.C 381 [51]. The FDA has the authority under the FD&C Act to

administratively restrict the importation of a product without demonstrating the adulteration [75]. Regarding the inspection authority see chapter 6.3.1.

GMP

All drugs must be manufactured in accordance with the current good manufacturing practice regulations otherwise they are considered to be adulterated within the meaning of the FD&C Act, Section 501(a) (2) (B). GMP is laid down in the Code of Federal Regulations (see chapter 6.3.2).

An API is not considered by FDA to be an “approvable” drug. But the API must be from an approved source. This is generally accomplished by the submission of a Drug Master File to FDA that is referenced by the holder of an approved New Drug Application for use in their product. For API’s the ICH Q7A guideline “Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients” applies.

Site Master File

A Site Master File is not required in the USA (see chapter 6.3.3 for more details). Due to the specific structure of the cGMP regulation it is difficult to assign the cGMP sections to the SMF chapters of the PIC/S guideline (see table 4). However, as the FDA is seeking for PIC/S membership an FDA GMP Harmonisation Working Group, which had the task of comparing CGMP against EU GMP and PIC/S GMP, finally came to the conclusion that: “there are many more similarities than differences among the various regulations…. “[76].

Table 4: Comparison SMF Chapters with subparts of cGMP of CFR part 211

SMF chapter	**Section in CFR cGMP regulation**
C.1 General Information	Not applicable
C.2 Personnel	Subpart B –Organization and Personnel 211.22, 25, 28 and 34
C.3 Premises and Equipment	Subpart C Buildings and Facilities 211.42, 44, 46, 48, 50, 52, 56 and 58 Subpart D Equipment: 211.63, 65, 67, 68 and 72
C.4 Documentation	Subpart J Records and Reports 211.160, 165, 166, 167, 170, 173 and 176
C.5 Production	Subpart E Control of Components and Drug Product Containers and Closures 211.80, 82, 84, 86, 87, 89 and 94 Subpart F Production and Process Controls 211. 100, 101, 103, 105, 110, 111, 113 and 115 Subpart G Packaging and Labelling Control 211.122, 125, 130, 132, 134 and 137 Subpart K Returned Product and Salvaged Drug Products 211.204 and 208
C.6 Quality Control	Subpart I Laboratory Controls 211.160, 165, 166, 167, 170, 173 and 176
C.7 Contract Manufacture and Analysis	Subpart B –Organization and Personnel Consultants 211.34 Outsourcing 211.22 (a)
C.8 Distribution, Complaints and Product Recall	Subpart H Holding and Distribution 211. 142 and 150
C.9 Self Inspection	Not implemented in CFR

4.4 ROW: Inspections, GMP, Site Master File

Inspections

Inspection procedures vary between countries and regions therefore please refer to appropriate national legislation regarding inspections.

GMP

The implementation of GMP varies between countries and regions therefore please refer to appropriate national requirements regarding GMP.

Site Master File

Many countries have adopted the PIC/S Guide for a SMF like South Africa [19], and Taiwan or they have their own SMF guideline like Canada [8]. But Canada would also accept the PIC/S format. Singapore published a special guidance note for preparation of a Site Master File for Good Distribution (GDP) certification [62]. This is amazing because there is no PIC/S guide for GDP available as the PIC/S has not yet adopted common standards regarding GDP.
Depending on national legislation it may be required to provide a SMF or not. Therefore, reference to appropriate national requirements is made whether it is mandatory to prepare a SMF. Different examples are:

- United Arab Emirates and Jordan: according to company internal experience a company registration is required for manufacturers of pharmaceutical products. A “Company Registration Form” has to be filled in and a SMF has to be provided. In Jordan the SMF is considered as a reference to pre-approval inspection.
- India: according to “The drugs and cosmetics Act, 1940 as amended” the applicant is required to ”prepare a succinct document in the form of Site Master File containing specific and factual Good Manufacturing Practices about the production and/or control of pharmaceutical manufacturing preparations carried out at the licensed premises“ in order to get an import license [11].

5. Definition, Content, Set up and Maintenance of a Site Master File

5.1 Definition

In the explanatory notes for industry on the preparation of a Site Master File PIC/s Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-Operation Scheme, PE 008-2 [3] the following definition of a SMF is given:

“The Site Master File is prepared by the manufacturer and contains specific information about the quality management system in place, the production and/or quality control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only

part of a pharmaceutical operation is carried out on the site, a Site Master File need only describe those operations, e.g. analysis, packaging, etc".

A Site Master File is therefore a comprehensive company description demonstrating the compliance of a manufacturer of a medicinal product, veterinary medicinal product, investigational medicinal product or a manufacturer of an active pharmaceutical ingredient (= active substance) with Good Manufacturing Practices (GMP) requirements. A SMF is even called as Plant Master File or Site Reference File [8, 61] and provides details of the manufacturing facility, equipment and procedures and should contain sufficient information to give the reader a good idea of what the facility looks like, the type of manufacturing processes carried out in it and the type of quality assurance processes in place.

When submitted to a regulatory authority prior to an inspection, the Site Master File can be useful in the efficient planning and undertaking of a GMP inspection. The purpose of the SMF is to provide the Inspector with an introduction to the company and its activities prior to the inspection taking place and to demonstrate to the Inspector that the site is ready for the inspection and has put a quality system in place. The inspector would use it as a reference document only and would not modify it.

As a demarcation to a Quality Manual a Site Master File reflects the chapters of the GMP guidelines. A Quality Manual describes ("only") how site procedures and processes interact to accomplish the objective of the site's quality system.

A Quality Manual must include the following [59]:

- Introduction about the organisation concerned and an outline of the structure of the quality manual or quality system documentation.
- The organisations quality policy.
- The quality policy and objectives of the organisation.
- A description of the organisational structure, responsibilities and authorities.
- A description of the elements of the quality system and any reference to documented quality system procedures.

5.2 Format and content of a Site Master File

Current guidance regarding a Site Master File can be found in the PIC/S explanatory notes for industry on the preparation on a Site Master File [3]. The structure of the PIC/S guidance note is that each chapter and the paragraphs noted under requirement are followed by "guidance" which provides details on how the requirements should be interpreted (see Annex 1 and 2).

As mentioned in chapter 5.1 in a SMF the facility demonstrates the inspector that it does comply with Good Manufacturing Practices (GMP) requirements. Therefore the chapters covered in the SMF reflect the chapters of the GMP guidelines (see table 1 and 4).

The SMF must contain, at a minimum, the following sections, as applicable to the activities performed at the site:

- General Information.
- Personnel.
- Premises and Equipment.
- Documentation.
- Production.
- Quality Control.
- Contract Manufacture and Analysis.
- Distribution, Complaints and Product Recall.
- Self Inspection.

A Site Master File should be succinct, should follow the current version of the PIC/S guide and, as far as possible, not exceed approximately twenty-five to thirty A4 pages. The amount of information provided should be relevant to the type of product being made. The content must be entirely non-promotional. A Site Master File should have an edition number and an effective date.

The SMF should be designed to be easily up-dated as the inspector will require an updated version prior to inspection. Wherever possible, simple plans, outline drawings or schematic layouts should be used instead of narrative. These plans etc should fit on A4 sheets of paper. A deliberate limit has been set on the length of the narrative of some sections [3].

5.3 Set up and maintenance of a Site Master File

A SMF must adequately reflect current practices at the site. The content is not limited to the items recommended in the PIC/S guidance notes. For example a description of the pest control system is not required but it may be useful to describe it because it is a general GMP requirement. The PIC/S document is a guideline and is therefore not legally binding. As stated in the purpose section of the PIC/S document it provides assistance to manufacturers in the preparation of a SMF and helps the pharmaceutical industry to comply with the requirements. If not otherwise requested by the national competent authority a manufacturer is not required to use the same format and content as provided in the PIC/S guideline.

For example in the EU the PIC/S format is to be used [I9]. It can be recommended to contact the competent authority and to ask for specific requirements regarding set up and content of a SMF. If specific national requirements do exist it may be necessary to modify the content and format to follow the national obligations.

From company internal experiences it can be recommended to set up the SMF in such a way that each chapter starts on a new page. This enables effective updating and that pages can be easily replaced, if necessary. In general the format and heading of the SMF should follow those given in the PIC/S guidance notes.

The heading can be structured in the following two ways:

1) Requirements only:
   The text outlined under each chapter cover each point of the requirements and guidance sections without a sub numbering system.

2) Requirements with sub numbering system of guidance section:
   The text outlined under each chapter is separated and cover the requirements and the guidance section by using the sub numbering section of the PIC/S guidance section.

The draft guideline on a format for a European Site Master File prepared by the European Commission [9] contains several tables which may be useful for individual structuring of a SMF.

The assessment of a SMF, if available, will be part of the inspection report. In the EU the National Competent Authorities routinely inspect all sites under their supervision no less frequently than once every 3 years. Therefore standard operating procedures of a company should be in place ensuring that the SMF is revised on an appropriate periodic basis. It can be recommended that revisions should be performed once a year or at least every two years. However, in every case an up dated version should be available prior to an inspection. If available, a SMF is part of the Quality Assurance System of a company.

Normally the QA department will be the owner of the document and will be responsible for set up, maintenance and approval of the SMF, but this may be handled different in different companies. Often the responsibility is delegated to the regulatory affairs department as the SMF is a competent regulatory document.

Challenge of set up and maintenance is that different departments are involved and their input is required. So the identification of the departments and individuals involved is a critical and important step in the creation of the document.

The following departments may be involved:

- General Management.
- Quality Assurance.
- Complaints (if not part of the QA department).
- Production.
- Quality Control.
- Warehouse and Distribution.
- Regulatory Affairs.
- Human Resources.
- Maintenance and Site Services.
- Engineering.

This extensive list of involved departments shows the interdisciplinary scope of the task which needs co-ordination. Therefore it may be necessary to assign a “SMF Document Coordinator” responsible for set up and maintenance of the SMF.

The SMF Document Coordinator will be responsible for starting and coordinating the whole process. The SMF Document Coordinator contacts department representatives to supply informational content as required by the current version of the PIC/S guideline. The SMF Document Coordinator can be either a staff member of

the QA department or a staff member from the Regulatory Affair department.
In the following two possible procedures will be described which may be appropriate to manage the set up of a SMF. With slight modification these procedures can be used for the periodic review as well. In both scenarios the procedure is a two step process: a first review step is followed by a final approval step.

Appropriate reviewers for the review step might be the involved department managers, Site Quality Manager and Site Regulatory Affairs Manager.
Appropriate persons for the approval step might be: General Manager; the head of the Quality Assurance department, the Head of the Quality Control department, the Head of Production, the Qualified Person (in the EU), the Head of the Regulatory Affairs department, and if applicable the Responsible Person for Wholesale.

The final approval of the document by dated signature by the approvers indicates that the appropriate personnel have reviewed the SMF and that the SMF adequately reflects current practices at the site.

Procedure 1:

The procedure can be summarised as follows (see also figure 2):

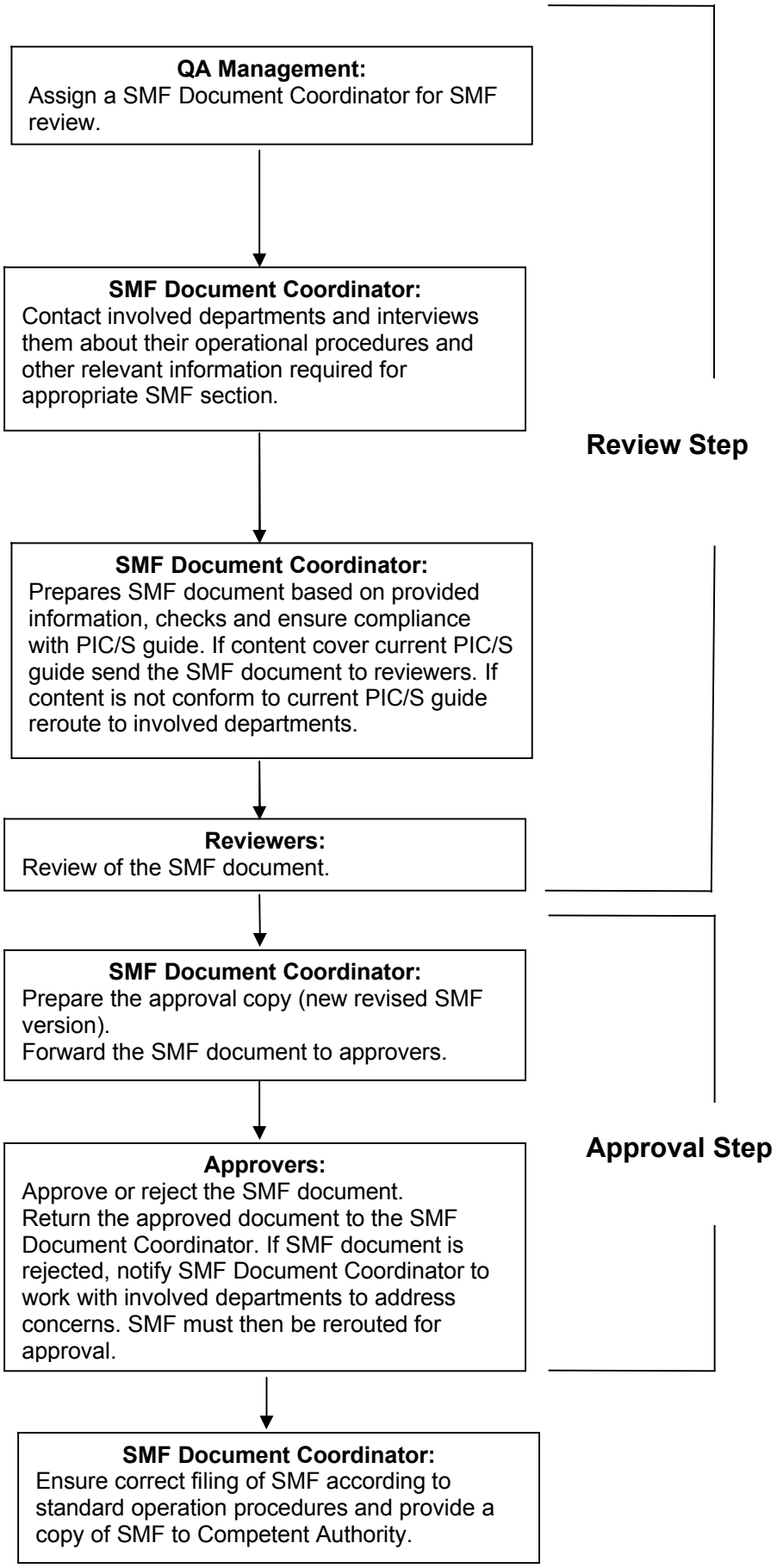
Step 1 (Review Step):

- The head of the QA department assigns a SMF Document Coordinator for set up (review) of the SMF document. The SMF Document Coordinator has to ensure that the required content is collected and formatted according to the current version of the PIC/S guidance document “Explanatory Notes for Industry on the Preparation of a Site Master File” found at http://www.picscheme.org.
- The SMF Document Coordinator contacts the designated department representatives for which content data is provided and interviews them about their operational procedures and other relevant information required for the appropriate SMF section according to PIC/S guideline. The involved departments will provide the required information and in addition maps or schematic drawings if necessary.
- The SMF Document Coordinator prepares (revises) the SMF document based on the interviews with the involved departments and according to the current PIC/S guide.
- The SMF Document Coordinator sends SMF document to designated reviewers, who review the document for accuracy and completeness. Finally the SMF Document Coordinator prepares the SMF document for the approval step.

Step 2 (Approval Step):

- The SMF Document Coordinator sends the SMF document to the approvers.
- The approvers will then approve or reject the SMF document. If the SMF is rejected the approvers notify the SMF Document Coordinator to work with involved departments to address the concerns. The SMF must then be rerouted for approval.
- After receipt of the final approval the SMF Document Coordinator will ensure the correct filing of SMF according to standard operation procedures and provide a copy of the revised SMF to Competent Authority.

Figure 2: Procedure for SMF set up and review according to procedure 1



Procedure 2:

This procedure is similar to procedure 1 and follows also two steps; a review and a final approval step (see figure 3).

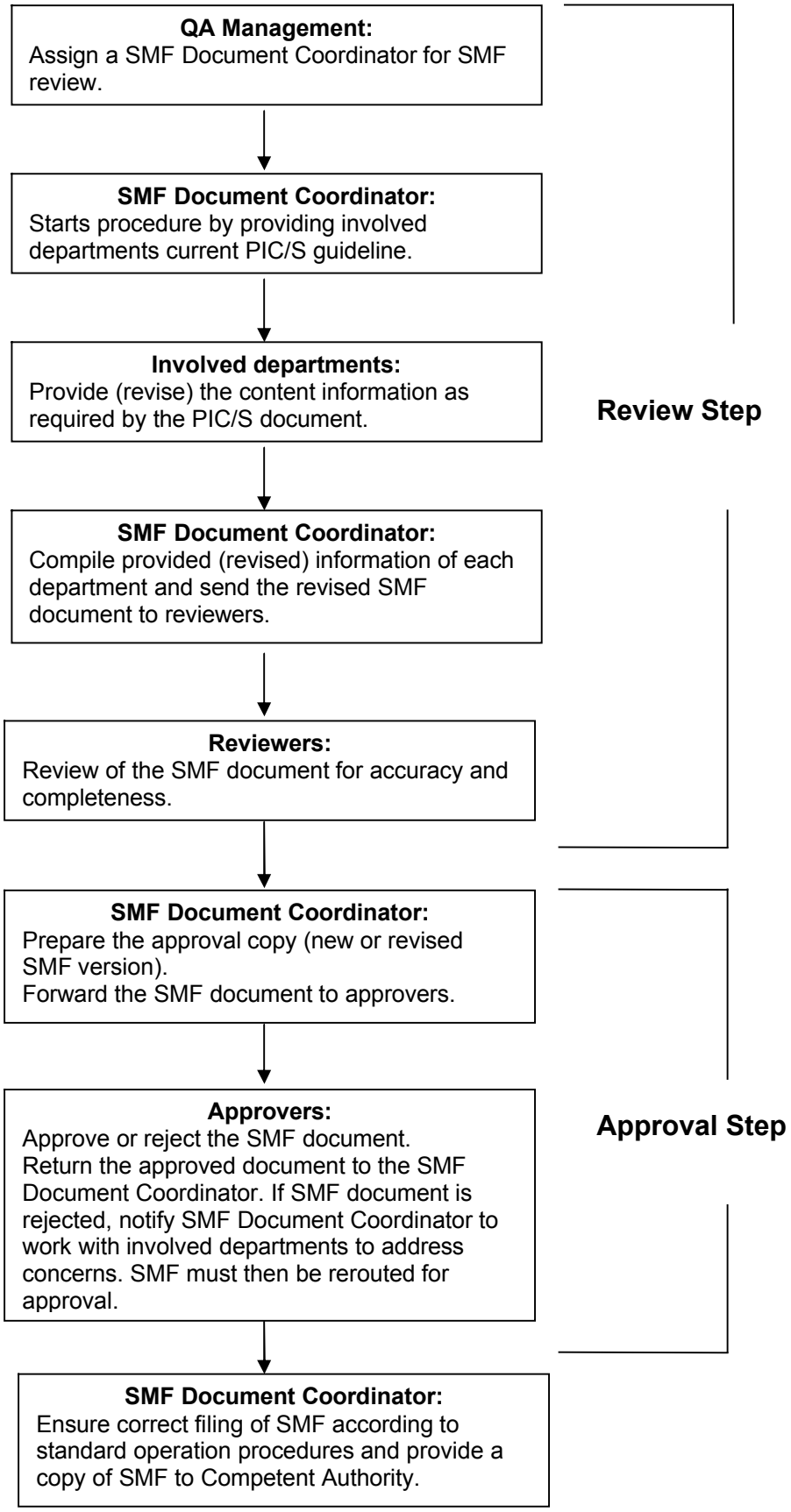
But in this procedure the SMF Document Coordinator is not responsible for checking the compliance of the SMF with the current PIC/S guide. The SMF Document Coordinator provides each department the current PIC/S guideline. Each involved department is responsible for preparation of their section and to make sure that the content is in accordance with current PIC/S guide. The whole SMF is prepared (checked) by the involved departments and not by the SMF Coordinator as in procedure 1.
The SMF Document Coordinator will then compile the information and send the SMF document to the reviewers. The reviewers will check the SMF document for accuracy and completeness. After this review step the process is similar to that of procedure 1.
A slight modification of procedure 2 is in place as company internal Standard Operating Procedure for preparing and maintaining the SMF document.

A comparison of the advantages and disadvantages of both procedures is provided in table 5 below.

Table 5: Comparison advantages/disadvantages of both procedures

Advantages/ Disadvantages	**Procedure 1**	**Procedure 2**
Advantages	➢ content unified and consistent ➢ time-saving for involved departments	➢ detailed department knowledge ➢ time required for set up and maintenance is lower
Disadvantages	➢ potential lack of detailed department knowledge ➢ high workload for SMF Coordinator ➢ time required for set up and maintenance is high	➢ non-unified content and effort may be required to make it consistent ➢ time-consuming for involved departments

Figure 3: Procedure for SMF set up and review according to procedure 2



5.4 Site Master File: a decision analysis

Both set up and maintenance procedures introduced in this master thesis demonstrate that set up and maintenance of a SMF is a quite complex task, which requires co-ordination and resources. The question is: should a manufacturing site of a company invest time and resources to prepare a SMF or not?

At the beginning of such a decision a realistic evaluation of the needs is required. This is a “go” or “no-go” decision (see figure 4). If a site works national only and the competent authority does not want a SMF it makes no sense to prepare one and to provide it to the competent authority. But if the site plans to work globally or perform contract manufacturing for a company which needs a SMF from the manufacturing site in order to support international marketing authorisations or import activities it may be considered and can turn to a go-situation (this option is marked by the “(?)” in figure 4).

A global working company and/or if additionally the competent authority requests a SMF and/or it can be expected that there is a need to submit a SMF in connection with international marketing authorisations or import activities in these cases it may be considered to set up a SMF.

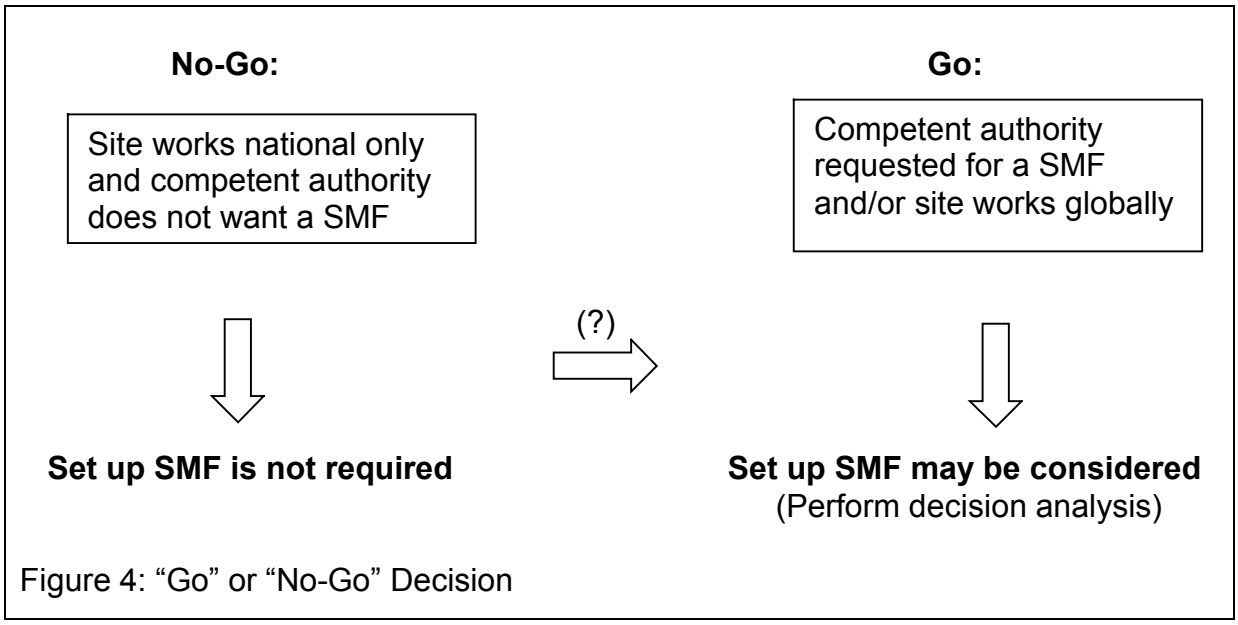


Figure 4: “Go” or “No-Go” Decision

When a company considers setting up a SMF it may be helpful to perform a decision analysis and to write down and weight the criteria to consider (see figure 5). The following criteria may be considered:

- Optimisation of the inspection process.
- Quality Assurance by continuous self-inspection.
- International harmonised site presentation.
- Co-operation of the involved departments.
- Cost/resources balance.

A fictive but realistic weight for each criterion can be found in the third column of figure 5, but this may be modified according to individual decision analysis.

In general it is necessary to differ between “must”-criteria (measurable, realistic or mandatory criteria) and “wants”-criteria (desirable criteria). A “must” criterion is “Quality Assurance by continuous self-inspection” because it is a GMP requirement. A “must” criterion has to be fulfilled in each option. If not this is again a “No-Go” decision for one option. All the other criteria are “want” criteria in this analysis.

The must criterion has to be transformed to a “want” criterion in order to assign the weights. 5 is the highest weight which indicates the highest priority; 1 is the lowest weight and indicates the lowest priority.

After the weighting it is necessary to score how well each option satisfy each criteria (column 4 and 6 in figure 5). The multiplication of each score by the “weight for criteria” provides the relative weight for each criterion. Finally the sum of the weights for each option has been added up. The highest result (total sum) shows the best option. In this fictive example this is option “SMF: Yes” with a total sum of 39.

This is amazing because the cooperation of the departments and costs/resource balance have a high score for the option “SMF: No” (mean no SMF: no additional costs and no complication with cooperation of departments). This is completely compensated by the high weight for the criterion “optimisation of the inspection process” as this is the main advantage of a SMF. The criterion “quality assurance by continuous self-inspection” has been scored identical in both options because it is not possible to judge on a theoretical base.

		Option	**SMF: Yes**		**SMF: No**	
Criteria	**Must/ Want**	**Weight for criteria**	**Score**	**Weight**	**Score**	**Weight**
Optimisation of Inspection process	W	5	3	15	1	5
Quality Assurance by continuous self-inspection	M	4	3	12	3	12
International harmonised site presentation	W	3	3	9	1	3
Cooperation departments	W	2	1	2	3	6
Costs/Resource Balance	W	1	1	1	3	3
Total Sum				**39**		**29**

(Score: 1 = low; 2 = middle; 3 = high)

Figure 5: Fictive Grid Analysis (Decision Matrix Analysis)

To find out the best balanced choice for the question “SMF yes or no” it is necessary to examine also the risks (adverse consequences) associated with each option.
Two examples taken from “real” inspection reports will show the possible outcome of a SMF assessment during an inspection:

1) Result from a company internal EMEA inspection report of a Non-EU facility:
“The Site Master File of XXXXX is not completely in compliance with European standards since it does not have schematic representation of water treatment system and air treatment system. It presents only a few unreadable maps without any information about the Grade classification, the confinement state and the realized operations for each room and it has not been updated regarding changes in organizational chart.”

2) Final FOI Inspection Report of Cobra Biologics Ltd., UK [55]:
Assessment of the Site Master File: “The Site Master File appears to be satisfactory and was recently updated.”

Consequently the main risk associated with set up and maintenance of a SMF is a major inspection finding which can be either that the SMF is not up to date or that the content is not GMP compliant. If the company has no appropriate set up and maintenance strategy the probability for this adverse consequence can be judged as high and the seriousness can be judged as very serious. The probability of getting a major inspection finding can be decreased by the following risk reducing actions:

- Perform set up and maintenance according to written procedures;
- Use only current PIC/S guide for set up and review procedure;
- Assign a SMF Co-ordinator and fix responsibilities;
- Make sure that General Management supports intention to prepare a SMF;
- Inform General Management if involved departments impede set up of a SMF or should have too many objections against the whole procedure.

A special attention should be paid that the provided maps, schematic drawings, organizational charts and CVs (if provided) are correct and kept up to date. In the PIC/S AIDE-Memoire: Inspection of Utilities [60] it is mentioned that the inspector confronts differences between design specifications, drawings (in SMF) and reality during the walk round tour.
By describing how the facility operates a SMF builds a holistic picture of the whole company and when kept up to date it provides helpful information and assures an international harmonised presentation of the site. From company internal experience a SMF, or reference to a SMF, is also used to answer to specific questions and questionnaires of regulatory authorities. In one case a SMF has been accepted to answer to a specific question raised by one regulatory authority instead of an inspection.
While preparing and revising a SMF companies may find it also useful to identify gaps in their system (= criterion continuous self-inspection). For new employees of a company it can be also helpful in making familiarise with the site.

Taking into account risk reducing actions and the results from the grid analysis there are more arguments for set up a SMF than against a SMF. However, if a company decides to prepare a SMF it is mandatory to establish a written set up and maintenance strategy. A SMF which is not kept up to date is neither helpful for the inspector nor the company. Only in this case it is advisable to better not to provide a SMF to the competent authority.

6. Selected Examples

6.1 EU: United Kingdom

6.1.1 Authority and Inspections

The licensing Authority in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA). The primary aim of the MHRA is to safeguard public health by ensuring that all medicines and devices on the UK market meet appropriate standards of quality, safety and efficacy. The MHRA was formerly known as the Medicines Control Agency (MCA), which was established in 1989 as an Executive Agency of the Department of Health. On 1 April 2003 the Medicines Control Agency (MCA) and the Medicinal Devices Agency (MDA) merged into a single executive agency, the MHRA [36]. The responsible department at the MHRA for inspections is the “Inspection and Standards Division”.

The MHRA GMP Inspectorate carries out regular and repeated inspections of manufacturing sites both in the United Kingdom and in those non-EU countries with which the EU does not have a Mutual Recognition Agreement. All sites named on a manufacturer’s licence are subject to regular inspections. Each site is inspected every 2-3 years depending on the nature and scale of operation. Inspection enables the Licensing Authority to confirm that licence holders are complying with the conditions of their licence, with the provisions of the Medicines Act and with GMP. The ability to demonstrate compliance with the principles of GMP will result in the issuing of a GMP certificate. Section 111 to 114 of the Medicines Act empowers the MHRA to:

- inspect the premises organised arrangements and procedures used in the manufacture, assembly, testing, storage and distribution of medicinal products;
- interview key personnel named on licences;
- take samples;
- require production and examine any documentation or records relating to the manufacture, assembly, storage and distribution of medicinal products in accordance with Part 8 of the Medicines Act.

The enforcement powers under the Medicines Act is the basis for inspections relating all types of licenses. It is a requirement of UK legislation that licence holders shall make their premises available for inspections by the Licensing Authority at any reasonable time.

Following an inspection, the Inspector prepares a summary of his findings. This inspection report is sent to the licence applicant asking for proposals to remedy them. In the most serious cases the report is referred to the Licensing Authority for more formal action which can include the refusal, variation, suspension or revocation of a licence, or part of a licence [18]. Under the Freedom of Information Act 2000 the MHRA is required to release certain information upon request. Commercial sensitive information will not be disclosed. Request for information can be made when using the Freedom of Information Request Form. The Agency is obliged to respond to requests within 20 working days.

6.1.2 GMP

The UK complies with the European legislation. The primary legislation in the UK is laid down in the “Medicines Act 1968 as amended”, which regulates in part the manufacture, distribution and importation of medicinal products. The principles and the guidelines of EU GMP applies and are even set out in the MHRA publication the Rules and Guidance for Pharmaceutical Manufacturers and Distributors usually known as “The Orange Guide”. From its first publication in 1971 the 'Orange Guide', has been an essential reference for all involved in the manufacture and distribution of medicines in Europe. The Orange Guide collates European and UK guidance documents and information on legislation relating to the manufacture and distribution of medicines for human use. The Orange Guide is available from TSO (The Stationary Office: www.tso.co.uk/bookshop).

A manufacturer’ license or a manufacturer’s special licence must be held before a medicinal product is manufactured, whether the product is for use within the UK or for export. The Manufacturing and Wholesale Dealing Regulations (SI 2005 No 2789) detail the obligations and standard provisions relating to manufacturer’s licenses. In the UK a manufacturer’ license is the same as a manufacturing authorisation. A manufacturer’s special licences is a license which permits the manufacture and supply of “exempt relevant medicinal products” i.e. unlicensed relevant medicinal products exempt from the requirement to hold a marketing authorisation. This exemption permits supply to meet the specific needs of an individual patient [30].

The facilities in third countries (non EU/EEA countries) must either be approved by a PIC member state or the UK Medicines Inspectorate. Inspections may be conducted. Non-EEA manufacturers will be required to sign undertakings in accordance with the SI 1977 No. 1038 (as amended by SI 1992 No. 2845 and SI 1994 No. 3144) to:

- permit premises where the product is or is to be manufactured and the operation carried on or to be carried on in the course of manufacturing it to be inspected by or on behalf of the United Kingdom licensing authority;
- comply with the conditions described by SI 1977 No. 1038, conditions of which are set out in the Schedule to this instrument;
- comply with any conditions attached to the marketing authorisation in relation to the manufacture of the product;

and declare that, in relation to the manufacture of the product, any requirements imposed by or under the law of the country in which it is or is to be manufactured have been or will be complied with [30].

6.1.3 Site Master File

The MHRA is the regulatory authority which provides the most information about a SMF and is extensively using modifications of the PIC/S Site Master File guideline for UK specific purposes. The preparation of a SMF facilitates the inspection process.

An application for a manufacturer’s licence (in the UK the manufacturing authorisation is a manufacturer’s licence) or a manufacturer’s special licence should be accompanied by a Site Master File. A SMF should be submitted either as a hard copy or as a CD Rom to the MHRA.

The following guidance notes regarding the preparation of a SMF are available on the MHRA homepage:

- MHRA Guidance Note 27 [15]: Guidance notes for industry on the preparation of a Site Master File.
- MHRA Guidance Note 28 [16]: Guidance notes for industry on the preparation of a Site Master File for an overseas site subject to inspection by the UK regulatory authority.
- MHRA Guidance Note 30 [17]: Site Master File Model. For Manufacturing "Specials" Licence holders or applicants for Manufacturing Authorisations relating to small-scale activities, including investigational medicinal products.

A SMF for an overseas site subject to inspection by the MHRA is UK specific and contains minor UK specific modifications of the PIC/S guide. For example under a new section 1.5.4 names, dosage forms and UK Product License number of all medicinal products are manufactured on site for the export to the UK should be provided. A template for a Site Master File can be found on the Thai FDA homepage [I7].

The Site Master File Model is a SMF for small-scale activities, including investigational medicinal products. The structure of the sections is completely different to the PIC/S guideline and is specific for the MHRA only.

A very interesting example for usage of a Site Master File in the UK is the company G&G Food Supplies Ltd. G&G made available their Site Master File on their homepage as a word document [65].

In the UK the SMF is an important tool to support inspections and inspection procedures.

6.2 EU: Germany

6.2.1 Authority and Inspections

The competent local authority of the Federal State, where the company is located, carries out GMP inspections. Due to the Federal political structure in Germany, the Federal States have the responsibility for supervision and inspection. The competent higher Federal authority BfArM or PEI are normally only involved in inspections prior to granting a marketing authorisation according to § 25 (5) or § 25 (8) AMG (see § 4 (1) AMGVwV) [68, 70]. The activities of the supervising authorities are regulated in the Administrative Instructions for the Enforcement of the Drug Law (AMGVwV) [70]. The AMGVwV considers the EU Community procedures for inspections and exchange of information [10].

Inspections may be carried out when a company applied for a marketing authorisation. Furthermore inspections are performed when a company has applied for a manufacturer's licence and periodically during the course of a licence. Inspections may be carried out if major changes to the scale of operations of the granted manufacturing licence are submitted to the authorities or for example for follow up of deficiencies raised previously, follow-up of recalls or information received from external sources. Inspections are normally performed every two years.
There is no legal requirement to notify the company prior to an intended inspection, so it may be pre-arranged or unannounced § 4 (5) AMGVwV. The competent authority of the Federal State in which the company is located carries out inspections of sites concerned with the manufacture and/or assembly or importation of investigational medicinal products as well [68].

Section 64 of the Germany Drug Law empowers the competent authority to perform inspections: "Enterprises and facilities in which medicinal products are manufactured, tested, stored, packaged or marketed, or in which any other form of trade with them takes place, shall be subject in this regard to supervision by the competent authority" [41]. The inspecting authorities are empowered to call in experts, to enter premises, to review and take copies of documents and to take samples. The officers in charge of supervision are authorised to issue provisional orders, also to close an enterprise in order to prevent hazard for public safety (§ 64 Drug Law) [68]. An inspection report is provided after the inspection. If a site is considered as compliant with GMP the competent authority issues a GMP certificate in the EU format.

According to section 66 of the Germany Drug Law enterprises or facilities have the obligation to tolerate and collaborate. Site's are obliged to tolerate inspections and give full support to the persons in charge of supervision in the fulfilment of their duties, in particular, indicating to them, upon request, the premises and transport facilities, opening rooms, containers and receptacles, giving information and enabling the taking of samples [41].

6.2.2 GMP

Germany complies with European requirements (see table 2) and guidelines regarding GMP. All medicinal products manufactured or imported into/exported from Germany must be manufactured in accordance with the legal requirements and guidelines of GMP. All drug substances including certain excipients used for the

manufacture of medicinal products and investigational medicinal products must also have been manufactured in compliance with GMP. Only active substances that have been manufactured in accordance with GMP must be used as starting material. The same applies for imported products (§13 (3) AMWHV [1]. GMP has been introduced into German Drug Law.

Section 54 of the German Drug law empowers the Federal Ministry to issue internal regulations by ordinance subject to the approval of the Bundesrat ("Betriebsverordnungen") for companies or facilities which bring medicinal products into the purview of the present Act or in which medicinal products – or active substances and certain excipients - are developed, manufactured, tested, stored, packaged. These internal regulations are laid down in the AMWHV (Decree of 03-Nov-2006 - GMP in the Manufacturing of Medicinal Products, Active Substances and Products of Human Origin) [1]. This decree has come into force on 10-Nov-2006 and set Decree of 08-Mar-1985 - Operating Procedure for Pharmaceutical Companies (PharmBetrV) - as amended by law of 10-Feb-2006 out of force.

The AMWHV implements the following European Directives: 2001/20/EC, 2001/83/EC as amended by Directive 2004/27/EC, 2003/94/EC, 2004/33/EC, 2004/23/EC, 2005/61/EC and 2005/62/EC. The national implementation of GMP-Directive 2003/93/EC in Germany is summarized in table 6.

A manufacturer’s licence is required before manufacturing a medicinal product, test sera, test antigens, or active substances of human, animal or microbial origin including their production by genetic engineering, and other substances of human origin intended for the manufacture of medicinal products on a commercial or professional basis intended for distribution to others (§ 13 (1) Drug Law).

This applies to manufacture in general, whether the product is for use within Germany or for export [68]. The company has to apply for a manufacturing licence by the competent local authority of the Federal State in which the manufacturer is located. The competent authority shall reach a decision on the application for an authorisation within three months (§ 17 (1) AMG). Section 14 of the German Drug Law it is stipulated that a manufacturing authorisation may only be refused if Para 1 (6) suitable premises and equipment for the intended manufacture, testing and storage of the medicinal products are not available [41].

When medicinal products manufactured in third countries (non EU/ EEA countries) shall be imported to Germany, an authorisation by the competent local authority is needed (§ 72 (1) Drug Law). Products from non-EU-countries must be re-tested and re-released for marketing in the European Union. This can be done in the country where the product enters the European Union from a non-EU-country (§ 17 (3) AMWHV). If the products are directly imported to Germany, the competent local authority may inspect the manufacturing site especially when the site cannot provide an EU GMP-certificate [68].

6.2.3 Site Master File

As in the EU it is not mandatory in Germany to have available a Site Master File. There is available an operational procedure regarding form and content of a SMF by the “Central Authority of the Laender for Health Protection Regarding Medicinal Products and Devices” (ZLG) [20]. The ZLG is the central coordination unit of the Laender regarding medicinal products for human and animal use. A SMF (company description) is considered as an important part of the companies Quality Assurance System required according to § 14 (1) no. 6a AMG and § 1 (3) AMWHV. The PIC content and format is introduced (Document PH 4/93, April 1993).

Prior to an inspection the local authority of the Federal States request for an up to date SMF including the most recent changes. According to Section 20 of the German Drug Law the marketing authorisation holder shall notify the competent authority in advance of any change to the information referred to in Section 14 sub-section 1 and submit evidence [41]. Therefore an update of the SMF is required if submitted to a competent authority. The verification of a SMF, if available, is considered as an essential part for the preparation of an inspection. [20].

Several competent local authorities of the Federal States request a SMF in connection to the application of a manufacturing license (e.g. Brandenburg [I12], Niedersachsen [I13], Oberbayern [I14], Schleswig-Holstein [I15], Schwaben [I16], Lüneburg [I17] and Hessen [I18]).

Therefore in Germany a SMF is a helpful tool to give full support to the persons in charge of supervision (§ 66 AMG).

Table 6: National implementation of GMP-Directive 2003/93/EC in Germany

Requirement	**Directive 2003/93/EC**	**Germany AMWHV**
Quality Assurance System	Article 6	§ 3
Personnel	Article 7	§ 4
Premises and equipment	Article 8	§ 5
Documentation	Article 9	§ 10
Production	Article 10	§ 13
Quality control	Article 11	§ 14
Work contracted out	Article 12	§ 9
Complaints, product recall	Article 13	§ 19
Self-inspection	Article 14	§ 11

6.3 US

6.3.1 Authority and Inspections

The Food and Drug Administration (FDA) is an agency within the Department of Health and Human Services (HHS). The FDA regulates human and veterinary drugs, biologics, medical devices, medical radiation products, blood and blood products, cosmetics, and food. The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health [42].

The Office of Regulatory Affairs (ORA) is the FDA's enforcement arm. ORA's mission is twofold: to safeguard the public health and to ensure honesty and fair dealing between the regulated industry and consumers. ORA achieve its mission by:

- participating in cooperative and educational efforts at home and abroad to inform those who need to know of the agency's legal requirements;
- surveying and inspecting regulated industry to assess compliance and implement corrective measures as warranted to achieve compliance; and
- seeking to deter fraud, intentional violations, and gross negligence related to FDA- regulated products.

ORA has the lead on international enforcement issues such as imports and foreign inspections. The Office ensures that products imported to the United States and regulated by the agency meet the same safety, efficacy and quality standards as those products manufactured domestically.
The new strategic vision for ORA is: "All food is safe; all medical products are safe and effective; and the public health is advanced and protected."

The ORA field organisation is divided into regional offices. Inspections are conducted by these offices. Currently there are five offices which are located as follows: Northeast (New York), Central (Philadelphia), Southeast (Atlanta); Southwest (Dallas) and Pacific (San Francisco) [I11].

Section 704 of the Food, Drug and Cosmetic Act (21 U.S.C. 374) provides the FDA with regulatory authority to make establishment inspections. With proper notice to the owner and appropriate credentials, an agent in charge is authorized to enter any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction. Inspectors are also authorized to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labelling therein [48]. Collecting samples is an important part of the inspection activities. FD&C Act, Section 702(a) [21 U.S.C. 372 (a)] gives FDA authority to conduct investigations and collect samples.

6.3.2 GMP

In the US GMP was first issued in June in 1963 [77]. The Food, Drugs and Cosmetics Act, enacted by the US Congress, empowers the Food and Drug Administration (FDA) to enforce food and drug laws. The FDA regulations which outline in more detail the meaning of “current good manufacturing practice” (= cGMP) of the Food, Drug and Cosmetic Act are published in the Code of Federal Regulations. The term "current" is used in order to emphasize that the expectations are dynamic.

The Food, Drug and Cosmetics Act requires the methods used in, or the facilities or controls used for, drug manufacture, processing, packing or holding to conform with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess [48].

That means that all drugs must be manufactured in accordance with the current good manufacturing practice regulations otherwise they are considered to be adulterated within the meaning of the FD&C, Section 501(a) (2) (B). This applies to imported drugs as well.

Today’s version of the CGMP regulation for human drugs has been issued in 1978 and is laid down in CFR parts 210 and 211 (finished pharmaceuticals only):

21 CFR Part 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General.
- 210.1: Status of current good manufacturing practice regulations.
- 210.2: Applicability of current good manufacturing practice regulations.
- 210.3: Definitions.

21 CFR Part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals (see Annex 6).

According to 21 CFR 207 a registration of all manufacturing sites is required. Owners or operators of all domestic and foreign drug establishments, that engage in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs, including blood products, and biologicals, are obliged to register each such establishment and to submit a list of every drug in commercial distribution, whether or not the output of such establishment or any particular drug so listed enters interstate commerce.
For initial registration form FDA 1656 for the code assignment and form FDA 2657 for a detailed listing of all drug products is required. An annual renewal is necessary [I11].

Since January 2006 the FDA is no longer issuing declarations on CGMP conformance (GMP certificates) and registration status of drug manufacturing establishments related to commercial exportation of drugs due to resources and budget constrains. A statement about the CGMP compliance of a site is included in an export certificate (Certificate of Pharmaceutical Product) for exported drug products.

6.3.3 Site Master File

A Site Master File is not required in the USA. Similar content as provided in a SMF was provided to the FDA in the past in form of a so called “Drug Master File Type I”. A Drug Master File (DMF) is a voluntary submission of information to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drugs and biological products.
As the submission of a DMF is not required by law or regulation, a DMF is submitted solely at the discretion of the holder. The information contained in a DMF may be used in order to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), biologics license applications (BLA), another DMF, an Export Application, or amendments and supplements to any of these. DMFs are generally used to allow a sponsor or applicant to reference the material in the DMF without disclosing the contents of the DMF to the sponsor or applicant. A DMF is not a substitute for an IND, NDA, ANDA, BLA or Export Application. FDA reviews the content only in connection with the review of an IND, NDA, ANDA, BLA or Export Application and does not approve or disapprove a DMF.

The general provisions for Drug Master Files are laid down in 21 CFR 314.420. In 21 CFR 314.42(a) historically the following five DMF types were described according to the kind of information to be submitted:

- Type I: manufacturing site, facilities, operating procedures, and personnel.
- Type II: drug substance, drug substance intermediate, and materials used in their preparation, or drug product.
- Type III: packaging materials.
- Type IV: excipient, colorant, flavor, essence, or materials used in their preparation.
- Type V: FDA-accepted reference information [43, 50].

In the Federal Register of January 12, 2000 [53], FDA published the final rule “New Drug Applications; Drug Master Files.” The final rule amended 21 CFR 314.420 by removing the provision for Type I DMFs. FDA considered the DMF type I as an “inadequate vehicle for information” as it contains only information that was not necessary either to conduct inspections of manufacturing facilities or to review the chemistry, manufacturing, and controls sections of INDs, NDAs, and abbreviated applications. The reasons for removing type I DMFs were [53]:

- The information contained was often outdated.
- Type I DMF was not always easily accessible.
- The review division in CDER did not review the contained information.
- Information concerning the facility is maintained onsite where it is available for the inspector.

In the final rule of January 12, 2000 [53] one interesting comments from a company on the proposed rule was provided by the FDA:

“Another comment suggested that instead of FDA eliminating Type I DMF’s, industry should be required to keep the information current. The comment stated that the privilege of incorporating Type I DMF information by reference should be denied on a case-by-case basis to those firms that do not keep information current.”

However, the FDA stated: “Information contained in Type I DMF’s is not reviewed by CDER reviewers, and it plays no role in processing a drug product application.” Furthermore the FDA believes that a current, accurate facility description at the manufacturing site and an inspection of the facility are the best sources of information for assessing a facility’s ability to meet FDA standards. The regulation became effective on July 10, 2000, and the agency has not longer accepted Type I DMFs as of that date.

A DMF Typ I was intended to assist FDA in conducting onsite inspections of foreign manufacturing facilities. It comprised information like a description of the manufacturing site, equipment capabilities, and operational layout. Furthermore it contained acreage, actual site address, a map showing the sites location with respect to the nearest city and an aerial photograph and or a diagram of the site (if helpful). A diagram of major production and processing areas describing the operational layout and a diagram of major corporate organizational elements, with key manufacturing, quality control, and quality assurance positions highlighted have been provided in a DMF Type I. Type I DMFs have been used to provide a list of all products manufactured or other general information such as floor diagrams or standard operating procedures (SOPs) that are common to multiple products or processes in the facility. DMF holders have also submitted information on contract testing facilities in Type I DMFs.

Anyway, some information about some types of facilities previously provided in a DMF type I can be submitted in a Type V DMF. A type V DMF is a DMF for miscellaneous information, duplicate information or information that should be included in one of the other types of DMFs. The DMF holder is required to submit first a letter of intent to the Drug Master File Staff. The FDA will then contact the holder and discuss the proposed submission.

The following types of DMF can be submitted as Type V DMF without submitting a letter of intent [45, 50]:

- Manufacturing Site, Facilities and overall manufacturing operations for sterile manufacturing plants (in support of sterility assurance for sterile products).
- Facilities for Production of Gene or Cell Based Therapies for Phase 1 and 2 Clinical Trials (to assess safety of these products in clinical trials under IND).
- Contract Manufacturing Facilities in Support of Biologics License Applications or Biologics License Application Supplements (to determine impact of other products handled at the facility).

Although it is not required for manufacturing sites in the US to provide a SMF this does not mean that US manufacturing sites does not have a SMF. From company internal experience the manufacturing site located in the US has a SMF because they supply EU and ROW countries and are subject to inspections by competent authorities which request a SMF. In this case a SMF is prepared by manufacturing sites in the US in order to support Non-US sites. From a company experience a SMF will be requested from contract manufacturing sites (mainly of manufacturers of the pharmaceutical form) to support marketing authorisation or import activities. Site Master Files from contract manufacturing site are helpful for the own company for planning of audits and making familiarise with the contract company.

6.4 ROW: Taiwan

6.4.1 Authority and Inspections

The central health authority in Taiwan is the Department of Health (DOH) which is responsible for the national-wide health administration and the guidance, supervision and coordination of local health authorities [31]. Operational units under the DOH include the Bureau of Pharmaceutical Affairs (BFA) and the Bureau of Food and Drug Analysis (BFDA). The Bureau of Pharmaceutical Affairs (BFA) is responsible for the handling of pharmaceutical regulation.

The Science and Technology Development Center (STDC), Taiwan's Good Manufacturing Practice (GMP) authority for pharmaceutical facilities, is responsible for GMP-related activities, including pharmaceutical facility supervision, international activity participation, quality management and licensing systems administration, and special project promotion. Pharmaceutical facility supervision includes quality documentation review and GMP site inspection for local and foreign facilities.
The inspection executive organization is BFDA. Starting from April 1990, the DOH authorized BFDA as the central authority to conduct GMP inspections, and the GMP-certified domestic pharmaceutical facilities were subjected to a biennial inspection program for keeping GMP compliance. These follow-up inspections are categorized as routine inspections and for-cause inspections.

The overseas GMP inspections are performed by the Bureau of Food and Drug Analysis (BFDA) inspectorate under the regulation requirement of DOH. To carry out the policy of Department of Health (DOH), and to ensure the quality of imported drug products, the BFDA has started to perform overseas inspections in December 2002.

The site and GMP related operations for importing the pharmaceutical products to Taiwan are included in the inspection scope. At the end of 2002 an inspection team was visiting a pharmaceutical facility in the United States for the first time. Up to January 2007, seventy-three overseas pharmaceutical facilities have been inspected. The Official language to be used during inspection is either Chinese or English [I3].

All medicines and medical devices, whether imported or locally produced, must be registered and licensed by the DOH before they can be marketed in the Taiwan area. Based on Article 8 of the Pharmaceuticals and Phamaceutical Companies Law, (announced on the 21st of April 2004): "DOH have the right to inspect pharmaceutical products manufactures and companies." Regarding the inspection on pharmaceutical products manufacturers, Taiwan DOH doesn't afford independent inspection regulations, only providing a checklist (Good Manufacturing Practices Validation Self Evaluation Check List) for reference. The content is based on related regulations of cGMP (GMP, GMP-for Manufacturing Blood Plasma Raw Material Standard of Process).

The local drug substance manufacturers and pharmaceutical products manufacturers should fill in "Drug Manufacture Site GMP Evaluation Form" (Drug Manufacture Software Evaluation Standard of Process) and propose the following documents to BFDA for application:

- Certificate documents passed evaluation of hardware GMP or manufacture registration identification issued by Industrial Development Bureau, Ministry of Economic Affairs.

- Site Master File (SMF).
- Validation process integrated plan.
- Manufacture ground plot.
- Air conditioner and Purity Water System Layout.
- Drug-manufacturing machines, tables of equipment classification, and tables of analysis devices classification.
- Site GMP and related SOP tables.
- Paid receipts for evaluation.

If the manufacturers have any objection on inspection results, or being asked to revise and improve, they have to propose to BFDA within a specific duration (see figure 6).

6.4.2 GMP

In June 1978 the Department of health (DOH) proposed a draft code of the Code of Good Manufacturing Practice of Pharmaceuticals (GMP code) by observing the U.S and Japan GMP regulations. This code was first promulgated and implemented in Taiwan in May 1982. GMP refers to the Good Manufacturing Practice Regulations based on Article 2-1 of the Standard for Setting Up Pharmaceutical Manufacturing Plant, which is promulgated by the DOH under the authority of the Pharmaceuticals and Pharmaceutical Companies Law require that manufacturers, processors, and packagers of drugs, medical devices and some foods take proactive steps to ensure that their products are safe, unadulterated, and effective. GMP is also sometimes referred to as "cGMP" in Taiwan as in the United States.
For example the Good Manufacturing Practice for medicinal products (GMP-DP) consists of thirteen chapters [54] with nearly the same scope and content as the ones published by other countries and organizations, e.g. ICH, PIC/s. Titles of each chapter in the GMP-DP are [54]:

1. General principles.
2. Environmental hygiene.
3. Buildings and facilities.
4. Process equipments.
5. Infrastructure and personnel.
6. Control of raw material, product container and closure.
7. In-process control.
8. Control of packaging and labelling.
9. Storage and distribution.
10. Quality control.
11. Records and documentation.
12. Compliant and management of recalls.
13. Attachments.

In April 1995, the DOH announced the GMP Validation Requirement of Sterile Products that stipulated domestic and foreign pharmaceutical facilities should enclose the validation document of product sterilization for drug product registration. Validation practicing is one of the most prominent tasks of cGMP in Taiwan. This should be achieved by qualification of various interior maintaining systems in a plant. Following the October 1999 announcement, the DOH issued the full scale of validation requirement of all drug products, including both sterile and non-sterile

pharmaceuticals. Domestic pharmaceutical facilities will need to meet validation requirement in a three stages timeframe by June 2004. In May 2001 the DOH issued that imported drug products should comply the GMP validation requirement in a three stages timeframe by December 2005.

In April 2002 the DOH introduced the GMP Guide for Active Pharmaceutical Ingredients (APIs), adopted from ICH Q7A, in order to ensure the quality of APIs. Since July 2006 the GMP Guide for APIs is a mandatory requirement for the marketing authorisation of all new chemical entities in Taiwan.

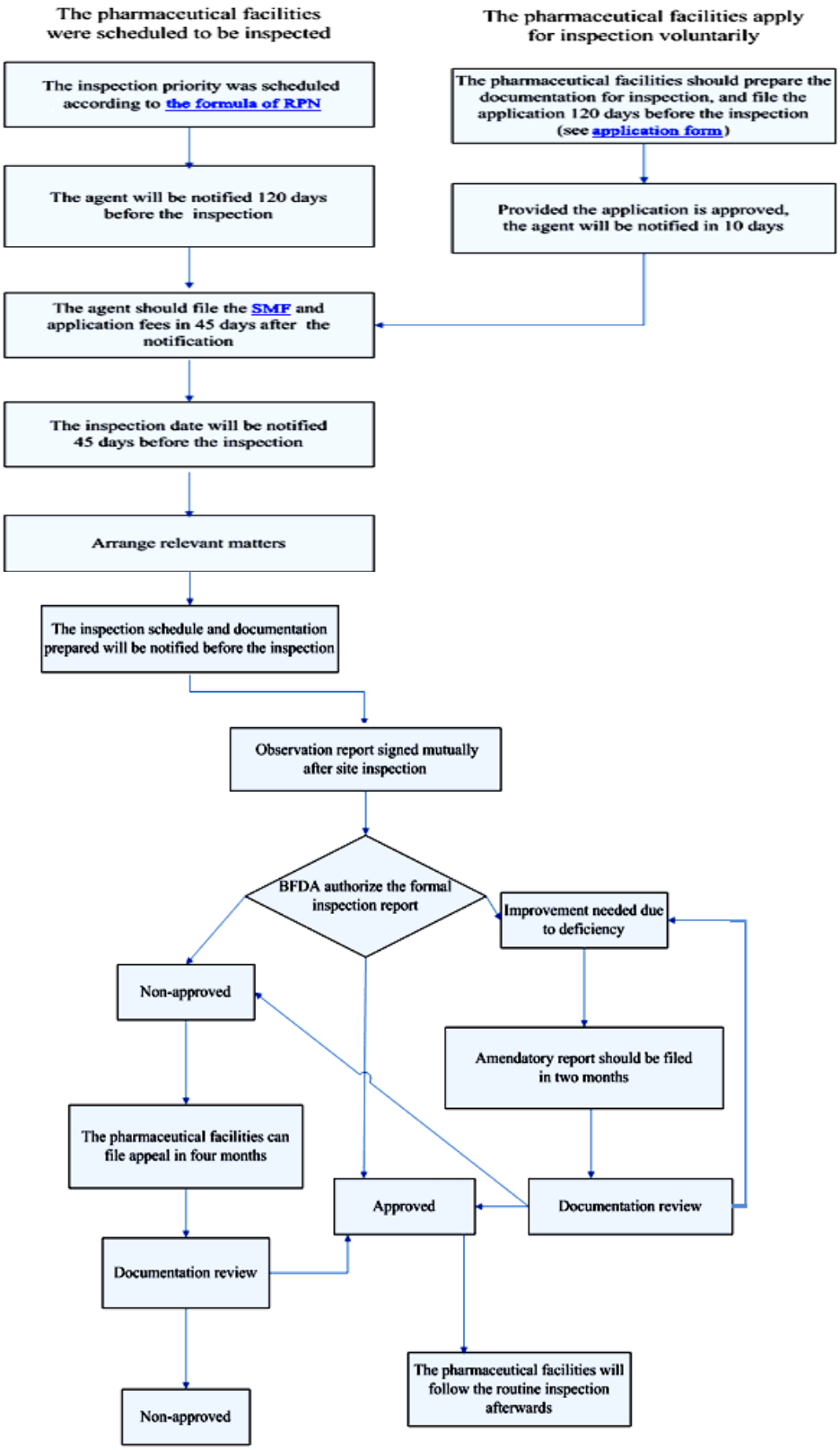
6.4.3 Site Master File

In June 1988 the DOH issued the requirement that sponsor of imported drug products should submit a Site Master File (here also called as Plant Master File, PMF) for document review prior to drug product registration.
This was established to ensure the quality of imported drug products and as a substitute for on site inspections. The objective of the review of SMF, as stated by the MOH itself, is: “to assess the manufacturing facilities/ processes of foreign pharmaceutical products in order to quality assure that they should meet the current good manufacturing practice regulation of DOH.” [I3].

In November 2006 the DOH has announced “Guidelines for Preparing a Plant Master File (PMF)” and “Plant Master File (PMF) Checklist for oversees pharmaceutical facilities” and provided guidelines for preparing a Plant Master File on the DOH homepage.
These guidelines for preparing a Plant Master File are identical with the requirements and guidance sections of the PIC/S explanatory note on a SMF (see Annex 1 and 2).
The checklist comprises of three main sections. The first section describes the PMF items to be covered. The second section is a “self review” section for the applicant. For each required item of the first section the applicant has to tick a checkbox if the information is provided or not. Additionally the appropriate pages of the SMF should be provided. Section three is to be filled in by the Taiwan DOH for review purposes (see Annex 4).

A pharmaceutical company can either apply voluntarily for an inspection or will be selected on a risk-based scientific approach by the BFDA. In the first case the company has to fill in an application form 120 days before the inspection. In the second case the agent will be informed 120 days before the inspection. The Site Master File has to be provided 45 days after the receipt of the inspection notification (see figure 6).

Figure 6: Scheme for Overseas Inspection in Taiwan



[I3]

7. Conclusion and outlook

The GMP implementation and regulations (and quality system expectations) still differ between regions and countries. ROW or so called emerging countries became more and more important for global working pharmaceutical companies. As a consequence the number of inspections of manufacturing sites has increased continuously. In this context it is necessary that PIC/S will go ahead to expand their membership and will go ahead working on global GMP harmonisation. From industry perspective it is hoped that any inspectorate will accept PIC/S and ICH inspections as the standard in the future [67].

A possible tool for manufacturing sites to facilitate the inspection process is to provide a Site Master File prior to the inspection to the competent regulatory authority. A Site Master File is a brief and comprehensive company description demonstrating the sites GMP compliance. Depending on national requirements a SMF is not required, can be either voluntary submitted or must be submitted to the national regulatory authority. As a general rule manufacturers are advised to refer to national regulations whether it is required to provide a SMF or not.

Information about a Site Master File is hard to find. A SMF is not mentioned in an ICH guideline [4, 5] or in a GMP guideline. The current version of explanatory notes on the preparation of a Site Master File of the Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-Operation Scheme (PIC/S) is the only available international guideline on a SMF. Many health authorities have implemented the PIC/S guideline, or a slight modification of the PIC/S guideline, as national guidelines.

Preparation and maintenance of a SMF is a complex task, which requires co-ordination and resources. A decision analysis with a fictive grid analysis was performed in order to clarify the question if there is a benefit for manufacturing sites to invest time and resources in order to prepare a SMF or not. For global working companies it is concluded that there are more arguments to set up a SMF than against a SMF.

There are great differences in the usage of a SMF in different regions. As examples the United Kingdom, Germany, the United States and Taiwan were selected. The EMEA considered a Site Master File as “helpful” for preparing and carrying out the inspection. The same applies for competent regulatory authorities in Germany, the MHRA in the United Kingdom and the regulatory authority of Taiwan. The UK has in addition UK specific modifications in place. The US FDA recognised among other things that the content a Drug Master File Type 1 (which had similar content to a Site Master File) was often outdated. As a consequence the FDA considered a Type 1 Drug Master File as an “inadequate vehicle” for information and has no longer accepted Type 1 Drug Master Files since July 2000.

It remains open if the ICH guideline Q10 on pharmaceutical quality systems, once adopted, will have impact on set up and usage of a SMF.

However, a SMF can serve as a competent regulatory document for manufacturing sites to answer to questions from regulatory authorities regarding production, quality control, quality policy and quality assurance system etc.

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List of Abbreviations

ANDA	Abbreviated New Drug Application
AMG	German Drug Law (**A**rznei**m**ittel**g**esetz)
AMGVwV	Administrative Instructions of 29-Mar-2006 for the Enforcement of the Drug Law.
AMWHV	Decree of 03-Nov-2006 on the Use of Good Manufacturing Practice in the Manufacturing of Medicinal Products, Active Substances and Products of Human Origin
API	Active Pharmaceutical Ingredient (= active substance)
ASEAN	Association of South East Asian Nations
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BLA	Biologics License Applications
CA	Competent Authority
CDER	Center for Drug Evaluation and Research
CEP	Certificate of the European Pharmacopoeia
CFR	Code of Federal Regulation
CHMP	Committee for Human Medicinal Products
cGMP	Current Good Manufacturing Practices
CVMP	Committee for Veterinary Medicinal Products
DMF	Drug Master File
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area: EU 27 + Norway, Liechtenstein and Iceland
EMEA	European Medicines Agency
EFPIA	European Federation of Pharmaceutical Industry Associations
EU	European Union
FDA	Food and Drug Administration
FIP	International Pharmaceutical Federation
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IMP(s)	Investigational Medicinal Product(s)
ISPE	International Society of Pharmaceutical Engineers
NDA	New Drug Application
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MP	Medicinal Product
MRA	Mutual Recognition Agreement
NCA	National Competent Authority
PDA	Parenteral Drug Association
PEI	Paul Ehrlich Institut
Ph. Eur	European Pharmacopeia
PIC	Pharmaceutical Inspection Convention
PIC/S	Pharmaceutical Inspection Co-Operation Scheme
QC	Quality Control
QM	Quality Management
QU	Quality Unit
ROW	Rest of the World (Non US and Non Europe countries)
SMF	Site Master File

Annex 1: Requirements PICS/Guideline

Chapter	Requirements
C.1	**General Information.**
C.1.1	Brief information on the firm (including name and address), relation to other sites and, particularly, any information relevant to understand the manufacturing operations.
C.1.2	Pharmaceutical manufacturing activities as licensed by the Competent Authorities.
C.1.3	Any other manufacturing activities carried out on the site.
C.1.4	Name and exact address of the site, including telephone, fax and 24 hrs telephone numbers.
C.1.5	Type of actual products manufactured on the site (see list at Appendix), and information about specifically toxic or hazardous substances handled, mentioning the way they are manufactured (in dedicated facilities or on a campaign basis).
C.1.6	Short description of the site (size. location and immediate environment and other manufacturing activities on the site).
C.1.7	Number of employees engaged in the quality assurance, production, quality control, storage and distribution.
C.1.8	Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis.
C.1.9	Short description of the quality management system of the firm responsible for manufacture.
C.2	**Personnel.**
C.2.1	Organisation chart showing the arrangements for quality assurance, including production and quality control.
C.2.2	Qualifications, experience and responsibilities of key personnel.
C.2.3	Outline of arrangements for basic and in-service training and how records are maintained.
C.2.4	Health requirements for personnel engaged in production.
C.2.5	Personnel hygiene requirements, including clothing.
C.3	**Premises and Equipment.**
Premises:	
C.3.1	Simple plan or description of manufacturing areas with indication of scale.
C.3.2	Nature of construction and finishes.
C.3.3	Brief description of ventilation systems.
C.3.4	Special areas for the handling of highly toxic, hazardous and sensitising materials.
C.3.5	Brief description of water systems including sanitation.
C.3.6	Maintenance (description of planned preventive maintenance programmes and recording system).
Equipment:	
C.3.7	Brief description of major production and control laboratories equipment.
C.3.8	Maintenance (description of planned preventative maintenance programmes and recording system).
C.3.9	Qualification and calibration, including recording system. Arrangements for computerized systems validation.
Sanitation:	
C.3.10	Availability of written specifications and procedures for cleaning manufacturing areas and equipment.
C.4	**Documentation.**
C.4.1	Arrangements for the preparation, revision and distribution of necessary documentation for manufacture.
C.4.2	Any other documentation related to product quality which is not mentioned elsewhere (e.g. microbiological controls on air and water).
C.5	**Production.**
C.5.1	Brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters.
C.5.2	Arrangements for the handling of starting materials. Packaging materials, bulk and finished products, including sampling, quarantine, release and storage.
C.5.3	Arrangements for reprocessing or rework.
C.5.4	Arrangements for the handling of rejected materials and products.
C.5.5	Brief description of general policy for process validation.
C.6	**Quality Control.**
C.6.1	Description of the Quality Control system and of the activities of the Quality Control Department Procedures for the release of finished products.
C.7	**Contract Manufacture and Analysis.**
C.7.1	Description of the way in which the GMP compliance of the contract acceptor is assessed.
C.8	**Distribution, Complaints and Product Recall.**
C.8.1	Arrangements and recording system for distribution.
C.8.2	Arrangements for the handling of complaints and product recalls.
C.9	**Self Inspection.**
C.9.1	Short description of the self inspection system.

(Slightly modified after [3])

Annex 2: Guidance PICS/Guideline

Chap-ter	Guidance
C.1	**General Information.**
C.1.1	In not more than 250 words (one A4 page) outline the firm's activities, other sites, in addition to the site which is the subject of this report.
C.1.2	Quote the relevant document as issued by the Competent Authority. State period of validity of licence document (if the validity of the document is given in the country concerned). Any conditions and/or restrictions should be stated.
C.1.3	This covers both pharmaceutical and non-pharmaceutical activities.
C.1.4	Name and Address of Site. C.1.4.1 Name of Company (and trading style if different). Postal Address including Code (street address if different). C.1.4.2 Telephone No. of contact person. C.1.4.3 Fax No. of contact person. C.1.4.4 24 hour contact Telephone No.
C.1.5	Type of Actual Products Manufactured. C.1.5.1 Quote the type of actual products as described at Appendix. C.1.5.2 Note any toxic or hazardous substances handled e.g. antibiotics, hormones, cytostatics. Note whether the products are manufactured in a dedicated facility or on a campaign basis. C.1.5.3 Mention if human and veterinary products are both prepared on the site.
C.1.6	(not more than 250 words/one A4 page) C.1.6.1 The location and immediate environment. C.1.6.2 The size of the site, types of buildings and their ages. C.1.6.3 Other manufacturing activities on the site.
C.1.7	(Note: Include employees working only part-time on full-time equivalent basis. Give the rate of the academic and non-academic persons). C.1.7.1 Quality Assurance. C.1.7.2 Production. C.1.7.3 Quality Control. C.1.7.4 Storage and distribution. C.1.7.5 Technical & Engineering Support Services. C.1.7.6 Total of the above.
C.1.8	For each outside contractor give: C.1.8.1 Name and address of the company. C.1.8.2 Telephone No. C.1.8.3 Fax No. C.1.8.4 Brief outline of the activity being undertaken in not more than 100 words (half an A4 page).
C.1.9	(Not more than 750 words or three A4 pages) C.1.9.1 State the firm's Quality Policy. C.1.9.2 Define the responsibility of the Quality Assurance function. C.1.9.3 Describe the elements of the QA system e.g. organisational structure, responsibilities, procedures, processes. C.1.9.4 Describe the audit programmes (self inspection or audits by external organisations undertaken). C.1.9.5 Describe how the results are reviewed to demonstrate the adequacy of the quality system in relation to the objective i.e. quality efficacy and safety of the product. See also paragraph 6.1.2. C.1.9.6 Record if standards such as ISO 9001-9004 are used by the company to assess its suppliers. C.1.9.7 When suppliers of critical starting materials and packing materials - actives, excipients, containers and closures and printed materials are assessed, give details of how this is done. C.1.9.8 Describe the release for sale procedure for finished products.
C.2	**Personnel.**
C.2.1	C.2.1.1 Organogram for quality assurance including production and quality control. Record senior managers and supervisors only.
C.2.2	C.2.2.1 Brief details of academic qualifications and work related qualifications and years relevant experience since qualifying.
C.2.3	Give brief details of the training programme and include induction and continuous training, as follows: C.2.3.1 Describe how training needs are identified and by whom. C.2.3.2 Give details of training relative to GMP requirements. C.2.3.3 State the form of training e.g. in-house, external, and how practical experience is gained and which staff are involved. C.2.3.4 Explain how the efficacy of the training is assessed e.g. by questionnaires. C.2.3.5 Explain how retraining needs are identified. C.2.3.6 Give brief details of records kept.
C.2.4	C.2.4.1 Who is responsible for checking health of employees? C.2.4.2 Is there a pre-employment medical examination? C.2.4.3 Are employees routinely checked from time to time depending on nature of their work? C.2.4.4 Is there a system for reporting sickness or contact with sick people before working in a critical area? C.2.4.5 Is there a system of reporting back after illness?

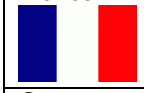
	C.2.4.6 Are those who work in clean areas (grade A-D) subject to additional monitoring?
C.2.5	C.2.5.1 Are there suitable washing, changing and rest areas? C.2.5.2 Is the clothing suitable for the activity undertaken? Briefly describe the clothing. C.2.5.3 Are there clear instructions on how protective clothing should be used and when it should be changed? Detailed procedures are not needed. Is in house or external laundry used?
C.3	**Premises and Equipment.**
C.3.1	C.3.1.1 Provide a site plan highlighting production areas (architectural or engineering drawings are not required). C.3.1.2 Provide a simple plan of each production area with indication of scale. Label areas and annotate plan with names. C.3.1.3 Plans should be legible and on A4 sheets of paper. Plans could be on A3 sheets of paper if considered necessary. C.3.1.4 For sterile product areas indicate room and area classification and pressure differentials between adjoining areas of different classifications.
C.3.2	Nature of Construction and Finishes (500 words/two A4 pages). C.3.2.1 To reduce narrative for a large complex plant, the details should be limited to critical areas. C.3.2.2 These areas must include all processing and packaging and critical storage areas. C.3.2.3 A narrative format is preferred.
C.3.3	(500 words/two A4 pages). Note 1: More details should be given for critical areas with potential risks of airborne contamination. This will include sterile product areas as well as areas for processing powders, granulation and tabletting. For sterile product areas a summary of the results of the most recent qualification/requalification should be given. Note 2: To reduce the narrative, schematic drawings should be used. The following data should be given: C.3.3.1 Design criteria e.g.: Specification of the air supply; Temperature; Humidity; Pressure differentials and air change rate, Simple pass or recirculation (%). C.3.3.2 Filter design and efficiency e.g.: Bag 99% eff., Hepa 99.997% eff. Details of any alarms on the ventilation system should be given. C.3.3.3 The limits for changing the filters should be given. C.3.3.4 If DOP (dioctyl-phthalate) is introduced, the point must be shown. C.3.3.5 Give the frequency of revalidation of the system.
C.3.4	C.3.4.1 Follow the same layout as 3.1 above.
C.3.5	(500 words / two A4 pages). Note: Schematic drawings of the systems are preferred. The following information must appear: C.3.5.1 The schematic must go back to the city supply system. C.3.5.2 The capacity of the system (maximum quantity produced per hour). C.3.5.3 Construction materials of the vessels and pipework. C.3.5.4 Specification of any filters in the system must be given. C.3.5.5 If water is stored and circulated, what is the temperature at the point of return. C.3.5.6 The specification of the water produced: a) chemical; b) conductivity; c) microbiological. C.3.5.7 The sampling points and frequency of testing. C.3.5.8 The procedure and frequency for sanitation.
C.3.6	(250 words/one A4 page). Note: For the purpose of this guide "Maintenance" is carried out by the manufacturer and "servicing" by an outside contractor. C.3.6.1 Describe the planned preventative maintenance programme. C.3.6.2 Are there written procedures and suitable reporting forms for maintenance and servicing? Do the documents record type frequency of services/checks, details of service, repairs and modifications? C.3.6.3 Are the maintenance routines that could affect product quality clearly identified? C.3.6.4 Are the reports made known to the users?
C.3.7	(250 words/one A4 page) Note: Makes and model numbers equipment are not required. However the following points should be addressed: C.3.7.1 Is the machinery constructed of appropriate material (e.g. AISI* grade 316 stainless steel for product contact equipment?). C.3.7.2 Have other materials been suitably validated e.g. polypropylene, chrome-plated brass, PVC (poly vinyl chloride), non-reactive plastic materials? C.3.7.3 Is the equipment designed with ease of cleaning in mind? C.3.7.4 Only a general description is required e.g. a rotary tablet press etc. If the equipment has additional devices, these should be recorded e.g. automatic weighing machines with printer; a labeller incorporating a bar code reader for the label; a lot number and expiry date over printer; a freeze drier equipped with a steam sterilisation facility. C.3.7.5 In the quality control laboratory only general descriptions such as pH meters, chromatographic equipment GLC (gas-liquid chromatography), HPLC (high performance liquid chromatography) with computer systems, particle size analysers. C.3.7.6 In microbiology use general descriptions such as incubators (temperature ranges) facilities for LAL (limulus amebocyte lysate) testing, membrane filtration sterility testing, antibiotic assay, etc. C.3.7.7 In particular give brief information on the use of computers, microprocessors etc. in the factory.
C.3.8	(250 words/one A4 page) C.3.8.1 Who is responsible for maintenance and servicing? C.3.8.2 Are there written procedures and contractual details for outside work? C.3.8.3 Are maintenance routines which could affect product quality clearly identified?

	C.3.8.4 Are records kept of: 1. type and frequency of service/check; 2. details of service repairs and modifications? C.3.8.5 Are reports made known to the users?
C.3.9	(750 words/three A4 pages) C.3.9.1 Briefly describe the Company's general policy and protocols for qualification and validation (prospective and retrospective). C.3.9.2 Is there regular revalidation of critical equipment? C.3.9.3 An outline of process validation may be given here or cross-referenced to production para 5.4. C.3.9.4 Describe the system for the release for sale or supply of development and validation batches. C.3.9.5 What are the arrangements for computer validation, including software validation? C.3.9.6 Describe equipment calibration policy and records kept.
C.3.10	(250 words/one A4 page) C.3.10.1 Are there written specifications and procedures for cleaning, cleaning agents and their concentration for the method of cleaning and the frequency? C.3.10.2 Are cleaning agents changed from time to time? C.3.10.3 Have the cleaning procedures been validated and what was the method of evaluating the effectiveness of cleaning? C.3.10.4 Are cleaning methods monitored routinely by chemical and/or microbiological methods? C.3.10.5 What are the cleaning methods (and their frequency) for the water supply system, air handling system and dust extraction system?
C.4	**Documentation.** (500 words/two A-4 pages) Note: This section refers to all documentation used in manufacture. Manufacture involves all activities relating to the production and control of pharmaceutical products.
C.4.1	C.4.1.1 Is there a description of the documentation system? C.4.1.2 Who is responsible for the preparation revision and distribution of documents? C.4.1.3 Where are the master documents stored? C.4.1.4 Is there a standard format and instruction of how documents are to be prepared? Are there documents for: 1. Product/Process Specifications. 2. Raw material specifications. 3. Packaging component specifications. 4. Standard process instructions including packaging. 5. Batch records including packaging. 6. Analytical methods. 7. QA release procedures. C.4.1.5 How is the documentation controlled? C.4.1.6 For how long are documents kept after release of the batch? C.4.1.7 Detail any arrangements for electronic or microfilmed records.
C.4.2	Are the following documents available and in use? C.4.2.1 Equipment specifications. C.4.2.2 Specifications for disposables i.e. cleaning materials. C.4.2.3 Standard operating procedures. C.4.2.4 Quality Control Procedures. C.4.2.5 Training procedures. C.4.2.6 Computer program specifications. C.4.2.7 Documentation control of process deviations. C.4.2.8 Calibration and test documents (see para 3.9.5). C.4.2.9 Validation documents (see paras 3.9 and 5.4). C.4.2.10 Reconciliation of batches of raw materials, major packing components i.e. product-contact and printed materials. C.4.2.11 List and briefly explain the use of any additional standard documentation used routinely.
C.5	**Production.**
C.5.1	This narrative should be kept to a minimum and generalized schematic layouts used where possible. The following points should be addressed: C.5.1 Describe the operations capable of being carried out at the site with the existing facilities and specify the types of pharmaceutical products. When packaging only is undertaken, give a brief description only, e.g. labelling, filling etc, and the nature of containers used e.g. sachets, tamper evident glass containers. If cytotoxic or radio-active substances are handled give details of the products. Describe the production operations using flow charts if possible. Technical details are not required. Describe how products are identified during production and how in-process storage is organized.
C.5.2	Identification of suppliers lot number with the company's lot number. Sampling plans. Status labelling e.g. by using labels or by computer. Issue of materials to manufacture and package. The control of weighing. Checking methods. How are materials being used for manufacture identified and released? C.5.2.1 Control of Bulk Manufacture: Checks on key parameters during manufacture e.g. blend times, filter integrity tests. Records of key parameters. In-process checks. Records of in-process checks. Compliance with the Marketing Authorisation. C.5.2.2 Packing: Release of bulk, semi-finished products, packing materials; Confirmation of identity and line clearance checks; In-process checks.

	C.5.2.3 Quarantine and release of finished products; compliance with the Marketing Authorisation. C.5.2.4 Explain the role of the Authorized Person(s).
C.5.3	C.5.3.1 What arrangements are in place for reprocessing or reworking batches of products?
C.5.4	C.5.4.1 Are reject materials and products clearly labelled? Are they stored separately in restricted areas? C.5.4.2 Describe arrangements for sentencing the materials and their disposal. Is destruction recorded?
C.5.5	An outline of process validation protocol only is required. (See para 3.9.3)
C.6	**Quality Control.**
C.6.1	C.6.1.1 (a) Describe the elements of the QC system e.g. specifications, test methods, and other quality related data collection. (b) Briefly describe the activities of analytical testing, packaging, component testing, biological and microbiological testing. C.6.1.2 If the review of batch documentation and release of final documentation takes place in this department, give details. (see also para 1.9.5)
C.7	**Contract Manufacture and Analysis.**
C.7.1	Describe briefly the details of the technical contract between the contract giver and acceptor and the way in which the GMP compliance is assessed to ensure product compliance with the Marketing Authorization.
C.8	**Distribution, Complaints and Product Recall.**
C.8.1	C.8.1.1 Is the warehouse secure? C.8.1.2 Is it environmentally controlled? C.8.1.3 Is there refrigerated storage? C.8.1.4 How are the materials stored e.g. pallet racking? C.8.1.5 How is the status of products controlled e.g. by computer, by label? C.8.1.6 What are the methods of distribution to customers? C.8.1.7 Does the despatch order ensure first in/first out and identify the lot number?
C.8.2	C.8.2.1 Complaints. C.8.2.1.1 Is there a written complaints procedure? C.8.2.1.2 Who is responsible for: 1. Logging; 2. Classifying; 3. Investigating complaints. C.8.2.1.3 Are written reports prepared? C.8.2.1.4 Who reviews these reports? C.8.2.1.5 For how long are complaints records kept? C.8.2.2 Product Recalls. C.8.2.2.1 Is there a written procedure which describes the sequence of actions to be followed including: 1. Retrieval of distribution data; 2. Notification of customers; 3. Receipt/segregation/inspection of returned product; 4. Investigation/reporting of cause; 5. Reporting corrective action. C.8.2.2.2 Who is responsible for coordinating product recalls? C.8.2.2.3 Who notifies the Competent Authority of complaints and recalls. C.8.2.2.4 Is the Competent Authority involved in complaints and the decision to recall? C.8.2.2.5 Can recalls be effected below wholesale level?
C.9	**Self Inspection.**
C.9.1	C.9.1.1 Describe how the self inspection system verifies that those activities that have a bearing on quality comply with the planned arrangement. C.9.1.2 Are the quality systems effective? C.9.1.3 Are there documented procedures for the self inspection system and for the follow-up actions? C.9.1.4 Are the results of the self inspection system documented, brought to the attention of the personnel having responsibility for the area and activities inspected? C.9.1.5 Does the system ensure that those responsible for the area or activity take timely corrective action on the deficiencies found?

(Slightly modified after [3])

Annex 3: PIC/S Participating Authorities (current list of April 2007)

Country	Name of Authority	Address
Australia 	Therapeutic Goods Administration	Department of Health and Ageing GPO Box 100 AU - WODEN ACT 2606
Austria 	AGES PharmMed	Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH, Schnirchgasse 9, AT - 1030 Vienna
Belgium 	Ministère des Affaires sociales, Santé publique et Environnement	Direction générale: Médicaments Cité Administrative de l'Etat Quartier Vésale BE - 1010 Brussels
Canada 	Health Products and Food Branch Inspectorate (HPFBI)	Health Canada Graham Spry Building, 2nd Floor, Room 201 250 Lanark Avenue, AL 2002B CA - Ottawa, Ontario, K1A0K9
Czech Republic 	State Institute for Drug Control	Srobárova 48 CZ - 100 41 Prague 10
Czech Republic	Institute for State Control of Veterinary Biologicals and Medicaments	Hudcova 56A CZ - 621 00 Brno
Denmark 	Danish Medicines Agency	1 Axel Heides Gade DK - 2300 Copenhagen S
Estonia 	State Agency of Medicines	1 Nooruse Str. EE - 50411 Tartu
Finland 	National Agency for Medicines	Mannerheimintie 103b P.O. Box 55 FI - 00301 Helsinki
France 	French Agency for the Safety of Health Products (AFSSAPS)	143-145 Boulevard Anatole France FR - 93285 Saint Denis
Germany 	Bundesministerium für Gesundheit (Federal Ministry for Health)	Am Probsthof 78a DE - 53121 Bonn Germany
	Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten (ZLG) (Central Authority of the Laender for Health Protection regarding Medicinal Products and Medical Devices)	Sebastianstrasse 189 DE - 53115 Bonn

Country	Name of Authority	Address
Greece 	National Organisation for Medicines (NOM)	Messoghion Ave 284 GR - Holargos 155 62 (ELLAS)
Hungary 	National Institute of Pharmacy	P.O. Box 450 HU - 1372 Budapest 5
Iceland 	The Icelandic Medicines Control Agency (IMCA)	Eidistorg 13-15 P.O. Box 180 IS - 170 Seltjarnarnes
Ireland 	Irish Medicines Board	Block A, Earlsfort Centre Earlsfort Terrace IE - Dublin
Italy 	Agenzia Italiana del Farmaco	Via della Sierra Nevada 60 IT - 00144 Rome
Latvia 	State Agency of Medicine http://www.vza.gov.lv/	15, Jersikas St. LV - 1003 Riga
Liechtenstein 	Kontrollstelle für Arzneimittel	Beim ALKVW Postplatz 2 LI - 9494 Schaan
Malaysia 	National Pharmaceutical Control Bureau	Ministry of Health Malaysia PO Box 319 46730 Petaling Jaya MY - SELANGOR
Netherlands 	Inspectorate of Health Care	P.O. Box 16119 NL - 2500 BC D
Norway 	Norwegian Medicines Agency	Sven Oftedals Vei, 8 NO - 0950 Oslo
Poland 	Main Pharmaceutical Inspectorate http://www.vza.gov.lv/	38/48 Dluga Stress PO - 00238 Warszawa
Portugal 	Instituto Nacional da Farmácia e do Medicamento (INFARMED)	Avenida do Brasil, no 53 Pavilhão 21-A PT - 1700 Lisbon
Romania 	National Medicines Agency http://www.anm.ro/en/home.html	Strada Maior Aviator Sanatescu 48 Sectorul I RO - Bucharest
Singapore 	Health Sciences Authority Singapore Centre for Drug Administration	11 Biopolis Way, #11-03 Helios SG - Singapore 168667
Slovak Republic 	State Institute for Drug Control http://www.sukl.sk/	Kvetná 11 SK - 825 08 Bratislava 26

Country	Name of Authority	Address
Spain 	Agencia Española de Medicamentos y Productos Sanitarios	Subdirección General de Inspección y Controlo de Medicamentos Division de Inspección y Control Farmaceútico C/Alcalá 56 ES - 28014 Madrid
Sweden 	Medical Products Agency	Box 26 SE - 751 25 Uppsala
Switzerland 	Swiss Agency for Therapeutic Products (Swissmedic)	Hallerstrasse 7 Postfach CH - 3000 BERN 9
United Kingdom 	Medicines and Healthcare Products Regulatory Agency (MHRA)	Market Towers 1 Nine Elms Lane Vauxhall GB - London SW8 5NQ

List of Associated Partners of PIC/S

Abbreviation	Name of Organization	Address
EMEA 	European Medicines Agency	7 Westferry Circus Canary Wharf UK - London E14 4HB United Kingdom
UNICEF 	UNICEF	UNICEF Plads Freeport DK - 2100 Copenhagen Ø Denmark
WHO 	World Health Organization	Avenue Appia 20 CH - 1211 Geneva 27 Switzerland

(List modified after http://www.picscheme.org/index.php?p=member)

Oman, Russia, Argentina, Malta, Israel, Lithuania, South Africa, the Ukraine and the US FDA are being assessed for PIC/S membership. Malta officially applied in October 2006 for membership [66]. Regarding the membership of the US FDA PIC/S had already prepared a list of questions to be addressed by the FDA [66]. Brazil, Cyprus, Indonesia Philippines, Slovenia, Cyprus and Thailand have indicated an interest in seeking membership.

For 2007 Brazil, China, India, Japan, Korea, Mexico, Russia and Turkey should be encouraged to apply to join the PIC/S. [14].

The Science and Technology Development Center (STDC) of Taiwan is also actively pursing accession for Taiwan to the PIC/S, mutual recognition agreements for GMP inspection of pharmaceutical facilities, and international conference participation.

Annex 4: Taiwan: Plant Master File Checklist

Checklist of Plant Master File (PMF) for Overseas Pharmaceutical Facilities

Reg. No.	

Item	Review and fill the table with labeling the pages by the applicant			Review by Taiwan DOH
A. BASIC INFORMATION				
1. Name				
2. Address Country	(Plant) (Office)			
3. Brief plant introduction		□ Yes □ No	P.	
4. Information for the whole plant		□ Yes □ No	P.	
5. Product list	a. Photocopy of the documents to cover the approved manufacturing items issued by local health authority.	□ Yes □ No	P.	
	b. A complete product list should be attached. The products should be categorized by dosage forms and the active ingredients of each product should be indicated too.	□ Yes □ No	P.	
	c. Specify if there is any toxic, hazardous substances (e.g. antibiotics, hormones, cytostatics) manufactured by this plant. And if they are manufactured using special facilities or they are manufactured by sharing the same facilities with other products.	□ Yes □ No	P.	
	d. State if human and/or veterinary products, biological products, radiopharmaceuticals, diagnostic reagents, medical devices, cosmetics, or food products are also manufactured on the site.	□ Yes □ No	P.	
6. Dosage forms intended to be registered				

Item		Self-Review		Review by Taiwan DOH
B. ORGANIZATION AND PERSONNEL				
1. Organization chart and employee number (number of employees engaged in the production, quality control, storage and distribution should be attached with organization chart.)		□ Yes □ No	P.	
2. Basic staff training and in-service training	a. Written procedures for basic and in-service Training and the filing of training record.	□ Yes □ No	P.	
	b. Special training for personnel involved in the aseptic processing area shall have particular training for such function (for sterile products only)	□ Yes □ No	P.	
3. Written procedures for staff operation sanitation practice		□ Yes □ No	P.	
C. BUILDINGS AND FACILITIES				
1. Building and facilities	a. Drawing(s) of the whole plan should be attached.	□ Yes □ No	P.	
	b. Drawing(s) of each buildings showing each floor separately with a list of rooms and facilities in detail	□ Yes □ No	P.	
※ Blueprints may be requested if necessary	c. The flows for personnel and materials should be Specified in the drawings.	□ Yes □ No	P.	
2. Ventilation systems should be described.		□ Yes □ No	P.	
3. Specific areas with potential risks of airborne contamination should be indicated, preferably in a diagram. Classification of the rooms (e.g. Class I,II,III,IV) used for manufacturing sterile products should be mentioned.		□ Yes □ No	P.	
4. Environmental monitoring for sterile products (for sterile products only).		□ Yes □ No	P.	
5. Special areas for the handling of highly toxic, hazardous and sensitizing materials should be indicated.		□ Yes □ No	P.	
6. Describing water treatment system as well as its periodical maintenance and testing procedures.		□ Yes □ No	P.	
7. If antibiotic products are manufactured in the plant, the facilities used for the operation relating to the manufacture, processing, and packing should be indicated. If they are not manufactured in an isolated area, documents should be provided to justify that there is no risk of cross-contamination or mix-ups.		□ Yes □ No	P.	
8. If penicillin drug products are manufactured in the plant: List the equipments used for the manufacturing, processing or packaging of penicillin products. State if the equipment is shared with other pharmaceuticals, or if the building is separated. In rare cases, the penicillin drug products may be manufactured in an area separate from other drug products in the same building if sufficient documentation is provided to show that the area is self-contained.	They are manufactured in a separate building：	□ Yes □ No	P.	
	Pressure differentials between rooms should be indicated.	□ Yes □ No	P.	

Item		Self-Review		Review by Taiwan DOH
D. PRODUCTION EQUIPMENTS				
1. A list of major manufacturing equipment is required. Equipment used in the manufacture, processing packing, or holding of a drug product shall be of appropriate design.		□ Yes □ No	P.	
2. Written operation documents for equipment cleanness, calibration and maintenance.		□ Yes □ No	P.	
E. CONTROL OF COMPONENTS, DRUG PRODUCT CONTAINERS,CLOSURES, PACKING AND LABELING				
1. Written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components, drug product containers, closures, labeling and packaging materials.		□ Yes □ No	P.	
2. Each component should be tested for each lot and full items to conform with all appropriate, written procedures. If reduction test is conducted, written QA or QC procedures should be included.		□ Yes □ No	P.	
F. PRODUCTION IN-PROCESS CONTROLS				
1. Written procedures for in-process control and the items of process control to ensure that the property, strength, quality and purity all fulfill the written specifications for a product.		□ Yes □ No	P.	
2. Description of the general policy for in-process quality control.		□ Yes □ No	P.	
3. Description of the specific operation procedures carried out for each individual dosage form.		□ Yes □ No	P.	
G. QUALITY CONTROL				
1. List the equipments and instruments used for quality control and laboratories control.		□ Yes □ No	P.	
2. Relevant written documents regarding the responsibility and authority of the Quality Control Department		□ Yes □ No	P.	
H. DOCUMENTING STERILIZATION PROCESS VALIDATION (NO NEED FOR PLANT WITHOUT STERILE PRODUCTS)		□ Yes □ No	P.	
I. CONTRACT MANUFACTURE AND CONTRACT ANALYSIS				
Description of the way in which the GMP compliance of the contract acceptor is assessed	1. Describe if contract manufacture or analysis exists.	□ Yes □ No	P.	
	2. Describe the condition of contract manufacture or analysis. If the PMF of contract manufacturer has been approved, relevant evidence should be provided.	□ Yes □ No	P.	
J. DISTRIBUTION, COMPLAINTS & PRODUCT RECALL		□ Yes □ No	P.	
K. INSPECTION AND INTERNAL AUDIT		□ Yes □ No	P.	

[I3]

Annex 5: General Structure of EU GMP Guide

Part I - Basic requirements for Medicinal products.

Chapter 1 Quality Management.
Chapter 2 Personnel.
Chapter 3 Premise and Equipment.
Chapter 4 Documentation.
Chapter 5 Production.
Chapter 6 Quality Control.
Chapter 7 Contract Manufacture and Analysis.
Chapter 8 Complaints and Product Recall.
Chapter 9 Self-Inspection.

Part II - Basic requirements for Active Substances used as Starting Materials.

Annexes

Annex 1 Manufacture of Sterile Medicinal Products.
Annex 2 Manufacture of Biological Medicinal Products for Human Use.
Annex 3 Manufacture of RadioPharmaceuticals.
Annex 4 Manufacture of Veterinary Medicinal Products other than Immunological Veterinary Medicinal Products.
Annex 5 Manufacture of Immunological Veterinary Medicinal Products.
Annex 6 Manufacture of Medicinal Gases.
Annex 7 Manufacture of Herbal Medicinal Products.
Annex 8 Sampling of Starting and Packaging Materials.
Annex 9 Manufacture of Liquids, Creams and Ointments.
Annex 10 Manufacture of Pressurised Metered Dose Aerosol Preparations for Inhalation.
Annex 11 Computerised Systems.
Annex 12 Use of Ionising Radiation in the Manufacture of Medicinal Products.
Annex 13 Manufacture of Investigational Medicinal Products.
Annex 14 Manufacture of Products derived from Human Blood or Human Plasma.
Annex 15 Qualification and validation.
Annex 16 Certification by a Qualified Person and Batch Release.
Annex 17 Parametric Release.
Annex 18 Good Manufacturing practice for active pharmaceutical ingredients (requirements for active substances used as starting materials from October 2005 covered under part II).
Annex 19 Reference and Retention Samples.

Annex 6: CFR PART 211- Current Good Manufacturing Practice For Finished Pharmaceuticals

Subpart	Section
A: General Provisions	211.1 Scope. 211.3 Definitions.
B: Organization and Personnel	211.22 Responsibilities of quality control unit. 211.25 Personnel qualifications. 211.28 Personnel responsibilities. 211.34 Consultants.
C: Buildings and Facilities	211.42 Design and construction features. 211.44 Lighting. 211.46 Ventilation, air filtration, air heating and cooling. 211.48 Plumbing. 211.50 Sewage and refuse. 211.52 Washing and toilet facilities. 211.56 Sanitation. 211.58 Maintenance.
D: Equipment	211.63 Equipment design, size, and location. 211.65 Equipment construction. 211.67 Equipment cleaning and maintenance. 211.68 Automatic, mechanical, and electronic equipment. 211.72 Filters.
E: Control of Components and Drug Product Containers and Closures	211.80 General requirements. 211.82 Receipt and storage of untested components, drug product containers, and closures. 211.84 Testing and approval or rejection of components, drug product containers, and closures. 211.86 Use of approved components, drug product containers, and closures. 211.87 Retesting of approved components, drug product containers, and closures. 211.89 Rejected components, drug product containers, and closures. 211.94 Drug product containers and closures.
F: Production and Process Controls	211.100 Written procedures; deviations. 211.101 Charge-in of components. 211.103 Calculation of yield. 211.105 Equipment identification. 211.110 Sampling and testing of in-process materials and drug products. 211.111 Time limitations on production. 211.113 Control of microbiological contamination. 211.115 Reproccessing.
G: Packaging and Labelling Control	211.122 Materials examination and usage criteria. 211.125 Labelling issuance. 211.130 Packaging and labelling operations. 211.132 Tamper-evident packaging requirements for over-the-counter (OTC) human drug products. 211.134 Drug product inspection. 211.137 Expiration dating.
H: Holding and Distribution	211.142 Warehousing procedures. 211.150 Distribution procedures.
I: Laboratory Controls	211.160 General requirements. 211.165 Testing and release for distribution. 211.166 Stability testing. 211.167 Special testing requirements. 211.170 Reserve samples. 211.173 Laboratory animals. 211.176 Penicillin contamination.
J: Records and Reports	211.180 General requirements. 211.182 Equipment cleaning and use log. 211.184 Component, drug product container, closure, and labelling records. 211.186 Master production and control records. 211.188 Batch production and control records. 211.192 Production record review. 211.194 Laboratory records. 211.196 Distribution records. 211.198 Complaint files.
K: Returned and Salvaged Drug Products	211.204 Returned drug products. 211.208 Drug product salvaging.

(modified after [74])

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Homberg/Ohm, den 30.05.2007

Unterschrift