Regulatory Requirements to the Quality of Parenteral Medicinal Products according to the Common Technical Document

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Regulatory Requirements to the Quality of Parenteral Medicinal Products according to the Common Technical Document

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1. List of Abbreviations

cfu	Colony forming unit
CPMP	Committee for Proprietary Medicinal Products
CTD	Common Technical Document
EDQM	European Directorate for the Quality of Medicines
FDA	Food and Drug Administration
GMP	Good Manufacturing Practices
GMP-Guide	Guide to Good Manufacturing Practices for Medicinal Products
HEPA	High efficiency particulate air filter
ICH	International Conference on Harmonisation
IU	International Units
MHW	Ministry of Health
MRA	Mutual Recognition Agreement
NfG	Note for guidance
PECA	Protocol of the European agreement on Conformity assessment and Acceptance of industrial products
Ph. Eur.	European Pharmacopoeia
PIC	Pharmaceutical Inspection Convention
PICS	Pharmaceutical Inspection Co-operation Scheme
ppm	Parts per million
SAL	Sterility Assurance Level

2. Introduction

Parenteral medicinal products comprise pharmaceutical forms like injections, infusions, concentrates for injections or infusions, powders for injections or infusions, and implants according to the definition of the European Pharmacopoeia (Ph. Eur.) [18]. For parenteral medicinal products there are different requirements for the quality in comparison to non-parenteral products. The reasons for such differences are mainly based on the essential need for clinical tolerance according to their specific way of administration. This leads to the main requirements on sterility, absence/ limitation of any bacterial endotoxins or pyrogens, limitation of particulate matters, pH, and osmolarity. A compliance must be assured at final release for parenteral medicinal products.

Since the requirements on particulate matters, pH, and osmolarity can be assured by choice of excipients, like e.g. addition of a specific solvent or salt, the requirements on sterility and limitation of bacterial endotoxins or pyrogens requires a sterilisation process.

However, due to the essential need for each single unit to be sterile and with limited bacterial endotoxins or pyrogens and the nature of statistical coincidence of testing single units of a whole batch at final release, the reliability of the manufacturing process provides a greater assurance to the quality than testing of samples alone. This differs to other test methods, like e.g. test of pH, osmolarity or content, where the quality can be statistically assured by a defined number of single units representing the whole batch. Consequently, more information about the manufacturing process must be provided in the marketing authorisation dossier.

It is the aim of this master thesis to describe and discuss the specific requirements for the quality-part of the marketing authorisation dossier for parenteral medicinal products. This master thesis covers only medicinal products containing chemical substances within the European Community. The differences to non-parenteral medicinal products should be emphasised based on requirements in manufacture and quality control (GMP requirements).

In addition some suggestions should be given for the revision or introduction of new guidelines and if possible a way to simplify the scope on information in the marketing authorisation dossier for parenteral medicinal products.

3. Legal background

3.1 Legal background on regulatory aspects and on manufacture and quality control

The basic legal background on regulatory aspects and for manufacture and quality control is laid down in two directives, supported by guidelines and recommendations in Europe. The first important directive is the Directive of the European Parliament and of the Council 2001/83/EC describing basic regulatory requirements and requirements for manufacture and quality control [17]. More specific requirements especially on the quality assurance system of manufacture and quality control are laid down in the Commission Directive 91/356/EEC [2].

3.1.1 Directive 2001/83/EC

The Directive 2001/83/EC applies to industrially produced medicinal products for human use intended to be placed on a national market in apart member states. The directive was recently codified by assembling different former single directives. This directive describes in title III the regulatory part of requirements including procedures as directed to an applicant for marketing authorisation. Finally the Annex I provides the formal requirements for the documentation of a marketing authorisation dossier.

In addition, the basic requirements as directed to the manufacturers regarding the manufacture and quality control are described in title IV. Further to articles 40 to 53 it is demanded for manufacturers of medicinal products to hold a manufacturing authorisation for manufacture, quality control and storage of specific medicinal products and pharmaceutical forms. This authorisation must be issued for a specific premises.

3.1.2 Directive 91/356/EEC (GMP Directive)

Having regard to the Directive 2001/83/EC more specific requirements for manufacturers of medicinal products are laid down in the Commission Directive 91/356/EEC. This directive describes the principles and requirements of good manufacturing practices (GMP). GMP means the part of quality assurance that ensures the consistency of produced and controlled medicinal products according to quality standards, regarding personnel, premises, equipment, documentation, production, quality control, contracting out, complaints, product recalls, and self inspection [2]. The content of this directive was implemented into national laws of the member states, e.g. in Germany it was brought into force as “Pharmabetriebsverordnung”.

A manufacturer responsible for batch release should hold a manufacturing authorisation confirming the compliance with this directive. The compliance is issued and inspected by a

national supervisory competent authority based on the location of the manufacturer in an EU member state or in a country with an operating mutual recognition agreement with the European Community (MRA or PECA).

3.2 Guidelines and recommendations for parenteral medicinal products

Based on the Directives 2001/83/EC and 91/356/EEC there are several guidelines and recommendations describing the more detailed information. In the following sections there are only the specific relevant guidelines for parenteral medicinal products briefly described. Further guidelines may be relevant in addition according to specific product characteristics.

The Guide to good manufacturing practice for medicinal products

The "Guide to good manufacturing practice for medicinal products" (GMP-Guide) publishes an interpretation of the Directive 91/356/EEC. The relevant sections especially for manufacture of parenteral medicinal products are:

- Annex 1 (manufacture of sterile medicinal products)
- Annex 12 (use of ionising radiation in the manufacture of medicinal products)
- Annex 17 (parametric release)

The European Pharmacopoeia

The European Pharmacopoeia, an official standard reference in the European Community [18] publishes standard monographs and general texts about quality of medicinal products. The relevant texts and methods for parenteral medicinal products are:

- Biological tests: Sterility/ pyrogens/ bacterial endotoxins
- General text on sterility: Methods of preparation of sterile products/ biological indicators/ efficacy of microbial preservation/ microbiological quality of pharmaceutical preparations/ F_0 concept to steam sterilisation of aqueous preparations

The Committee for Proprietary Medicinal Products (CPMP)

Several CPMP-guidelines cover regulatory aspects for the marketing authorisation dossier and recommendations for manufacture and quality control as well. They are published by the Committee for Proprietary Medicinal Products (CPMP), an official scientific committee laid down in the Directive 2001/83/EC. The following CPMP-guidelines concern the quality aspects of parenteral medicinal products:

- The use of ionising radiation in the manufacture (CPMP 3AQ4A)
- Excipients in the dossier (CPMP 3AQ9A)
- Plastic primary packaging material (CPMP 3AQ10A)
- NfG on specifications and control tests on the finished product (CPMP 3AQ11A)
- NfG on antioxidants and antimicrobial preservatives (CPMP/CVMP/QWP/115/95)
- Decision trees for selection of sterilisation methods (CPMP/QWP/054/98)
- NfG on development pharmaceutics (CPMP/QWP/155/96)
- NfG on quality of water for pharmaceutical use (CPMP/QWP/158/01)
- NfG on limitation to the use of ethylene oxide (CPMP/QWP/159/01)
- NfG shelf-life of sterile products after first opening (CPMP/QWP/159/96)
- In-use stability testing of human medicinal products (CPMP/QWP/2934/99)
- NfG on parametric release (CPMP/QWP/3015/99)
- NfG on manufacture of the finished dosage form (CPMP/QWP/486/95)
- NfG on process validation (CPMP/QWP/848/96)

The International Conference on Harmonisation (ICH)

The International Conference on Harmonisation (ICH) an international association publishes common harmonised ICH-guidelines based on a five-step approach for the regions of the European Union, USA and Japan. Especially this guideline was issued by ICH and the CPMP and includes specific requirements for parenteral medicinal products:

- Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances (ICH Q6A) or (CPMP/ICH/367/96)

The Pharmaceutical Inspection Convention (PIC) and Pharmaceutical Inspection Cooperation Scheme (PICS)

Further recommendations cover requirements for manufacture and quality control of medicinal products. These guidelines are published by international associations for mutual recognition of inspections of manufacture of medicinal products, the Pharmaceutical Inspection Convention (PIC) and Pharmaceutical Inspection Cooperation Scheme (PICS). Especially the following PIC/PICS guidelines should be considered for parenteral medicinal products:

- Recommendation on the validation of aseptic processes (PI 007-1, July 2001)
- Recommendation on sterility testing (PE 001-2, April 2000)

- Recommendation on isolators used for aseptic processing and sterility testing (PI 014-1, June 2002)

4. GMP requirements for parenteral medicinal products

This section describes briefly the requirements for manufacture and quality control of parenteral medicinal products having regard to the Directives 2001/83/EC and 91/356/EEC, the GMP-Guide and other relevant guidelines providing recommendations as directed to the manufacturers. This description does not claim to be complete for parenteral medicinal products. Its intention is to provide an overview and to support the subsequent evaluation of the regulatory requirements.

4.1 Common requirements of parenteral medicinal products

4.1.1 Common tests in quality control

The following tests in quality control are needed for parenteral medicinal products comprising pharmaceutical forms like injections, infusions, concentrates for injections or infusions, powders for injections or infusions, and implants [18] in demarcation to non-parenteral products:

- Sterility
- Absence/ limitation of bacterial endotoxins or pyrogens
- Particulate matter of the ready to use product
- pH of the ready to use product
- Osmolarity of the ready to use product

These test methods for quality control are standardised according to the European Pharmacopoeia but need to be validated for the product concerns.

4.1.2 Common requirements in manufacture

Clean room area classification

As already mentioned the requirements for parenteral medicinal products on defined particulate matters, osmolarity and pH can be usually achieved by choice of an appropriate formulation, like e.g. addition of suitable salts, solvent or/ and emulsifier or by an appropriate solvent for reconstitution of solid forms. However, in order to comply with requirements like sterility and absence of/ limited bacterial endotoxins or pyrogens a suitable sterile process is

needed to be included in manufacture. The need for an appropriate sterile process is the main difference in manufacture of parenteral medicinal products comparing to non-parenteral products.

The basic requirement for sterile processes is to minimise the risk for microbial, particulate and pyrogen contamination during processing. This can be achieved by appropriate skills, training and attitudes of the involved personnel. The other aspect is an appropriate environment during manufacture and its assurance by monitoring testing. The environment of a specific cleanliness is supplied with air filtered through appropriate filters, like high efficiency particulate air (HEPA) filters. Table 1 shows recommended limits for microbial and particulate monitoring of clean areas during operations according to the GMP-Guide, Annex 1.

The clean area of grade A provides the highest assurance against particulate and microbial contamination. This is the local zone for high risk operations by using normally a laminar air flow work station, e.g. for preparatory and filling procedures in aseptic processing. The clean area grade B is the background environment for grade A zone. Clean areas of grade C and D are applicable for less critical steps in manufacture of sterile products [30]. In demarcation to the manufacture of non-parenteral products there is not such a strict limitation.

Table 1: Recommended maximum limits for particulate and microbial monitoring of clean areas during operation

Grade	Particulate contamination		Microbial contamination (average values)			
	Particles of 0.5 µm particles/m³	Particles of 5 µm particles/m³	Air sample cfu/m³	Settle plates (∅ 90 mm)[2] cfu/4 h	Contact plates (∅ 55 mm) cfu/plate	Glove print 5 fingers cfu[3]/glove
A	3500	0	< 1	< 1	< 1	< 1
B	350 000	2 000	10	5	5	5
C	3 500 000	20 000	100	50	25	-
D	Not defined[1]	Not defined[1]	200	100	50	-

[1] Limits depend on the nature of operations.

[2] Individual settle plates may be exposed for less than 4 hours.

General monitoring of sterile processes

For sterile manufacturing processes the microbial and particulate contamination is needed to be monitored in defined periods. The periodical monitoring covers the measurement of the particulate and microbial content in the air, of the water system, the premises and production area, the personnel, and any surfaces of machines, worktops, equipment, and materials relating to the clean room classification. In addition any utilised disinfectants and detergents and residues after disinfection are needed to be monitored as well. For the grade A and B working areas they have to be sterile.

For monitoring appropriate acceptance limits should be defined, divided into individual working, alert and action limits. The working limits define the regular acceptable range during the routine process. An exceeding alert limit indicates a non-regular value still in compliance with the specification. However, this value is needed to be observed for corrective actions towards reaching the working limits. An exceeding action limit indicates a value out of specification. In such a case corrective actions are necessary [30].

4.2 Sterile manufacturing processes for parenteral medicinal products

Besides the common requirements for parenteral medicinal products there are certain differences in manufacturing processes depending on the drug substance, the dosage form, the excipients, technological configurations and equipment of the manufacturing site. An appropriate sterilisation method should be integrated into the manufacture.

For the choice of the adequate sterilisation method the method with the highest possible sterility assurance should be applied for the specific product. It is possible to achieve an individual sterility assurance level (SAL) for each sterilisation process. The SAL is expressed as the probability of a non-sterile item in a population of items after sterilisation and is established by validation procedure. That means, for example, for an SAL of 10^{-6} a probability of not more than 1 viable miroorganism in 10^6 sterilised items of the product [26].

The manufacturing methods can be divided into two main categories according to the sterilisation process:

- Terminal sterilisation
- Aseptic processing with/ without aseptic filtration

It is recognised that other than these sterilisation methods are acceptable if properly validated and justified and if the sterility assurance level is equivalent to the known methods.

In the following sections the different manufacturing methods are briefly described in addition to some special technologies, that are used in sterile manufacture. Modifications and combinations of the methods may be applied if confirmed by validation.

4.2.1 Terminal sterilisation

Terminal sterilisation is a sterilisation process of a product or material in its final container or of a container or closure itself. In general terminal sterilisation is the most preferred sterilisation method with the highest sterility assurance. An exemption is the gas sterilisation (see below). Where it is not possible to carry out such a terminal sterilisation the alternatives are aseptic processing with/ without aseptic filtration. Terminal sterilisation involves usually the preparation steps in an environment of clean room grade D, for exceptional cases in grade C. The filling prior to terminal sterilisation should be carried out in classification grade C. Consequently, prior to sterilisation the product, containers, and closures are of a low bio burden, an expression for a high microbial quality but are not sterile. The microbial content should be minimised to support the subsequent sterilisation process. Terminal sterilisation comprises the following processes:

- Steam sterilisation, especially for aqueous products
- Dry heat sterilisation, especially for non-aqueous liquids, semi-solid or dry powder products
- Radiation sterilisation, especially for non-aqueous liquids, semi-solid or dry powder products
- An exception of terminal sterilisation methods is the gas sterilisation, due to its toxicological profile. This method should only be used in exceptional cases where no suitable alternatives exist.

Up from these methods the steam sterilisation using saturated steam under pressure provides usually the highest SAL with values of 10^{-6} or better. Further to the Ph. Eur. the reference conditions for aqueous preparations are at minimum of a temperature of 121 °C for 15 minutes. In cases of different conditions a so called F_0 concept according to Ph. Eur. can be applied for steam sterilisation.

For using the dry heat sterilisation the reference conditions are at minimum of 160 °C for at least 2 hours according to the Ph. Eur. For sterilisation and depyrogenation of glassware the dry heat is employed at temperatures of higher than 220 °C.

For the ionising radiation sterilisation method the reference absorbed dose is 25 kGy provided by gamma radiation according to the Ph. Eur..

The use of gas sterilisation with substances like ethylene oxide is only acceptable when no safer alternatives exist. For this sterilisation it is required that first the penetration of gas and moisture into the product to be sterilised must be ensured and furthermore any residues of ethylene oxide should be reproducible below the limited concentration [11].
The conditions of the Ph. Eur. should preferable be adopted for all terminal sterilisation methods. Modifications may be acceptable if validated and justified within the established tolerances during the routine process [26].

Parametric release

For manufacturing methods including a validated terminal sterilisation process like steam, dry heat or ionising radiation sterilisation, a parametric release can be accepted after approval of the competent authority. Parametric release means that not all tests at final release are needed to be carried out for the finished drug product, if the appropriate quality can be assured by process data. For sterile products the parametric release can be applied for sterility testing, but only applicable for the above mentioned terminal sterilisation methods. An example can be the manufacture of sterile sodium chloride solution or of water for injection with an applied steam sterilisation procedure and experiences based on historical batch results [30],[26],[14].

Validation of terminal sterilisation

Process validation of terminal sterilisation covers:

- Tests with biological indicators according to Ph. Eur.
- Physical tests of process conditions
- Integrity testing of container-closure system, if applicable

Biological indicators are standardised preparations of selected microorganisms. They are characterised by the species, number of strain in original collection, number of viable spores and the D-value (standard conditions of a sterilisation method to reduce 10 % of original viable organisms). The indicators are preferable placed at critical locations and incubated to indicate the success of sterilisation.
The process validation of process condition profiles covers:

- *Steam or dry heat sterilisation*: the cycle parameters like time, pressure, temperature, F_0-value for loading, heating, sterilisation, cooling, and reloading should be estimated. Admitted air should be passed through a HEPA filter.
- *Radiation sterilisation*: the cycle parameters like time, radiation dose rate for loading, sterilisation phase, and reloading, the loading patterns with loading densities and

distances to the source, and the distribution of total absorbed radiation dose should be estimated by dose mapping. The minimum and maximum limits of absorbed dose should be defined afterwards.

- *Gas sterilisation* with ethylene oxide: the time, temperature, moisture, pressure profile for the equilibrium phase, loading, sterilisation, and degassing phase should be estimated. Furthermore, the penetration of gas and moisture and the residues of ethylene oxide should be validated according to acceptance limits.

The validation of *container-closure integrity* is only mentioned in the guidelines for parametric release [14], but in some cases this might be requested for other applications, too. A description is shown in the following section 4.2.2 *Aseptic processing with/ without filtration*.
Finally the validity of the terminal process is needed to be verified at least annually or after critical modifications of the process respectively [11].

Monitoring of terminal sterilisation

Besides the monitoring of general methods for sterile processes on environmental conditions (see in section 4.1.2 *Common requirements in manufacture*) the following tests should be considered in monitoring of terminal sterilisation [23],[30],[31]:

- The tests of bioburden. This is the number of viable microorganisms on or in the product prior to final sterilisation.
- Processing including biological indicators
- Test of processing parameters, like sterilisation time, temperature, humidity, pressure, F_0-value, dosage profile of radiation (by dosimetry), gas flow, gas concentration profile and gas residues.

4.2.2 Aseptic processing with/ without filtration

In cases where no terminal sterilisation method is possible aseptic processing with/ without aseptic filtration should be chosen, e.g. for heat-labile and/ or radiation-labile substances.

Aseptic processing with filtration

Aseptic processing including a final aseptic filtration should be chosen as it provides a higher level of SAL than without filtration. The environmental conditions, the need of preparatory

sterilisation processes for used containers, closures, materials and any equipments are the same as employed for aseptic processing (see below).
For filtration a sterile filter of nominal pore size of 0.22 micron or less or of at least equivalent micro-organism retaining properties should be used. A final filtration step should be carried out preferable directly prior to filling into the previously sterilised final container.

Aseptic processing without filtration

For some products where neither a terminal sterilisation method nor aseptic filtration can be employed aseptic processing remains as an applicable manufacturing method, e.g. for some heat-labile and radiation-labile non-aqueous liquids or semi-solid forms. For such a case the starting materials, like drug substance(s) and excipients are sterilised separately, by using a suitable sterilisation method with the highest possible SAL.

Aseptic processing

Any equipment and materials that will get in contact with the finished product, the containers, and closures are needed to be sterilised separately. Due to the lack of a terminal sterilisation all preparations, handling and filling procedures should be done in an environment of grade A with grade B background. In order to avoid any risk of contamination and the possibility of errors a minimum of equipment, material, and personnel should be involved [30].

Validation of aseptic processes

A process validation of aseptic processing comprises:

- Simulation of the aseptic process by media fills
- Integrity testing of container-closure system
- Filter validation in aseptic processing with filtration (filter integrity test)

The *simulation process* (media fills) should emulate the regular routine process regarding a process line, equipment, personnel and time. Three consecutive satisfactory tests (in dependence of the batch size, but at least 3000 units per test) are performed per process line first or after critical modifications. After successful validation the validity is needed to be verified on one simulation test at least twice a year.
The monitoring of validation procedure covers at least the regular monitoring of sterile processes (see section 4.1.2 *Common requirements in manufacture*). The results should indicate suitable test frequencies and sampling areas for the periodical monitoring during

routine process. Some regular possible “worst case” situations and interventions are integrated in validation. The simulation process is performed with a suitable sterile nutrient medium replacing the product. It should be chosen according to the environmental in-house flora and the dosage form:

- Aerobe microorganisms and liquids: A common medium is soybean casein.
- Anaerobe microorganisms and liquids: A common medium is fluid thioglycollate.
- Solid dosage forms (e.g. lyophilsates): Suitable media are polyethylene glycol 8000 or carboxymethyl cellulose. The media should not be subject to freezing.
- Semi-solid dosage forms: The same as used for liquids with additional thickening agents like agar or carboxymethyl cellulose.

The filled media are incubated at a temperature of 20-25 °C for 14 days or at 20-25 °C for 7 days following at 30-35 °C for further 7 days. For results the contamination rate should be less than 0.1 % at 95 % confidence level.

In addition the *integrity of container-closure system* should be established by process validation. The containers are filled with suitable sterile growth medium and inserted in a broth of a defined number of suitable microorganisms. After disinfections the containers are incubated for 14 days in order to indicate any failures of the closure system.

The *filter validation* of any integrated filter systems is performed by a *microbial challenge test* simulating “worst case” conditions. In dependence on the product which may affect filtration (e.g. bacteriostatic or bacteriocidal), filter validation is performed with product or with a replacement. The maximum permitted pressure is evaluated for routine process [37].

Monitoring of aseptic processes

During the regular routine process of aseptic processing the following test methods should be included in monitoring besides the monitoring of general methods for sterile processes (see section 4.1.2 *Common requirements in manufacture*) [30]:

- The test of bioburden: the number of viable microorganisms prior to a final sterile filtration step
- The content of bacterial endotoxins or pyrogens should be tested prior to a final sterile filtration step, where appropriate
- The filter integrity prior and after each filtration process (see filter validation)

4.2.3 Special technologies for sterile processes

Two special technologies for sterile processes are introduced:

- The isolator technology, applied for aseptic processing and sterility testing
- The blow-fill-seal-technology, applied for terminal sterilisation and aseptic processing

Isolator technology

Isolator technology applied in aseptic processing can decrease a risk on microbial contamination during the process comparing to usual aseptic processing. The isolator provides a protective barrier system, that isolates two process areas. Consequently, the product area of clean room class A is completely separated from the operators' area. The product is protected from human-borne contamination and the operator is protected from product's exposure. At the surrounding area of the isolator an environment of at least grade D should be installed. In most cases a pressure differential ensures the containment and sterility of the product. Operating procedures are usually performed through aid of gloves. Materials, products, and equipment are transferred via a transfer port. Prior to use a decontamination of the process area with suitable agents is needed (sporicidal process/ sanitisation), e.g. vapour hydrogen peroxide, formaldehyde, acetic acid [38].

Blow-fill-seal-technology

The blow-fill-seal-technology is an special technology applied in terminal sterilisation processes and aseptic processing. It is an automatic continuous operating process performed in one machine. The process includes the steps: starting with forming of the final container (= parison) from thermoplastic granulates, filling with product and sealing directly afterwards. The processing takes place inside of the machine, separated from the operators' area.
For aseptic processing the blow-fill-seal-equipment is fitted with an air shower providing the appropriate classification grade A/ B. Prior to use a decontamination of the processing area is needed as described for isolator technology, too. For applied terminal sterilisation an environment of at least grade D is installed [37],[30].

Validation of special technologies

The validation of special technologies covers the followings [37],[38]:

- For media fills: The integrated "worst case" situations should be adopted to the specific process, e.g. the following should be considered at simulation process:

For isolator technology: the transfer of material in and out, the change of gloves, sleeves or suits during processing, change of a filling needle, change of a filter

For blow-fill-seal-technology: interventions during the parison formation, parison transfer, the filling procedure, change of a filling needle, change of a filter.

- The decontamination or sanitisation process prior to first processing: Validation of effectiveness of sanitisation with aid of biological indicators. The removal must be assured afterwards. This validity is needed to be verified within a reasonable time period, especially for isolator technology at least every three years.

Other validation procedures may be applicable in dependence on the specific design.

Monitoring of special technologies

Upon the validation results the monitoring should cover besides the monitoring of general methods the followings [37],[38]:

- Microbial and particulate monitoring especially in critical zones
- Temperature, humidity, pressure, airflow inside and outside of processing area and at critical zones
- Leak testing in the processing area and at critical zones
- The filter integrity of microbial retentive HEPA air or fluid filters
- Testing of other specific parameters to indicate functionality

Other test methods may be applicable in dependence on the specific design.

5. Formal regulatory requirements: the Common Technical Document (CTD)

It is the intention of the following sections to describe the requirements for the marketing authorisation dossier (regulatory requirements) of parenteral medicinal products. The Common Technical Document describes the format and structure of documentation whereas the subsequent section includes an evaluation of the specific regulatory requirements in demarcation to non-parenteral products.

5.1 History and current status of the CTD

Since July 1997 a harmonised document providing common requirements on format and structure of documentation for marketing authorisation in the ICH regions has being developed: the Common Technical Document (CTD). It was the intention of harmonisation

regarding the structure of documentation to accelerate the time for assessment at authorities and to simplify electronic submissions in the three ICH regions.

The CTD was published in the ICH guideline M4 (= CPMP/ICH/2887/99). The document achieved Step 4 and is consequently acceptable to the regulatory authorities of Japan (MHW), the USA (FDA) and the European regulatory authorities including Norway and Iceland. At present the CTD is still being implemented. The three ICH parties have made a public commitment to adopt the CTD format on a voluntary basis by 01 July 2003 with mandatory adoption in some further years in future [1]. Especially for Europe it was published that the new CTD format can be used optionally for applications during an experimental period. However, by 01 July 2003 the use of the CTD format will be mandatory for each first application for marketing authorisation in the European Community [1].

5.2 Structure of the CTD

The ICH guideline M4 describes the general organisation of the CTD format and provides further information regarding the sections: *Quality*, *Safety* and *Efficacy*. For the European Community the document was published as *Notice to Applicants, Volume 2B – Presentation and content of the dossier – CTD Edition 2001*. This document has been valid since July 2001 in parallel to the previous format of *Notice to Applicants Volume 2B – Edition 1998*.

The CTD is organised into five modules.

Module 1 is not harmonised and is therefore specific to each region. The Modules 2, 3, 4, and 5 are organised in common structures [35]:

- Module 2 contains summaries and overviews of documentation.
- Module 3 covers the information about the quality of the product regarding manufacture, pharmaceutical development, characterisation including impurity profile, specifications and quality control, excipients, container system and stability of the active drug substance and the finished drug product. This is the relevant module of this master thesis regarding the regulatory requirements for marketing authorisation.
- Module 4 contains reports on animal and in vitro tests providing the information about pharmacology, pharmacokinetics, and toxicology.
- Module 5 contains the human study reports and related information.

Table 2: Organisation of the Common Technical Document (CTD)

Module	Description	Content
Module 1:	Administrative information (Module 1 is not part of the harmonised CTD)	1. Comprehensive table of contents The following documents of module 1 are specific to each region, in the EU-CTD the sections are: 2. Application forms[1] 3. Summary of product characteristics, labelling, package leaflet[1] 4. Information about the experts[1] 5. Spec. requirements for different types of application[1] Annex I Environmental risk assessment[1] Annex II Orphan medicinal products – demonstration of significant benefit[1]
Module 2:	CTD summaries	1. Overall CTD table of contents 2. Introduction 3. Quality overall summary 4. Nonclinical overview 5. Clinical overview 6. Nonclinical summary 7. Clinical summary
Module 3:	Quality	1. Module 3 table of contents 2. Body of data 2.S. Drug substance 2.P. Drug product 3. Literature references
Module 4:	Nonclinical study reports	1. Module 4 table of contents 2. Study reports 3. Literature references
Module 5:	Clinical study reports	1. Module 5 table of contents 2. Tabular listing of all clinical studies 3. Clinical study reports 4. Literature references

[1]Section only of the EU-CTD

6. Regulatory requirements for parenteral medicinal products

The *Module 3* of the CTD, in particular section *2. Body of data* indicates the format regarding the quality of the marketing authorisation dossier. In *Module 2*, section 3 *Quality Overall Summary* the documentation of the part *Quality* is summarised. Especially in Europe this summary is given as a critical assessment by an expert. Nevertheless, the relevant module of quality is actually *Module 3*, the *2. Body of data* with its sections *S. Drug substance* and *P. Drug product.* As there are not necessary in all parts of these sections major differences in regulatory requirements for parenteral medicinal products in comparison to other non-parenteral products, only the different parts are subject of this evaluation [35].

6.1 P.1 - Composition of the Drug Product

This section covers the description of the dosage form, its qualitative and quantitative composition including all components in one unit of the drug product. In addition the used container and closure should be mentioned. There are no specific requirements for parenteral medicinal products. Besides the active drug substance, all excipients like e.g. salts, solvents, antioxidants and antimicrobial preservatives are needed to be mentioned. In case of additional accompanying solvents for reconstitution these solvents are needed to be described, too.

6.2 P.2 - Pharmaceutical Development of the Drug Product

The characteristics of the drug substance, the properties and suitability of excipients leading to the formulation of the drug product, the development of manufacture with indicated critical steps should be described and justified [9]. Suitable documents of development studies should be added in support. The guideline *CPMP - NfG on development pharmaceutics* should be considered for parenteral medicinal products and other products. Any differences are given based on the specific requirements of parenteral medicinal products (see section 4.1.1 *Common tests in quality control*): sterility, absence of/ limited bacterial endotoxins or pyrogens, particulate matter, physiological osmolarity and pH.

6.2.1 Components of the drug product

According to characteristics of the drug substance, the intended dosage form, way of administration, and interactions to other excipients the suitable excipients should be chosen in order to fulfil the requirements on particulate matter, physiological osmolarity and pH, like

e.g. specific salts, solvents or/ and emulsifiers. It is preferred to add excipients that are standardised according to the Ph. Eur. [9].

The development studies should further cover the determination of physicochemical and biological properties of the drug substance like heat and/ or radiation sensitivity and microbial attributes. Especially this should be considered for the subsequent choice of an appropriate sterile process. The development should be described and justified by providing suitable data.

In some cases for parenteral medicinal products it is recommended to include antioxidants or antimicrobial preservations, i.e. due to microbial attributes of the drug substance or for an extension of stability of the drug product. An example for such a case is a multi-use product. An acceptance for an inclusion of these substances to reduce contamination require the following information in documentation [7]:

- Reason for an addition to formulation
- Development studies should proof its efficacy in formulation
- A test method for quality control should be developed, preferable the adoption of a standard method in the Ph. Eur..
- Referring to details about intended labelling with a link to *Module 1*, section 3 of *Summary of product characteristics, labelling and package leaflet.*
- Referring to safety information with a link to *Module 4*, non-clinical studies or to *Module 5*, clinical studies.

6.2.2 Formulation and manufacturing process development

Within the scope of pharmaceutical development an appropriate sterility method should be selected to ensure SAL in order to comply with the requirement on sterility and on absence of/ limited bacterial endotoxins or pyrogens. Due to the specific physicochemical characteristics of the drug substance especially the heat and/ or radiation sensitivity, the intended dosage form, way of administration, excipients and possibly interactions to container-closure system the optimal sterilisation method with the highest possible SAL should be chosen. The *Annex of the CPMP - NfG on development pharmaceutics* provides suitable decision trees for an appropriate choice of sterile processes considering the relevant parameters. Finally the reason and decisive parameters for the method are needed to be justified [8],[9].

In addition the complete manufacturing process should be developed, possibly involving other steps. The documentation of manufacturing process development should provide a link to the final resulting manufacturing process and the confirmation by process validation [9].

6.2.3 Development of container-closure system

The container-closure system should confirm during development the compatibility with the drug substance and excipients. In addition safety and functional aspects for the intended way of administration, the compatibility with the sterilisation process and any attributes of the material to prevent microbial contamination should be considered. Additional development studies should be carried out, if the material of container-closure system is not described in the Ph. Eur. [9],[5],[22],[28]. The *CPMP – NfG on development pharmaceutics, NfG on plastic primary packaging material* and the *Ph. Eur. - General notes on materials for containers and containers* should be taken into account.
In addition and although it is recommended especially for aseptic processing in process validation, the development studies may carry out a container-closure integrity testing (a short description see in 4.2.2 *Aseptic processing with/ without filtration*).

6.3 P.3 - Manufacture of the Drug Product

The information about manufacture covers the involved manufacturer(s), the batch formula, a description of the manufacturing process supported by a flow diagram indicating critical steps and intermediates with process control methods, and a process validation. It should be stated comprehensively that the final manufacturing is based on development studies and confirmed by process validation. Especially in description of the manufacture with in-process control it should be considered that only the quality relating aspects are needed to be stated for the product. In particular it is generally sufficient to state a main technological principle, without a specific name or serial number of an applied instrument. This should be considered for parenteral medicinal products and for other products [15]. The *CPMP - NfG on manufacture of the finished dosage form* should be followed.

6.3.1 Compliance with GMP

First, the manufacture of each medicinal product authorised in the European Community must follow the requirements of GMP. This is confirmed in a manufacturing authorisation issued by the supervisory national competent authority of the European Community or of a country

with a mutual agreement (MRA or PECA). However, this authorisation confirms only the general ability in manufacture of a specific pharmaceutical form in compliance with GMP. Therefore, it is generally needed to describe the manufacture for the individual product in the marketing authorisation dossier for parenteral medicinal products and for other products. Some differences can be seen in the description of the manufacturing process, in-process control and process validation.

6.3.2 Documentation of manufacture of terminal sterilisation

As mentioned before the reference conditions of the Ph. Eur. should preferable be applied for terminal sterilisation processes. These processes can be defined as standard sterile processes in demarcation to non-standard processes. There is less information on process validation needed for a standard sterile process processes, as such a process is widely assured by production under GMP. Such a division into standard and non-standard processes is only mentioned in the guideline *CPMP - NfG on process validation* in comparison to others like *CPMP- NfG on manufacture of the finished dosage form* [16],[15]. However, this definition as mentioned in one of the relevant guidelines of recent date can be generally adopted to manufacturing processes (division into non-standard and standard processes).

Description of the manufacturing process of terminal sterilisation

At description of the manufacturing process the following is needed to be stated for all terminal sterile processes in minimum:

- Way of decontamination of the drug substance, excipients, containers-closure system, and equipment before getting in contact with the product and prior to sterile processing.
- Description of the applied sterilisation processes with its essential individual process conditions for loading, sterilisation phase, and reloading and as part of the whole manufacture.
- The number of units to be sterilised during one sterilisation cycle
- The loading patterns
- The final filling and closuring procedure of the product prior sterilisation. If there is still the possibility for the product to be opened after final sterilisation, the precautions must be indicated how to avoid any risks for recontamination of the product.

The differences in description of manufacturing processes within different terminal sterilisation procedures are mainly based on the individual processing:

For *heat sterilisation* including steam and dry heat sterilisation the cycle parameters like time, temperature, pressure, F_0 concept for loading, heating, sterilisation, cooling phase and reloading should be stated.

For *radiation sterilisation* first the source of radiation should be stated. The loading density and distances to this radiation source should be indicated at loading pattern. The processing parameters cover the time, the minimum achieved and the maximum permissible radiation dose per cycle. When using electron beam radiators the electron energy, the beam current, width, and conveyor speed should be stated, too. In cases with applied conditions below of Ph. Eur. reference conditions the maximum limits for bioburden are further needed to state [3].

In some cases *gas sterilisation* is applied as a terminal sterilisation method. As mentioned in section 4.2.1 *Terminal sterilisation* gas sterilisation should only be applied when no safer alternatives exist, due to its toxicological potential. First the qualitative and quantitative composition of the applied gas mixture and the description of apparatus for sterilisation should be described in addition to the above mentioned information. The data of processing cycle covers the time, temperature, humidity, and gas concentration for loading, gas exposure phase, gas removal phase, and reloading [11].

Description of in-process control of terminal sterilisation

The following in-process methods should be applied and stated for all terminal sterile processes:

- The test methods for bioburden prior to the final sterile process
- Verification of loading patterns
- Control of cycle parameters during sterile processing
- Control of the process with integrated biological indicators, if applicable

Some differences for in-process control methods of terminal sterilisation are caused by the individual physicochemical principles of sterilisation method:

The in-process control of cycle parameters is performed at *radiation sterilisation* by test methods on dose mappings as described in the *CPMP Guidance 3AQ4A – The use of ionising radiation in the manufacture of medicinal products* and *GMP Guide - Annex 12* [3],[31].

For *gas sterilisation* the residual gases should be tested during processing. The residual gases should be limited according to Ph. Eur. like shown [11]:

- For ethylene oxide: Not more than 1 ppm
- For ethylene chlorhydrin or other halogenated ethylenehydrin: Not more than 50 ppm

Process validation of terminal sterilisation

The process validation should provide the evidence of effectiveness of the manufacturing process and of appropriate control methods for critical steps. In cases if a non-standard sterilisation process the process validation should be performed on three consecutive batches of production-scale, otherwise two consecutive batches of production-scale supported by pilot batches are sufficient for standard processes [16]. As mentioned in section 4.2.1 *Terminal sterilisation* of GMP requirements the following validation are requested for terminal sterilisation:

- Process validation including the process conditions by using biological indicators
- Validation of the container-closure integrity, if applicable

A process validation with *biological indicators* should indicate the following information:

- Characterisation of biological indicators regarding the name of species, the number strain in original collection, number of viable spores and the D-value (see in section 4.2.1 *Terminal sterilisation* of GMP requirements)
- The preparatory actions to indicators prior to sterilisation procedure
- Description of validation procedure indicating the cycle parameters for loading, sterilisation, and reloading and in-process control methods
- The conditions of incubation of biological indicators after sterilisation
- Sampling plan
- Test methods for analysis
- The results for the obtained Sterility Assurance Level.
- The general time frame of validation related to routine processing

The differences of validation within terminal sterilisation procedures are mainly based on the individual physicochemical principles of sterilisation method:

Especially for *radiation sterilisation* the process validation should be performed with the aid of a dosimeter during sterile processing (= dose mapping) indicating the radiation dose for each phase of sterile process. In addition the absorbed radiation dose in dependence on the loading patterns, loading density and distances to the radiation source should be tested [3].

Especially the results of validation of *gas sterilisation* should cover in addition the testing of the gas mixture before sterilisation and a 100 % control of units on residual gases afterwards.

In some specific cases especially for new materials or a new functionality of the applied container-closure system the validation should cover a container-closure integrity test (see section 4.2.2 *Aseptic processing with/ without filtration* of GMP requirements). If applicable, the following information should be given:

- Description and preparatory actions of the medium and of the microorganism containing broth
- Description of the procedure with in-process control
- The conditions of incubation of samples
- Sampling plan
- Test methods for analysis
- Results and conclusion

The mentioned differences between non-standard and standard processes in process validation are shown in the scope on details for the description of a procedure and on the requested additional documents especially for non-standard processes, like validation report and certificates of analysis.

6.3.3 Documentation of manufacture with applied parametric release

The application for parametric release is a certain circumstance for manufacture and quality control. This means the replacement of the sterility test at final release by appropriate

processing data. An application should base on sufficient experiences and is only applicable for terminal sterilisation by steam, dry heat or radiation.

First, the manufacturer's quality assurance system is evaluated resulting in a risk analysis by the inspector of the supervisory national competent authority. A positive opinion of the supervisory inspector confirms the ability for parametric release of the non-product specific manufacture including steam, dry heat or radiation sterilisation respectively.

The marketing authorisation dossier of the individual product should cover in principle the same as requested for standard processes of steam, dry heat or radiation sterilisation with additional details for the indication of critical steps. In addition the in-process control with corresponding limits should be justified for reliability in relation to the specification for final release.

The process validation should provide the robustness of the manufacturing process resulting to reliable in-process controls and acceptance limits. In addition historical batch data should be provided. Hereby it is acceptable to provide data of an established similar product. In general the *CPMP - NfG on parametric release* and the *GMP Guide – Annex 17* should be followed [14],[32].

6.3.4 Documentation of manufacture of aseptic processing

Aseptic processing is generally defined as a non-standard process, due to their consequences for GMP regarding the cleanliness. This leads to the need to describe the manufacture including in-process control in more details and to provide additional data at process validation in comparison to standard processes, that are widely assured by production under GMP [16]. For heat and/ or radiation sensitive drug substances the aseptic processing remains as an acceptable sterilisation procedure. Whenever possible, the aseptic processing with an integrated filtration step should be applied directly before final filling and closuring.

Description of manufacturing process of aseptic processing

The following information should be stated in the manufacturing process of aseptic processing:

- Preparatory steps, like sterilisation procedures or decontamination including a description of the process conditions of the drug substance, excipients, containers-closure system, utilised materials, and equipment before getting in contact with the product.

- Detailed description of the whole manufacturing steps from the starting materials up to the filling and closuring procedure.
- Specific critical steps of the manufacture should be indicated
- Some procedures should be described how to avoid any possible risks for recontamination of the product during the process.

The differences in description of manufacturing processes of aseptic processes with or without aseptic filtration are based on the processing steps:

For *aseptic processing with filtration* the filtration procedures are needed to be described as additional manufacturing steps. The types of bacteria-retentive filter with their pore sizes should be mentioned. For aseptic filtration the nominal pore size is 0.22 micron or less [18]. This is acceptable without further justification. Larger pore sizes in combination with an additional sterilisation step are acceptable when validated and justified during pharmaceutical development [26].

As an *aseptic processing without filtration* is a critical sterilisation procedure without any concrete sterilisation process on the finished drug product, all preparatory steps of ingredients like drug substance, excipients and container-closure system and of equipment and materials are very important. They have to be sterilised separately before getting in contact with the product. Each single sterilisation procedure must be described individually. A test on sterility and on the amount of bacterial endotoxins or pyrogens should be included in quality control. At documentation of the manufacturing process the details about the sterilisation conditions should be given in details.

Description of in-process control of aseptic processing

The following in-process methods or tests in monitoring should be stated for aseptic processing in general [15]:

- The test methods for bioburden prior to sterilisation procedure should comply with the limit of not more than 10 cfu/ 100 ml (cfu = colony forming unit, the visible outcome of growth of microorganisms).
- Applied testing methods to indicate microbial contaminations of the production area and environment

- The additional especially for *aseptic processing with filtration* the in-process method should cover the test of filter integrity testing prior and after each filtration procedure.

Process validation of aseptic processing

As the process validation provides important information about the effectiveness of a process especially for aseptic processing as a non-standard sterilisation process the validation should be performed on three consecutive batches of production-scale [37]:

- Simulation processing by media fills
- Filter validation for aseptic processing with filtration
- Validation of the container-closure integrity, if applicable

In particular the following information about *media fills* should be stated:

- The number of tested units per validation batch and the general time frame of validation in comparison to routine processing
- The choice and characterisation of the medium
- Description of validation procedure and of control tests in monitoring
- The results of positive grow promotion testing of the medium
- The conditions of incubation of the medium
- Sampling plan
- Test methods for analysis
- Results and conclusion regarding contamination rate

For *filter validation* the following should be stated:

- A description of medium to be filtered with or without presence of the product
- Description of the procedure with processing data (pressure) and process control
- Sampling plan
- Test methods for analysis
- Results and conclusion regarding the maximum permitted pressure

For *container-closure integrity* the same documentation as requested for terminal sterilisation methods should be stated (see section 6.3.2 Documentation of manufacture of terminal sterilisation).

Especially for aseptic processing there are different recommendations in the relevant guidelines about the required scope on information especially for process validation. According to the *CPMP- NfG on manufacture of the finished dosage form* it is stated that the results of media fills fall within the field of GMP and a presentation in the marketing authorisation dossier is only required in certain circumstances [15]. In contrast to this it is stated in the *CPMP-NfG on process validation* that aseptic processes are defined to be non-standard processes which require data demonstrating the validity of the process [16]. The last recommendation is of recent date and provides a comprehensible explanation for such a procedure that can be influenced by a lot of quality relating parameters. Therefore, it is recommended to add further documents at process validation of aseptic processes, like validation report and/ or certificates of analysis.

6.3.5 Documentation of manufacture of special technologies at sterile processes

The documentation of manufacture of special technologies is described in this section exemplary for the isolator technology and the blow-fill-seal-technology. As the isolator technology is mainly applied for aseptic processing and the blow-fill-seal technology for terminal sterilisation and for aseptic processing the corresponding regulatory requirements as described for these processes should be considered. This section emphasises only additional requirements as far as possible to be standardised.

Description of the manufacturing process of special technologies

For applied specific technologies the following information should be given about the manufacturing process:

- The step for implementation of this technology into the process
- The technology itself should be appropriately described. Especially the critical zones should be indicated.
- The functional conditions during processing should be indicated.
- Specific preparatory steps of the active drug substance, excipients, container-closures or respectively the granulates, and of any equipment before getting in contact with the product and the way of integration to the process should be described, e.g. via transfer port or under pressure via filling pipeline.

Due to the functional conditions the information differs between the technologies:

For *isolator technology* the functional conditions like temperature, humidity and pressure, identification and concentration of gas, gas flow rate inside and outside of processing area should be stated [38].

For *blow-fill-seal-technology* the functional conditions like processing flow rate, the identification and concentration of gas, temperature and pressure during filling with granulates, parison formation, filling with product, and sealing are needed to be stated [30], [37].

Description of in-process control of special technologies

The following methods for in-process control should be stated in addition to the regularly requested methods of the applied sterile process:

- Testing of functionary processing data, like e.g. temperature, humidity, pressure, airflow inside and outside of processing area and at critical zones.
- Microbial monitoring adopted to the specific technology
- Leak testing
- Filter integrity of utilised filter systems

Process validation of special technologies

The validation procedures for the applied sterilisation processes should be adopted to the functional conditions and design of the specific applied technology (see in sections 6.3.2 *Documentation of manufacture of terminal sterilisation,* and 6.3.4 *Documentation of aseptic processing*). In addition to these requested validation procedures the following procedures are usually required [37],[38]:

- Validation procedure should cover the decontamination (sporicidal process/ sanitisation) prior to processing by using biological indicators with applied agents.
- Filter validation of all relevant integrated filter systems (see in section 6.3.4 *Documentation of aseptic processing*)

Due to the lack of concrete recommendations for the required validation procedures for these technologies, the above mentioned recommendations are adoptions and interpretations of *PI 007-1– Recommendations on the validation of aseptic processes* and of *PI 014-1 Recommendation on isolator used for aseptic processing and sterility testing.*

The validation procedures should be described according to the same principles and with the same scope of information as usually requested for process validation in general, according to the *CPMP – NfG on process validation*. These technologies can be defined to be non-standard processes [16]. Therefore, and due to the variability of different functional designs of these technologies, it should be expected that additional information and documents are needed for addition, like e.g. technical drawings, validation reports, results of monitoring and certificates of analysis.

6.4 P.4 - Control of excipients of the drug product

Information should be given regarding the specifications, the analytical procedures with corresponding validation, and a justification of the specification of the included excipients. It is preferred to apply excipients as described in the Ph. Eur.. The *CPMP Guidance 3AQ9A - excipients in a dossier for application for marketing authorisation of a medicinal product* should be considered for parenteral medicinal products and for non-parenteral products. However, some differences of excipients in parenteral medicinal products are given in dependence of the applied sterilisation method, dosage form or characteristics of the active drug substance:

- Excipients, when applied in manufacture of aseptic processing
- Water included as excipient
- Excipients included as antioxidants and antimicrobial preservatives

6.4.1 Excipients applied in aseptic processing

In aseptic processing the excipients should be tested on microbial contamination and on bacterial endotoxins or pyrogens before implementation into the process. In the test of microbial contamination the limits should be at least not more than 10 cfu/ 100 ml according to the Ph. Eur.. This is the usual limit of the bioburden testing for the drug product, too.

Especially for aseptic processing without sterile filtration it is absolutely necessary to integrate the excipients as sterile starting materials. Therefore an appropriate sterilisation method is needed at manufacture of the excipients. All relevant information about manufacture with sterile process of each single integrated excipients should be stated. Consequently, the scope on information to be provided should be the same as required for a sterile drug substance [4].

6.4.2 Water included as excipient

If water is included for parenteral medicinal products, it must comply with the standards of the Ph. Eur. for *Water for Injections* with the highest requirements for water in medicinal products. The different definitions for *Water for injections in bulk* and *Sterilised water for injection* should be considered according to the Ph. Eur. monograph. The requirements differ to water of other quality grades, like *Portable Water*, *Purified Water* and *Highly Purified Water* that can be included to non-parenteral medicinal products in dependence to their need.
According to the standard of *Water for Injection* it is required to use water prepared by a validated distillation process according to the Ph. Eur.. During production and storage before use the total viable counts and content of bacterial endotoxins or pxrogens should be tested to ensure the quality. Quality control of *Water for Injection* should cover the following tests preferable according to Ph. Eur. in addition to the tests for *Purified Water* [10]:

- The content of bacterial endotoxins limited to not more than 0.25 IU/ml of endotoxins
- Conductivity
- Total organic carbon

6.4.3 Excipients included as antioxidants and antimicrobial preservatives

The justification for inclusion of excipients as antioxidants and antimicrobial preservatives and their corresponding requirements are discussed in section 6.2.1 *Pharmaceutical development – components of the drug product*. For quality control the same requirements as requested for other excipients should be fulfilled (preferable according to Ph. Eur.) [7].

6.5 P.5 - Control of Drug Product

The test methods in quality control of the finished drug product for final release should be stated in this section. Information should be given about the specification, the defined test procedures with corresponding method validation, results of batch analysis, the impurity profile, and a justification of the specification. The guidelines regarding specifications and control tests of medicinal products *ICH Q6A – Specifications* and *CPMP Guidance 3AQ11a specifications and control tests on the finished product* should be considered [33],[6]. This is generally required for non-parenteral products and for parenteral medicinal products.

6.5.1 Quality control for parenteral medicinal products

The following test methods with appropriate limits are especially required in quality control for final release of all parenteral medicinal products to guarantee quality [33]:

- *Sterility*: All sterile products inclusive parenteral medicinal products need to have a test method with acceptance limits for sterility included in quality control for final release. An exemption is parametric release applicable for terminal sterilisation methods by heat or radiation. For such cases this test method is replaced by additional processing data (see in section 6.3.3 *Documentation of manufacture with applied parametric release*).
- *Bacterial endotoxins or pyrogens*: A test procedure on bacterial endotoxins should be preferable included in quality control for final release. Alternatively a test on pyrogenicity may be proposed when justified.
- *Particulate matter*: A test method for particulate matter with appropriate limits adopted to the dosage form should be included in quality control for final release, like e.g. adopted to solutions, solids for reconstitution, and suspensions.
- *pH:* The parenteral medicinal products should provide a physiological or at least approximately physiological pH. This should be tested with appropriate limits at final release.
- *Osmolarity:* The parenteral medicinal products should provide a physiological or at least approximately physiological osmolarity. This should be tested with appropriate limits at final release as well.
- *Extractables from container-closure system:* Extractables from the container-closure system should be tested at final release. Especially for parenteral medicinal products this test method is considered to be more important than for other application forms due to the need for clinical tolerance, which can be impaired by containing extractables of the container-closure system.

  However, this test method may be excluded out of quality control at final release if assured by evident data of pharmaceutical development and stability studies.
- *Impurities/ degradation products:* Due to the same reasons as argued for extractables of the container-closure system a test method indicating the content of impurities and degradation products should be integrated in quality control.
- *Uniformity of dosage units:* In general this test method covers the uniformity of mass or of content of the drug substance respectively. In quality control one of these test

methods should included. In some cases it is acceptable if this test is integrated in in-process control.

For these methods it is preferred to apply the methods according to the Ph. Eur.. Especially the requirements for testing the content of *extractables from container-closure, impurities/ degradation products* and the test method on *uniformity of mass/ content* were not emphasised as requirements in this master thesis so far, since these methods are not special methods only for parenteral medicinal product. Certainly, the content of extractables from container-closure system and impurities/ degradation products should be strictly limited and the uniformity of mass/ content should be ensured for parenteral medicinal products. However, these requirement are generally needed to be considered for other products as well [33].

6.5.2 Specific test methods in quality control of parenteral medicinal products

Besides the mentioned general required test methods for final release there are additional requirements in quality control for specific parenteral medicinal products in dependence to the dosage form, delivery system or excipients. The specific requirements are briefly mentioned in the following sections.

Quality control of solids or other non-aqueous parenteral preparations for reconstitution

For solids or other non-aqueous parenteral dosage forms the following test methods are further applicable in addition to the general requirements for parenteral medicinal products:

- *Water content*: A test procedure with appropriate acceptance limit should be integrated in quality control for final release. When assured by evident data about the water content in pharmaceutical development, the test method on *loss on drying* is normally considered sufficient.
- *Reconstitution time*: For parenteral medicinal products which require reconstitution the test on reconstitution time including the diluent with appropriate acceptance limits should be integrated in quality control. This test method may be excluded out of quality control especially for rapidly dissolving products based on a skip lot testing (testing at predetermined intervals rather than on batch-to-batch) and assured in development studies.

Quality control of injectable suspensions

For parenteral medicinal products provided as injectable suspensions the following test methods are further applicable in addition to the general requirements:

- *Particle size distribution*: A test of particle size distribution with appropriate limits should be included in quality control. This test may be proposed in place of dissolution testing, if assured in pharmaceutical development by evident data confirming the particle size as the main factor to influence dissolution.
- *Redispersibility*: A test of redispersibility with appropriate limits should be provided for injectable suspensions which settle on storage to product sediment. This test method may be excluded out of quality control based on skip lot testing and assured in development studies.

Quality control of products including antioxidants and/ or antimicrobial preservatives

In addition to the general requirements for parenteral medicinal products with included excipients acting as antioxidants and/ or antimicrobial preservatives their contents are needed to be tested usually at final release. The acceptance limits should be based upon the results of development studies regarding the proposed usage and shelf life. For antimicrobial preservatives the lowest acceptable limit should be defined based on results of a pharmacopoeial antimicrobial preservative effectiveness test. For antioxidant preservatives it is in some cases sufficient to test the content during in-process control [33].

Quality control of products with a specific delivery system

Some parenteral medicinal products are provided in a specific delivery system, like e.g. pre-filled syringes or autoinjector catridges. For these pharmaceutical forms an additional test on functionality should be included in quality control usually at final release. The testing parameters may be in dependence of the function, i.e. syringeability, pressure, or seal integrity. This test or only some attributes of testing may be excluded out of quality control as well, if assured by evident data provided during pharmaceutical development. In some cases this test may be performed during in-process control.

Quality control of parenteral medicinal products manufactured by applied gas sterilisation

Parenteral medicinal products when manufactured by applied gas sterilisation should include an additional test method on residual gases in quality control for final release. The content should be limited according to Ph. Eur. and the *CPMP - NfG on limitation to the use of*

ethylene oxide in manufacture of medicinal products, as described in section 6.3.2 *Documentation of manufacture of terminal sterilisation*.

6.6 P.7 – Container-Closure System

The section covers the identity of materials and construction with their test methods in quality control. The corresponding *CPMP Guidance 3AQ10A - Plastic primary packaging material* and the *monographs of primary packaging materials of the Ph. Eur.* should be followed for parenteral medicinal products and for other products as well.

6.6.1 Container-closure system for parenteral medicinal products

There are fine distinctions in acceptance of materials between the use for parenteral medicinal products and for non-parenteral products, e.g. for plastic materials. Since for non-parenteral medicinal products a material in compliance to the Community legislation (Directive 907128/EEC) for getting in contact with foodstuffs is acceptable, the material for parenteral medicinal products should comply with requirements according to the Ph. Eur.. If the requirements are not fulfilled, appropriate pharmaceutical development studies should assure the required quality of the material. The following information should be given for the container-closure system of parenteral medicinal products in comparison to non-parenteral products [5]:

- The name of the manufacturer (also called converter) of the material and of the final container-closures system
- The complete qualitative and quantitative composition of the material including additives
- The test methods in quality control should cover the test of microbial contamination

6.6.2 Container-closure system for specific applications of parenteral medicinal products

Especially for parenteral medicinal products manufactured by aseptic processing or by blow-fill-seal technology there are specific requirements in comparison to parenteral medicinal products in general.

Documentation of container-closure system for aseptic processing

For aseptic processing with/ without filtration it is necessary to integrate the container and closures as sterile materials. If the container-closure system is not sterilised during manufacture of the drug product, it has to be integrated as sterilised material. For such a case the following information should be stated:

- The applied sterilisation procedure including the process conditions
- The tests at quality control should cover the test of sterility and a test on bacterial endotoxins or pyrogens

These information is possibly provided by the supplier and manufacturer of the single containers or closures. In some cases additional information may be requested like e.g. drawings, certificates of analysis and documents indicating the conditions for the sterilisation.

Documentation of container-closure system for blow-fill-seal technology

As especially for the blow-fill-seal technology only the material is integrated into the process as granules first (see description of blow-fill-seal technology in section 4.2.3 *Special technologies for sterile processes* of GMP requirements), the documentation should cover only the requirements for the materials itself. Consequently, the requirements as described only for the material for parenteral medicinal products should be fulfilled. In addition, possibly the test method of particle size for the integrated granules should be integrated in quality control.

6.7 P.8 – Stability of the Drug Product

Stability studies are usually performed after finalisation of pharmaceutical development on at least three primary batches. The batches should be in minimum in the scope of pilot batches produced by the same method of manufacture with the same formulation and ingredients. The information about summary and conclusion of stability studies, post-approval stability studies including details about storage conditions, in-use storage conditions if applicable, shelf-life specification, and the results of stability studies should be given in the dossier. The shelf-life specification should be defined based on the quality control for final release [34]. The different relevant *CPMP and ICH guidelines on stability* should be taken into account for parenteral medicinal products and for other products as well.

Especially for parenteral medicinal products during stability studies the specific requirements on sterility, absence of/ limited bacterial endotoxins or pyrogens, particulate matter, pH and osmolarity, the content of extractables from the container-closure system and impurities/ degradation products should be tested in shelf-life specification. In addition other tests of specification at final release are required (see section 6.5.1 *Quality control for parenteral medicinal products*) too. The *ICH Q6A Guideline on Specifications* should be considered for definition of the shelf-life specification.

In addition and especially for parenteral medicinal products the maximum shelf-life or in-use stability of the product regarding the microbial contamination and physicochemical degradation after first opening or following reconstitution should be established. This is needed to be considered for unpreserved, for preserved, for single-use, and for multi-use sterile products [13],[12].

Another certain circumstance at parenteral medicinal products is the application of parametric release. As a logical consequence for the required assessment of parametric release stability data should cover the test on sterility in the shelf-life specification. This is needed to assure the quality during the storage regarding the specific test that should be removed at final batch release.

6.8 S - Documentation of Drug Substance

The documentation of the drug substance covers all information about the active drug substance regarding e.g. characteristics, manufacture, quality control, container-closure system and stability. The *CPMP and ICH guidelines for active drug substances* should be considered. In general there are no differences between parenteral medicinal products and other products.

The only exemption is given for aseptic processing of parenteral medicinal products at manufacture of the drug product. As especially for aseptic processing without filtration there is no concrete sterilisation method, the active drug substance has to be included as sterile ingredient. Consequently, in quality control of the drug substance the test on microbial contamination or sterility and a test on bacterial endotoxins or pyrogens should be included. Further requirements are resulted by an integrated filtration step.

6.8.1 Drug substance in aseptic processing with filtration

If aseptic processing with aseptic filtration step is applied in manufacture of the finished drug product the quality control of the drug substance should comprise at least the same test methods and acceptance limits as applied for excipients used in aseptic processing of the drug product (see section 6.4.1 *Excipients applied in aseptic processing*).

6.8.2 Drug substance in aseptic processing without filtration

As mentioned before at aseptic processing without filtration steps the drug substance must be sterile. In such a case the quality dossier of the drug substance should cover all relevant information on the sterilisation process and quality control as requested for a sterile finished drug product (see sections from 6.1 *P1 – Composition of the Drug Product* to 6.7 *P8 - Stability of the Drug Product*).

7. Discussion and Conclusion

Based on the GMP requirements the previous sections of the regulatory requirements provide an evaluation and interpretation of the requirements and recommendations for a marketing authorisation dossier of parenteral medicinal products in comparison to non-parenteral medicinal products.

It is first the intention of this master thesis to analyse the differences between parenteral medicinal products and non-parenteral medicinal products and to provide some suggestions for guidelines and recommendations. In addition, this discussion and conclusion should suggest a possible procedure to simplify the scope of documents to be added to the marketing authorisation dossier without losing the required assurance of quality.

Analysis of different regulatory requirements between parenteral and non-parenteral medicinal products

The main differences between parenteral and non-parenteral medicinal products in regulatory requirements are especially shown in pharmaceutical development, manufacture, and quality control of the drug product, resulting to further distinctions in documentation of the control of excipients, of the container-closure system, of stability and the drug substance. Only some of the differences are the results of different dosage form or other aspects.

The main differences especially in pharmaceutical development, manufacturing processes with in-process control and process validation are caused by the need for a safe administration

to avoid clinical reactions and provide a clinical tolerance for parenteral medicinal products. This leads further to the need to choose and develop an appropriate sterilisation procedure. This process needs to be controlled and validated according to its specific requirements. Therefore, especially the sections of development pharmaceutics, manufacture and quality control of the marketing authorisation dossier emphasise these specific characteristics for parenteral medicinal products resulting to the differences to non-parenteral medicinal products.

Suggestions for guidelines and recommendations

Furthermore, it was worked out in the sections of regulatory requirements that some differences are indicated within different sterilisation procedures. Such differences are seen especially between standard and non-standard sterilisation processes. In general for non-standard processes there are more quality relating and product-specific parameters with a higher risk for errors. Therefore, additional quality relating documents can proof the reliability of this specific process.

This is not needed for standard processes that are widely assured by non-product specific parameters. Consequently, a periodical inspection of the general process and its quality assurance is widely sufficient. This is confirmed by the added GMP certificate as a manufacturing authorisation.

It was further seen in the section of regulatory requirements that only in one relevant Guideline *CPMP – NfG on process validation* the division between standard and non-standard processes were found. As this definition is able to clarify requirements and may be also relevant for the regulatory sections of pharmaceutical development and manufacture of the drug product, this definition should be adopted to the relevant guidelines *CPMP – NfG on pharmaceutical development* and *CPMP – NfG on manufacture of the finished drug product.* These three guidelines should provide comprehensive recommendations. In addition the controversial recommendation regarding the addition of media fills to the process validation for aseptic processing (see section 6.3.4 *Documentation of aseptic processing*) should be harmonised.

Furthermore, for some non-standard-processes like aseptic processing, isolator technology and blow-fill-seal technology there are only PIC/PICS Guidelines available falling under the scope of GMP. Hereby it is needed to interpret and adapt these recommendations for the marketing authorisation dossier. Although there is a high variability between different

processes, the increasing scientific knowledge and experiences of marketing authorisation dossiers should support a standardisation.
Therefore, it is suggested to develop specific CPMP guidelines for aseptic processing, isolator technology and for blow-fill-seal technology providing concrete information for the marketing authorisation dossier based on the corresponding available PIC/PICS Guidelines and on experiences with authorised products.

Suggestion for a simplification of regulatory requirements

It is further the intention of this master thesis to provide a suggestion to simplify the scope on information in the marketing authorisation dossier especially for parenteral medicinal products. The regulatory requirements showed that a high scope on information is needed in the marketing authorisation dossier for parenteral medicinal products. This leads to extensive endevours in preparation and assessment.
In order to simplify the endevours the regulatory requirements should be analysed regarding the replacement of possible documents. Afterwards a suitable procedure for simplification should be suggested without losing the required assurance of quality.

It is generally the aim of a marketing authorisation dossier to provide the specific information of an individual medicinal product. However, there are some sections where non-product specific documents are requested. For these non-product specific requirements an assessment could be separated. The quality conformity can be issued in a certificate without the need for an additional assessment. Such a procedure should be suggested as a simplification.

In particular for parenteral medicinal products the following sections cover requirements of non-product specific characteristics:

- The documentation of excipients in the section *Control of the excipients of the Drug Product*
- The documentation of the containers and closures in the section *Control of the Container-closure system*

A simplification of regulatory requirements should be possible for excipients and container-closure systems when manufactured and controlled according to the Ph. Eur.. As the Ph. Eur. provides already standardised methods for quality control and manufacture any integrated excipients, containers or closures could be assessed on compliance with Ph. Eur. standards separately. Especially for an application in parenteral medicinal products some additional

tests on bioburden and on bacterial endotoxins or pyrogen should be performed to support a subsequent sterile process. Consequently, these excipients, containers, and closures can be approved as applicable for sterilisation procedures.

An assessment on compliance should be requested by a manufacturer or supplier at the European Directorate for the Quality of Medicines (EDQM), a scientific committee evolved from the technical secretariat of the European Pharmacopoeia. The EDQM can assess the documentation on compliance with the current edition of the Ph. Eur. and issue the approval in a corresponding certificate stated *applicable for sterilisation procedures*.

Such a procedure is already utilised for drug substances known as the *Certificate of Suitability* which is assessed and issued by the EDQM as well. The procedure ensures the quality by separate assessment and reduces the scope of documents in the marketing authorisation dossier.

It is recognised that the assessment is shift from the regulatory competent authority to the EDQM, but for usually applied excipients and container-closure systems of parenteral medicinal products the number of multiple assessments can be reduced.

Consequently, it is suggested to introduce a *Certificate of Suitability, applicable for sterilisation procedures* that is issued by the EDQM on compliance for excipients, containers, and closures. There will be only one certificate that can be added to the sections:

- *Control of the excipients of the Drug Product* for each excipient
- *Container-closure system of the Drug Product* for each component of the container-closure system.

and can further replace any additional documents for the relevant components.

8. Summary

Based on the Directives 2001/83/EC and 91/356/EEC there are several guidelines and recommendations providing interpretation and descriptions for the marketing authorisation dossier and the requirements according to good manufacturing practices (GMP) for manufacture and quality control of parenteral medicinal products. It was the intention of this master thesis to work out the regulatory requirements of parenteral medicinal products including chemical drug substances based on the GMP requirements for manufacture and quality control with an analysis and evaluation in comparison to non-parenteral medicinal products. In addition some suggestions for further guidelines and a procedure for simplification should be provided.

First as a basic background the GMP requirements for manufacture and quality control of parenteral medicinal products were briefly described. The main requirements of parenteral medicinal products are to be sterile, without or defined limits of bacterial endotoxins or pyrogens, particulate matter, pH and osmolarity. These requirements result to the need for an implementation of a sterilisation method. Sterilisation methods can be divided into:

- Terminal sterilisation like steam, dry heat, radiation and gas sterilisation
- Aseptic processing with or without aseptic filtration

In addition two special technologies, like isolator technology and the blow-fill-seal technology were further described. Each single sterilisation process requires specific test methods in monitoring and process validations.

Subsequently, the regulatory requirements of parenteral medicinal products were evaluated based on information regarding GMP according to the format of the Common Technical Document (CTD).

For the regulatory evaluation only the different parts of CTD sections were evaluated. At pharmaceutical development some differences between parenteral and non-parenteral medicinal products are shown for cases of excipients acting as antioxidants or antimicrobial preservations and for the choice of an appropriate sterilisation method.

At manufacture, in particular at description of manufacture, the in-process control and process validation the requirements differ in comparison to non-parenteral medicinal products. The requirements were emphasised for terminal sterilisation processes, aseptic processing with/

without filtration and for special technologies like isolator and blow-fill-seal technology regarding the required information and additional documents, if applicable.
At documentation of excipients the differences in comparison to non-parenteral medicinal products were shown by sterilised excipients for aseptic processing, specific requirements on water as excipient, and for antioxidants or antimicrobial preservations.
The control of the drug product covers the required quality control at final release of parenteral medicinal products, like sterility, bacterial endotoxins or pyrogens, particulate matters, pH, and osmolarity. In addition the content of extractables form container-closure system, impurities/ degradation products, and the uniformity of dosage units are required for non-parenteral medicinal products as well.
For the control of the container-closure system the requirements differ for the use in aseptic processing and in blow-fill-seal technology in comparison to non-parenteral products.
Specific requirements for parenteral medicinal products at stability are given for the in-use stability and the stability after first opening.
The documentation of the drug substance is only specific when applied in aseptic processing without filtration. In such a case the same requirements as required for sterile drug products is needed.

Finally it was discussed and concluded that the main differences in the marketing authorisation dossier between parenteral and non-parenteral medicinal products in pharmaceutical development and manufacture are caused by the choice and use of a sterilisation method. These are the consequences of the need for parenteral medicinal products regarding the clinical tolerance.
Furthermore, it is suggested to revise the guidelines *CPMP – NfG on pharmaceutical development* and *CPMP – NfG on manufacture of the finished drug product* to adapt the definition and division of standard and non-standard processes. Especially for non-standard processes like aseptic processing, isolator technology and for blow-fill-seal technology it is suggested to develop regulatory CPMP guidelines based on the PIC/PICS Guidelines and on experiences with authorised products.
Finally, a procedure for a *Certificate of Suitability, applicable for sterilisation procedures* for excipients, containers and closures of parenteral medicinal products that is assessed and issued by the EDQM on compliance is suggested as a simplification.

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