Regulatory Challenges Due to Globalisation of Drug Development and Manufacture Focusing on the Quality of Medicinal Products

Wissenschaftliche Prüfungsarbeit
zur Erlangung des Titels
“Master of Drug Regulatory Affairs”

der Mathematisch-Naturwissenschaftlichen Fakultät
der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

Katrin Hofmann

aus Dillenburg

Hattersheim 2011

Betreuer und 1. Referent: Dr. Josef Hofer

Zweiter Referent: Herbert A. Jopp

Abstract

The globalisation in the development and manufacture of medicinal products and drug substances is increasing. Due to high costs for research and development, international competition, reduced life time of products and austerity measures of health policy cost saving considerations are a big concern for pharmaceutical companies.

This pressure in pricing and competition leads to development and manufacture in lower cost countries like India and China.

The quality of medicinal products is the base for safety and efficacy. Past incidents with substandard medicinal products particullary point out that quality defects of medicinal products can harm patients.

This thesis deals with the challenges for the quality of medicinal products which are caused by globalisation of development and manufacture and on how to handle these challenges.

The challenges for the quality of medicinal products which are evoked by globalisation include the assurance of Good Manufacturing Practice compliance, new impurities in drug substances induced by alternative manufacturing routes, long lasting transports of drug substances and medicinal products passing various climatic zones, complex supply chains and product transfers.

In a globalised world cooperation and harmonisation are of course the best approaches to handle the challenges connected to globalisation. The European Union had a pioneering role in harmonisation activities. The International Conference on Harmonisation, the Pharmacopoeial Discussion Group (PDG), the World Health Organisation are some of the organisations which are engaged in the harmonisation of requirements. The European Medicines Agency cooperates with various authorities and organisations. Intensive collaboration is conducted with the United Staates Food and Drug Administration.

An approach on how to deal with the challenges of transportation in a mid-sized pharmaceutical company is proposed in this thesis. The main factors which might influence the quality of medicinal products are discussed. Subsequently a worst-case approach using the concept of the Mean Kinetic Temperature is proposed assuming an extreme transport temperature. A maximum acceptable transport time for uncontrolled transports is calculated. It is proposed that transports which are finished within the maximum acceptable transport time can be transported without any further precautionary measures.

Transports exceeding the maximum acceptable transport time according to the worst case approach need to be assessed in detail in order to find the best transport conditions, considering the characteristics of the specific product and the transportation route. Decission analysis has proven to be an adequate tool to figure out the best transport conditions for a transport of a specific medicinal product when it is anticipated that the maximum acceptable transport time is exceeded.

Decision analysis and cause and effect analysis have proven to be suitable tools to liase with complex challenges as shown in the approach for transportation of medicinal products. These tools would certainly be valuable to handle further globalisation challenges too.

Table of Contents

1 Introduction

In the recent years globalisation of development and production of medicinal products and drug substances increased.

Purchase of drug substances as well as development and manufacture of medicinal products especially generics is increasingly shifted to countries with lower production costs like India and China [**1**].

Beside the opportunities like cost saving and enhancement of global availability of medicines, globalisation poses new challenges for the quality of medicinal products.

Different mentality and standards (e.g. Good Manufacturing Practice (GMP) and pharmacopoeial monographs) and consequently problems in assuring compliance with these standards especially in low cost countries may potentially result in substandard medicines. Furthermore the multiplicity of drug substances sources and synthetic routes with various process related impurities challenges control of drug substances [**2**].

Complex supply chains complicate communication, increase the demands for technical agreements and facilitate the potential of counterfeit medicinal products. Of growing importance in the context of globalisation are also the requirements on packaging material, stability of the products and precautionary measures during transport (controlled transport, transport validation) due to long transportation routes for drug substances, bulk and finished products through different climatic zones. Increased shifting of production sites elevates the relevance of technological and method transfer.

Pharmaceutical industry and competent authorities have to accept these challenges. Global collaboration and harmonisation are playing a decisive role in establishing appropriate approaches for the problems which accompany globalisation.

Science and risk based approaches and decision making techniques are valuable tools to deal with these complex challenges.

1.1 Meaning and Relevance of Pharmaceutical Quality

Quality is defined by the International Standardisation Organisation (ISO) as *”degree to which a set of inherent characteristics fulfills requirements''* [**3**].

With regard to medicinal products quality is defined as *''the suitability of either a drug substance or drug product for its intended use”* by the International Conference on Harmonisation (ICH). *“This term includes such attributes as the identity, strength, and purity''* [**4**].

In the context of medicines suitability for its intended use is to be interpreted as safe and efficient for the patient. In other words consistent pharmaceutical quality is the base for safety and efficacy of the medicinal product as demonstrated in the clinical studies. In reverse conclusion insufficient pharmaceutical quality can result in risk for patients. It is important to

keep in mind that *''quality cannot be tested into products; i.e. quality should be built in by design''*, by development, by in-process controls, by process validation, by specifications and compliance with GMP [**4**] [**5**].

In order to become aware of the relevance of pharmaceutical quality and its impact on the safety of medicines it is expedient to review past incidents where substandard quality affected the safety of patients. An overview is given inTable 1.

Two of the incidents, the Tryptophan incident and the Heparin incident are discussed more detailed in the following sections.

Table 1: Examples for substandard quality incidents in the last decades

Year	Drug Substance / Drug Product	Incident	Harm	Affected Country	
1937	Sulfanilamide preparation	Diethylenglycol poisoning	Renal failures, 105 documented deaths	USA	[**6**]
1969	Sedatives	Diethylenglycol poisoning	Renal failures, 7 documented deaths	South Africa	[**6**]
1985	Silver sulfadiazine preparation	Diethylenglycol poisoning	Renal failures, 5 documented deaths	Spain	[**6**]
1986	Glycerine	Diethylenglycol poisoning	Renal failures, 21 documented deaths	India	[**6**]
1989	Tryptophan	Modifications in the production process triggered formation of impurities	> 1500 cases of Eosinophilia-myalgia syndrome (EMS) in the USA; 100 cases of EMS in Germany 37 documented deaths in the USA	USA, Germany	[**7**] [**8**] [**9**]
1990	Paracetamol preparation	Diethylenegylcole contamination	Renal failures, 47 documented deaths	Nigeria	[**6**]
1990 - 1992	Paracetamol preparation	Diethylenegylcole poisoning	Renal failures, 236 documented deaths	Bangladesh	[**6**]
1996	Paracetamol preparation	Diethylenegylcol poisoning	Renal failures, 88 documented deaths	Haiti	[**6**]
1998	Cough expectorant	Diethylenegylcol poisoning	Renal failures, 33 documented deaths	India	[**6**]
1998	Paracetamol preparation	Diethylenegylcol poisoning	Renal failures, 8 documented deaths	India	[**6**]

Year	Drug Substance / Drug Product	Incident	Harm	Affected Country	
2000	Gentamycin	Impurity contamination (sisimicin and further impurities)	60 documented deaths	USA	[**7**] [**10**]
2006	Cough syrup	Diethylenegylcole contamination	Renal failures, 78 documented deaths	Panama	[**6**]
2006	Armillarisin-A preparation	Diethylenegylcole contamination	Renal failures, 12 documented deaths	China	[**6**]
2008	Teething syrup	Diethylenegylcole contamination	Renal failures, 12 documented deaths	China	[**6**]
2008	Heparin	Contamination with oversulfated chondroitin sulfate	Anaphylaktoide reactions in EU and USA, 19 documented deaths in the USA	Canada, China, Europe, Japan, New Zealand, USA	[**7**] [**11**] [**12**] [**13**] [**14**] [**15**] [**16**] [**17**].

1.1.1 The Tryptophan Incident in 1989

In 1989 the use of L-Trypthophan produced by the Japanese company Showa Denko K.K. caused more than 1500 cases of Eosinophilia-myalgia syndrome (EMS) and 37 deaths in the USA. L-Tryptophan was available as food supplement without prescription in the USA. Therefore the product was not regulated or approved by the Food and Drug Administration (FDA). L-Tryptophan was widely used in the USA for treatment of insomnia, premenstrual syndrome and depression, whereas the manufactuer of the product did not make any health claims. In November 1989 FDA issued a warning asking consumers to discontinue the use of L-Tryptophan followed by a recall of all L-Tryptophan products [**7**] [**8**].

In Germany more than 100 cases of EMS were assosiated with the use of L-Tryptophan. The marketing authorisation of 27 medicinal products containing L-Trypophan have therefore been suspended by the *"Bundesgesundheitsamt"* [**9**].

The illness was propably triggered by modifications in the fermentative production process of L-Tryptophan. Showa Denko K.K. changed the genetically modified strain used for fermentation to *B. amyloliquefaciens* strain V as well as subsequent purification i.e. reduction of the amount of powdered activated charcoal but assumed that these changes did not significantly impact the purity of L-Tryptophan. This later turned out to be wrong. After the incident six contaminants were found in the corresponding L-Tryptophan batches which are associated with EMS [**7**] [**8**].

1.1.2 The Heparin incident in 2008

Heparin is an anticoagulant drug which is widely used. In 2008 the number of adverse reactions after Heparin administration reported to FDA significantly increased. The adverse events oberved were anaphylactoid reactions and hypotension. About 900 cases of adverse events were associated with the use of Heparin in 2008. 19 people died in the USA in context with Heparin use.

An increase in anaphylactoid reactions after Heparin administration has also been detected in Germany. More than 30 adverse reactions were caused by a contamination of Heparin.

This resulted in recalls of Heparin manufactured by Baxter International Inc. in the USA and recalls of Heparin manufactured by Rotexmedica in Germany. Further manufacturers also recalled Heparin from the market e.g. Sanofi Aventis in Australia, Sweden and Great Britain.

The contaminant identified after extensive analytical search was oversulfated chondroitin sulfate (OSCS).

The drug substance manufacturer of Baxter International Inc. was the Chinese company Changzhou International but FDA investigated 12 Chinese manufacturers which proved to have sold OSCS contaminated Heparin drug substance.

Heparin is manufactured by extraction and isolation from pig intestinal mucosa. 70 % of the Heparin for the US market is sourced from China. The supply chain from the slaughterhouses to the exporteurs of Heparin are very intransparent. The exporteurs source the Heparin from multiple small workshops where extraction and isolation is performed. These workshops are not controlled by the Chinese State Food and Drug Administration (SFDA) and are far off the standards which are usual in western pharmaceutical production facilities.

Obviously OSCS was intentionally added to Heparin. OSCS is manufactured semisynthetically and is not naturally present in Heparin. OSCS has anticoagulant properties like Heparin but is about 200 times cheaper. It is assumed that Chinese Heparin manufacturers startet already in 2006 to add OSCS to Heparin and increased its amount until 2007. The amounts of OSCS found in batches from 2007 contained up to 35 % of OSCS. The high concentration of OSCS in Heparin observed in 2007 might be associated with a lethal viral pig disease which decimend the pig population in China in 2007 and resulted in shortage of pig intestines and correspondigly increase in prices.

The presence of OSCS in Heparin was not noted during quality control of the drug substance as the pharmacopoeial gel electrophoretic purity methods of United States Pharmacopoeia (USP) and European Pharmacopeoia (Ph. Eur.) were not capable to detect OSCS.

After the incident therefore analytical methods were developed which are capable to detect OSCS. These methods are capillary electrophoresis (CE) and nucelar magnetic resonance spectroscopy (NMR). Heparin finished product manufacturers were instructed by FDA and the *"Bundesinstitut für Arzneimittel und Medizinprodukte"* (BfArM) to perform these tests.

In June 2008 the methods were included in the USP and the Ph. Eur. by an ad-hoc revision of the Heparin monographs. Slightly later the Japanese Pharmacopoeia monograph was also

revised. Further regular revisions of Ph. Eur. and USP monographs were performed which were valid from August 2010.

OSCS contaminated batches were found in multiple countries around the globe which is an impressive example for spreading of products over the world due to globalisation [**7**] [**11**] [**12**] [**13**] [**14**] [**15**] [**16**] [**17**].

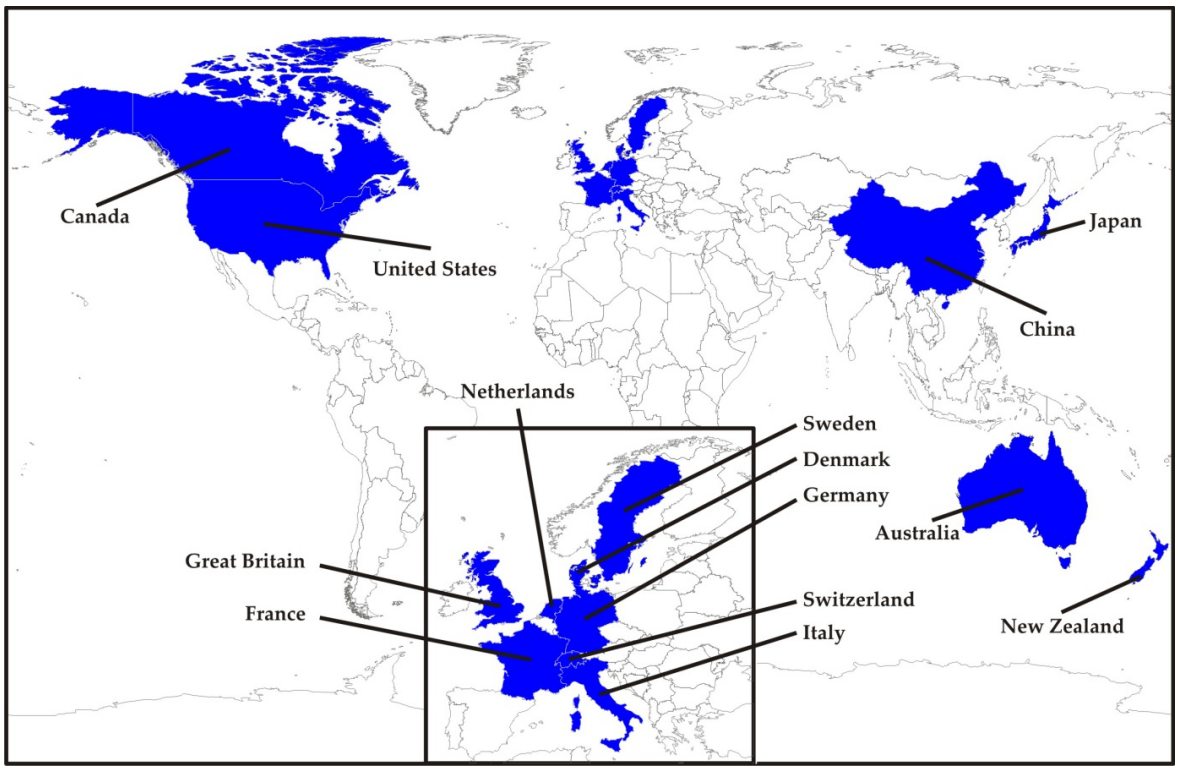

Figure 1**: Countries where Heparin containing OSCS was found – one example for spreading of products over the world due to globalisation [7] [9] [10] [11] [12] [13] [14] [15].**

1.1.3 The Tryptophan Incident versus the Heparin Incident

The Tryptophan incident and the Heparin incident are differing in their quality:

The Tryptophan incident was the result of a misjudgement of the impact of a change on the quality of the medicinal product due to lacking process understanding.

Heparin was intentionally produced substandard by criminal minds in order to save costs.

The Tryptophan incident highlights the importance of process understanding and process controls, process validation and quality control testing of medicinal products especially of products manufactured by biotechnological means.

The Heparin incident on the other hand highlights that supplier qualification, supplier evaluation and auditing are important to assure the quality of medicinal products. As the quality of the substance could not be detected by the pharmacopoeial methods more sophisticated methods might help to detect intentionally contaminated medicinal products.

2 Globalisation

According to an Organisation for Economic Co-operations and Development (OECD) definition the term globalisation describes *"the increase of internationalisation of markets for goods and services, the means of production, financial systems, competition, corporations, technology and industries''* [**18**].

An important feature of globalisation is the splitting of production processes into various steps and to allocate their production in different countries all over the world with the aim to improve efficiency or to access new markets (international sourcing). International sourcing is not only observed within the countries of the European Union (EU) but is increasingly moving out of the EU to emerging markets like China and India as shown in Figure 2 and Figure 3. International sourcing is not only relevant for production steps that can be performed by non-skilled workers. Knowledge intensive business functions like engineering, research and developement, which are typical for pharmaceutical industry, are also subject of international sourcing.

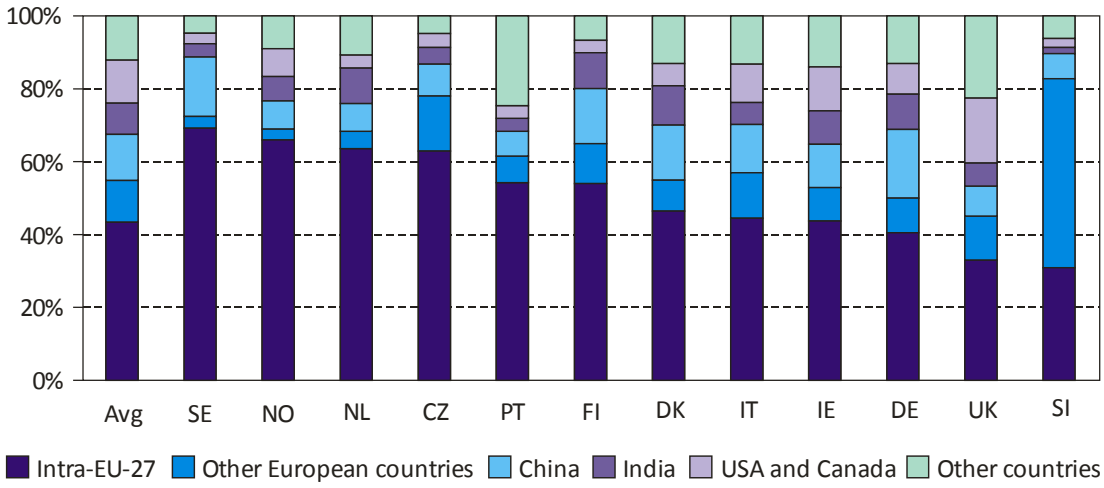

Figure 2: Destination of international sourcing - Share of core and/or support functions sourced internationally. A huge share of international sourcing is performed within the EU. Noteworthy share of international sourcing are also found in countries like India, China, USA and Canada. The data was collected by means of a survey and includes companies with at least 100 employees which performed international sourcing from 2001 to 2006. Abbreviations used: Avg: Average, SE: Sweden, NO: Norway, NL: The Netherlands, CZ: Czech Republic, PT: Portugal, FI: Finland, DK: Denmark, IT: Italy, IE: Ireland, DE: Germany, UK: United Kingdom, SI: Slovenia [19].

Figure 4 shows that most companies preferred insourcing rather than oursourcing when sourcing from abroad as this has the advantage of keeping the control within the enterprise [**19**]. Insourcing means sourcing from companies which belong to the concern, while outsourcing means sourcing from third companies.

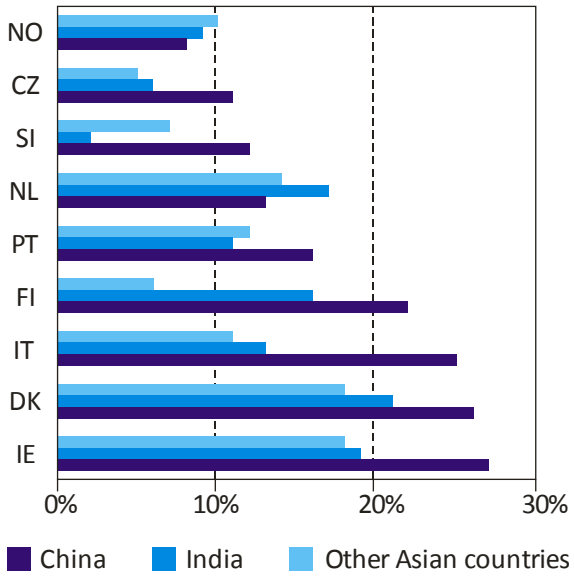

Figure 3: Sourcing to Asia - Share of enterprises having sourced core and or support functions internationally. An impressing number of companies perform sourcing from Asia. The data was collected by means of a survey and includes companies with at least 100 employees which performed international sourcing from 2001 to 2006 [19].

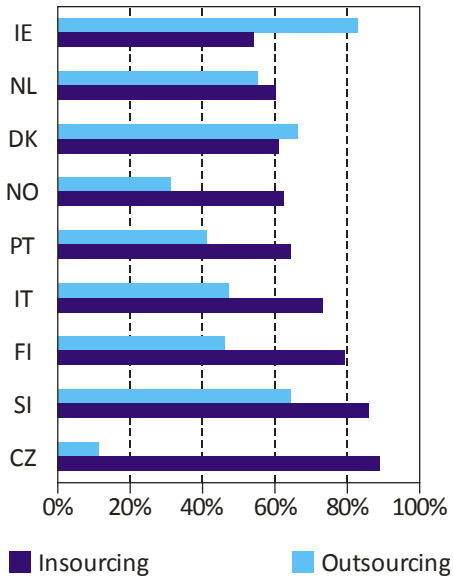

Figure 4: Insourcing vs. outsourcing to China - Share of enterprises having sourced to China. Most companies preferred insourcing, i.e. sourcing within the concern to outsourcing i.e. sourcing from third companies when sourcing from China. The data was collected by means of a survey and includes companies with at least 100 employees which performed international sourcing from 2001 to 2006 [19]

2.1 Globalisation of Pharmaceutical Development and Manufacture

The pharmaceutical industry mainly differs from other industry sectors in its intensive expenditures for research and development and its dependence of the regulatory environment. Beginning in the 1980s cooperations, acquisitions and mergers increasingly occured. Actually the high costs for research and development, international competition, reduced life time of products and austerity measures of health policy induce efforts in reducing production costs [**20**].

A strategic option many pharmaceutical companies follow, is focussing on their core business or optimisation of their product portfolio which may result in outsourcing and sales of business parts [**21**].

In the past the value added chain in the pharmaceutical industry mainly was integrated from drug substance synthesis to distribution of the final products [**22**]. Today drug substances are sourced internationally. 385 European sites, 227 Asian sites and 206 Indian sites hold a Certificate of Suitability (CEP) in 2009 as can be seen in Figure 5 [**23**].

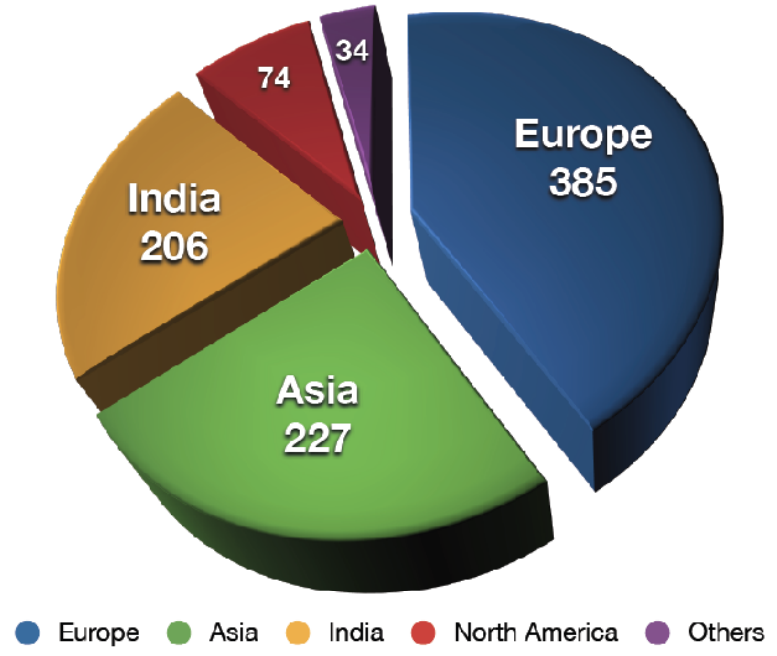

Figure 5: Number of sites linked to CEP per zone (taken from [23] and modified)

This means that the number of sites which were granted a CEP in India and Asia minimally exceeds the number of sites which were granted a CEP in Europe. This highlights the important role of India and Asia in the production of drug substances for the European market. Approximately 80 % of all drug substances used in European medicinal products are sourced from India or China and Indian and Chinese companies make efforts to export also final products to Europe [**24**].

3 Challenges Due to Globalisation

3.1 GMP-compliance

3.1.1 GMP definition

GMP is the abbreviation for Good Manufacturing Practices and means a set of quality assurance measures which should safeguard the quality of medicinal products [**25**].

3.1.2 GMP at international level

On an international level the WHO (World Health Organization) has published GMP guidelines for medicinal products [**26**] and drug substances [**27**]. The GMP guidelines for active substances in the EU and also the WHO guideline are based on the ICH guideline Q7A [**28**]. Additionally the Pharmaceutical Inspection Co-operation Scheme (PIC/S) should be named when talking about GMP on an international level. PIC/S is an organisation of various countries which aims in the harmonisation and enhancement of GMP standards [**29**].

The international GMP regulations are non-binding recommendations only. On a national level Europe and US have settled GMP requirements in law.

3.1.3 Legal Basis for GMP in the EU

The legal basis for Good Manufacturing Practice for Human Medicinal Products in the European Union is found in the directive 2001/83/EC.

Article 46 (f) of the above mentioned directive obliges manufacturing authorisation holders *"to comply with the principles and guidelines of good manufacturing practice for medicinal products and to use as starting materials only active substances, which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials. This point shall also be applicable to certain excipients…"*

Article 47 of the same directive states that the principles of GMP for medicinal products shall be laid down in a directive and details in the form of guidelines. GMP requirements for drug substances shall be defined in detailed guidelines [**30**].

The directive claimed in Article 47 is the directive 2003/94/EC [**25**]. Detailed guidance on GMP for medicinal products and drug substances is provided in Eudralex Volume 4 [**31**] [**32**].

The Good Manufacturing Practice legislation and guidance documents define standards which have to be followed in the manufacture of medicinal products, drug substances and certain excipients. Provisions on the following topics are covered by GMP for medicinal products [**32**]:

- quality management
- personnel
- premises and equipment
- documentation
- production
- quality control

- contract manufacture and analysis
- complaints and product recall
- self inspection

The transition of the GMP directives in German law can be found in the *"Arzneimittelgesetz"* (AMG) and the *"Arzneimittel – und Wirkstoffherstellungsverordnung"* (AMWHV) [**33**] [**34**].

The EU-GMP requirements are applicable to both – manufacturers located within Europe and third country manufacturers which export drug substances or medicinal product to Europe.

Regular inspections of medicinal product manufacturers by the competent authorities assure that GMP principles are followed. Assurance of GMP compliance of drug substance manufacturers is mainly laid in the hand of the medicinal product manufacturer who has to assure by supplier qualification and performance of audits that the GMP principles are followed. GMP compliance of drug substance manufacturers has to be declared by the qualified person (QP) in marketing authorisation applications, renewals and variations which concern either a change of drug substance manufacturer or the change of medicinal product manufacturers. This declaration is known as Annex 5.22 to the application form for marketing authorisation application or as "QP declaration" [**35**] [**36**] [**37**].

The EDQM (European Directorate for the Quality of Medicines & Health Care) initiated an inspection programme for drug substance manufacturers which hold or applied for a CEP. The inspections which are performed on a risk-based approach have mainly been performed in India and China and were followed by numerous CEP suspensions due to failures in GMP compliance [**38**].

3.1.4 Legal Basis for cGMP in the US

In the US the legal basis for GMP is set in the Code of Federal Regulations (CFR), Title 21, Parts 210 and 211. This means that GMP is hard law in the USA. When the GMP requirements of the USA are meant usually the abbreviation cGMP is used which means current Good Manufacturing Practice.

FDA performs inspections within the USA and at the manufacturing facilities which export medicinal products and drug substances in the USA [**39**].

3.1.5 GMP is not the same everywhere

Even though there are big efforts to harmonise GMP requirements actually GMP is not the same everywhere in the world. Even where wording of GMP requirements is nearly the same different interpretations and mentalities lead to various understandings of GMP requirements.

The manufacture of drug substances for European medicinal products is performed in Asia to a huge extent. There are estimations that more than 80 % of drug substances for the European and US market are sourced from third countries e.g. India and China where GMP regulations are in place that differ from European standard [**7**] [**24**] [**40**].

But also in countries which are known to have a high standard in the manufacture of medicinal products like USA, Japan and Europe the interpretation of GMP requirements differs [**41**].

3.1.6 Challenges in assuring GMP compliance

Assuring GMP compliance is a big challenge for authorities and industry. For industry i.e. drug product manufacturers one challenge is to assure GMP compliance of the drug substance suppliers. This item is further discussed in section 3.1.6.1. A further issue for drug product manufacturers is matching the specific GMP standards and its interpretations of other countries for example USA or Japan. This issue is not discussed any further in this thesis.

3.1.6.1 GMP compliance of supplying drug substance manufacturers

Drug substance manufacturers are obliged to perform supplier qualification of drug substance manufacturers. The procedures for drug substance supplier qualification certainly vary from company to company but usually start with a check of paper documentation provided by the drug substance manufacturer e.g. GMP supplier questionnaire, GMP-certificates, the Applicants part of the ASMF (Active Substance Master File) and if available the Certificate of Suitability. The next step comprises analysis of samples and an audit of the drug substance manufacturing site. If deemed necessary stability batches of the medicinal product are produced using the drug substance of the proposed manufacturer. The assessment of a new supplier involves various functions in a pharmaceutical company i.e. the purchasing department, the production department, quality control, quality assurance and regulatory affairs.

The prevalent location of mainly drug substance manufacturers in low cost countries like India or China leads to various challenges.

The drug product manufacturer has to assure by supplier qualification and auditing that the drug substance manufacturer operates in compliance with the EU-GMP requirements. In this context he is faced with geographical, cultural and linguistic barriers.

Furthermore the number of sites which have to be audited in regular intervals, of at least 3 years, is enormous. The use of third-party audits performed by qualified and experienced auditors might be an option especially for mid-sized companies to cope with the number of audits to be performed. But using third-party audits is also related with some disadvantages. The direct contact with the drug substance manufacturer during the audit can strengthen relationship between drug substance manufacturer and drug product manufacturer. If the audit is performed by a third party this is not possible. Furthermore using third party audits needs the drug product manufacturer to convince himself about the qualification of the auditor i.e. he has to perform a supplier qualification of the third-party auditor and confidentiality agreements have to be established with the auditor to facilitate the exchange of the required information [**7**] [**42**].

A risk-based approach for prioritisation and performance of audits as proposed for planning of inspections by the EMA (European Medicines Agency) [**43**] is reasonable for performance of GMP audits [**44**] and should therefore be considered by drug product manufacturers in order to use their resources for auditing in an efficient way.

The results of the EDQM inspection programme illustrate that not all drug substance manufacturers which deliver to the European market manufacture fully in accordance with GMP requirements. In 2010 16 CEPs were suspended and 8 CEPs were withdrawn following an

inspection [**45**]. This leads to the impression that there is need for improvement in the supplier qualification procedures of drug product manufacturers, as those are obliged to assure the GMP compliance of their drug substance suppliers.

Consequently a change of the EU legislation was initiated in correlation with the pharmaceutical package on falsified medicines with the aim to strictly oblige drug product manufacturers to perform audits of drug substance manufacturers. The corresponding directive has already been adopted by the European Parliament and the Council. It will come into operation from 2 January 2013 and amends directive 2001/83/EC [**46**].

3.2 Impurities

Impurities are classified in organic impurities, inorganic impurities and residual solvents. The organic impurities are further distinguished in starting materials, by-products, intermediates, degradation products, reagents, ligands and catalysts. These are highly dependent on the synthetic route which is followed. Inorganic impurities can result from the manufacturing process and include reagents, ligands and catalysts, heavy metals and residual metals. Solvents are used in the manufacturing process for preparation of solutions or suspensions and are therefore also linked to the manufacturing process [**47**].

A drug substance specification has to include limits for the organic impurities including limits for each specified identified impurity, each specified unidentified impurity, any unspecified impurity and total impurities. The acceptance criterion for unspecified impurities should be not more than the identification threshold. The limits for specified impurities should be justified by toxicological safety data and should reflect the batch analysis data and stability data on commercial drug substance batches nonetheless leaving adequate room for usual manufacturing and analytical variability [**47**].

Furthermore the drug substance specifications should include residual solvent specifications for the solvents which are used in the manufacturing process. The specifications should be in line with the requirements given in ICH guideline Q3C which is reproduced in Ph. Eur. General Chapter 5.4 and which therefore is applicable for new as well as for existing products. Solvents are classified based on their toxicological properties in 3 classes.

Class 1 solvents should principally be avoided due to their carcinogenic or environmental effect. If their use is unavoidable, they are to be controlled at very low concentration levels e.g. 2 ppm for the carcinogen Benzene.

Class 2 solvents are solvents that should be limited due to their toxic potential. The acceptance criteria defined in ICH guideline Q3C are calculated based on their permitted daily exposure (PDE) limits, which represent the maximum acceptable intake of the residual solvent per day. An example for a Class 2 solvent is Acetonitrile with a PDE of 4.1 mg/day resulting in a concentration limit of 410 ppm assuming a maximum intake of 10 g of the pharmaceutical preparation. Class 2 solvents used in the last step of the drug substance synthesis have to be included in the drug substance specification. Class 2 solvents used prior to the last step of synthesis have to be included in the drug substance specification also, except it was demonstrated on a number of consecutive batches that their concentration limits are not more than 10 % of the concentration limits defined in ICH guideline Q3C.

Class 3 solvents have low toxic potential with PDE of not less than 50 mg/day resulting in a concentration limit of 5000 ppm. Class 3 solvents are adequately controlled by the unspecific Loss on Drying test (Ph. Eur. 2.2.32) with a limit of not more than 0.5 %. If this limit is exceeded the class 3 solvents need to be identified and quantified [**48**] [**49**].

Inorganic impurities are also part of the drug substance specification. They often result from metal catalysts or metal reagents used in the manufacturing process. In the past they were usually determined by unspecific pharmacopoeial test methods like Sulphated Ash (Ph. Eur. 2.4.14) or Heavy metals (Ph. Eur. 2.4.8) test. This situation changed in the recent years. A Committee For Medicinal Products For Human Use (CHMP) guideline was published in 2008 which defined classes for metals based on their toxic potential analogous to the approach used for the Residual Solvents Guideline ICH Q3C:

Class 1 metals bear significant safety concern, Class 2 metals bear low safety concern and Class 3 metals have minimal safety concern. Class 1 metals are further divided in Class 1A, Class 1B and Class 1C.

The acceptance limits defined in the guideline depend on the route of administration. The limits for parenteral exposure are tighter than the limits for oral exposure. For the Class 1A metals Palladium and Platinum the PDE for parenteral exposure are 10 µg/day resulting in a maximum concentration limit of 1 ppm assuming a dose of 10 g pharmaceutical preparation. The PDE for Class 1 metals for oral exposure is ten times higher than the PDE for parenteral exposure [**50**].

There is an ICH guideline under development in order to harmonise the requirements for metal impurities in USA, Europe and Japan [**51**].

Furthermore the synthesis of the drug substance must be assessed for potential impurities with genotoxic properties and if required limits for these substances should be included in the specification. The "ALARP" (as low as reasonable possible)-principle should be followed for genotoxic impurities. The genotoxic impurities are distinguished in *"compounds with sufficient evidence for a threshold mechanism"* and "*compounds without sufficient threshold mechanism"*. For the first class the PDE concept as also applied for residual solvents and metal catalysts can be used. For the second class a PDE cannot be established. Therefore a general limit called *"Threshold of Toxicological Concern"* (TTC) was defined at a level of 1.5 µg/person/day [**52**].

The above said highlights the linkage between the drug substance manufacturing process and the resulting specification. A drug substance specification cannot thoroughly be established without having knowledge of the manufacturing process as the organic impurities as well as the inorganic impurities, residual solvents and genotoxic impurities which are present in a drug substance strongly depend on the manufacturing process used.

Pharmacopoeial monographs are always established under consideration of the synthetic routes which are known to the point of elaboration. Generally a drug substance monograph of the Ph. Eur. does not include limits for specific residual solvents but as referred to in the General Monograph *"Substances for Pharmaceutical Use"* the principles of Ph. Eur. General Chapter 5.4 are to be followed.

If a manufacturing process is followed which has not been considered during elaboration of the monograph or specification, there is a risk that the analytical methods described in the monograph are not suitable to detect the impurities present in the drug substance. Drug substance manufacturers which refer to a Ph. Eur. monograph e.g. in a CEP application are therefore required to demonstrate that the methods of the monograph are suitable to control the quality of the drug substance. Where an impurity is present which is not listed in the transparency list of the Ph. Eur. monograph at a level above the relevant reporting threshold, it must either be demonstrated that the monograph is suitable to control the impurity or an additional validated method must be implemented which is capable to control the impurity [**53**].

Globalisation leads to the use of different drug substance sources using different synthetic routes, e.g. to circumvent existing patents. This bears the risk that impurities are generated which cannot be detected with the analytical methods described in the pharmacopoeial monographs [**54**].

It is important to keep this in mind, for pharmaceutical companies who consider sourcing drug substances from new manufacturers, and adequately address this in their supplier qualification procedure. Furthermore it is a challenge for the committees responsible for elaboration of the pharmacopoeias to adapt the monographs in order to cover multiple synthetic pathways and their corresponding impurities.

3.2.1 Impact on the qualification of new drug substance suppliers

Due to the fact that different synthetic routes used in the manufacture of a drug substance may lead to new impurities a careful assessment of the proposed new supplier has to be performed with regard to the manufacturing process and impurities.

If a manufacturer holds a CEP for the respective drug substance the suitability of the monograph has already been demonstrated by the drug substance manufacturer and was assessed by EDQM assessors in the certification procedure. If additional tests to those described in the Ph. Eur. monograph are required these are listed on the CEP with established limits and the corresponding methods are appended.

If a CEP is not available for the drug substance the ASMF – Applicants Part should give the relevant information and should be assessed and compared to the established drug substance sources.

It should be kept in mind that the ASMF is separated in an Applicants Part and a Restricted Part. The Applicants part is shared with the drug product manufacturer and the Applicant while the Restricted Part is shared with the competent authorities only. For most sections of the ASMF it is clearly defined whether to be included in the Applicants Part or in the Restricted Part. But for some chapters the drug substance manufacturer has some freedom to decide which information is relevant for the applicant and which information is regarded as confidential. All sections which are regarded as confidential are related to the manufacturing process of the drug substance. The Applicants Part section 3.2.S.2.2 – *"Description of Manufacturing Process and Controls"* usually comprises of a flow chart and short description of the manufacturing process only. The sections 3.2.S.2.3 – *"Controls of Materials"*, 3.2.S.3.5 –

"Process validation and/or Evaluation" and 3.2.S.2.6 – *"Manufacturing Process Development"* are generally part of the Restricted Part only. For sections 3.2.S.2.4 –*"Control of Critical Steps and Intermediates"*, section 3.2.S.3.2 *"Impurities"* and section "3.2.S.4.5 – *"Justification of Specification"* the drug substance manufacturer can decide considering the relevance of the information for the applicant / drug product manufacturer and the confidentiality of information which information is placed in the Restricted Part only and which information is shared with the applicant / drug product manufacturer [**55**]. This means that the drug product manufacturer has to check during the assessment of the ASMF Applicants Part, if there is a hint that information with relevance for the drug product might be presented in the Restricted Part only and if so, this should be discussed with the drug substance manufacturer for example during the audit.

For substances intended for the use in the US where a US-DMF is available only, which is completely regarded as confidential information and usually not shared with the applicant / drug product manufacturer, it is nevertheless important to gain information about the drug substance. It should therefore be agreed with the drug substance manufacturer that a "technical package" is provided, which contains all relevant information about manufacture and control of the drug substance.

Furthermore it is absolutely necessary to liaise with the drug substance manufacturer to inform the drug product manufacturer about all changes in the manufacturing process as they could affect the quality of the drug substance.

The documentation the potential supplier provides is worthless if it is only "paper" as the supplier does not follow the manufacturing process as described either due to lacking GMP and / or due to intentional misleading. It is therefore of fundamental importance on the one hand to find trustworthy drug substance suppliers and on the other hand to control compliance with the documentation by regularly performing audits.

3.2.2 Impact on the European Pharmacopoeia

The General Monograph *"Substances for Pharmaceutical Use"* was first published in Ph. Eur. 4th edition. It reflected the concepts and threshold of ICH guideline Q3A and in consequence these became applicable also for existing drug substances. Therefore old monographs with a purity method which is not state-of-the-art, e.g. TLC method with acceptance limits of not more than 0.5 % for single impurities, and monographs without a transparency list were not acceptable any more for new CEP applications and CEP revisions, new marketing authorisation applications and renewals and relevant variations. In those cases the applicant was requested to propose new methods and specifications which then served as basis for revision of the monograph [**56**]. In the recent years most monographs have been revised to include a transparency list naming the impurities, which can be controlled with the analytical method and the acceptance criteria in accordance with the monograph *"Substances for Pharmaceutical Use"* [**54**].

But today already new challenges arise for Ph. Eur., for example the necessity for rapid adaption of monographs to incidents occurred with substandard medicines e.g. the Heparin incident described in chapter 1.1.2. Another challenge is the inclusion of new analytical methods, which either are less time consuming and cost saving like Fast HPLC, or methods,

which are more suitable to detect substandard medicines as HPLC e.g. NMR or HPLC-MS [**57**]. In order to ensure the quality of drug substances, the possibility is discussed to use, in addition to the established Ph. Eur. methods, orthogonal methods, i.e. methods with other selectivity, in order to detect impurities, which are not expected from the route of manufacture [**10**].

3.3 Transportation

The extent to which drug substances, bulk products and final products are stored and transported is increasing with supply chains becoming more complex due to globalisation. The goods might even pass different climatic zones during transportation. An example for transports passing different climatic zones are all transports from India or China to Europe. As highlighted before the share of Indian and Chinese drug substance manufacturers exporting to Europe is enormous and also the share of drug products imported from India is growing.

Environmental conditions during transport like temperature, humidity or light might adversely affect the quality of finished products, bulk products and drug substances. The worst case scenario of such quality deterioration would be harm to the patient. This might occur if the quality damage impacts safety or efficacy of the finished product and was not detected before reaching the patient. Deviations from transport conditions thus might necessitate the disposal of goods which means financial damage for the company. As a consequence high attention must be given to temperature and humidity conditions during transport.

A further relevant topic in context of increasing transport of goods is the supply chain security and traceability to prevent counterfeits. This issue is not regarded within this thesis.

It is essential to be aware about the climatic conditions on the transportation route. Concerning the stability conditions of medicinal products the earth is divided into climatic zones. These are described in section 3.3.2.

In order to understand how the climatic zones were stipulated, it is fundamental to understand the meaning of the Mean Kinetic Temperature (MKT). The MKT is furthermore an essential dimension in the context of temperature evaluation during transport. MKT is therefore explained in section 3.3.1.

Section 3.3.3 deals with the regulatory situation in Germany, Europe and beyond Europe with regard to transportation of medicinal products.

3.3.1 Mean Kinetic Temperature (MKT)

According to the ICH guidelines the MKT is *"a single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period"* [**58**].

The MKT concept is based on the fact that chemical degradation increases logarithmically at higher temperatures. This relationship is expressed in the Arrhenius equation. The Arrhenius equation is included in the Haynes formula for calculation of the MKT [**59**] [**60**].

The MKT is based on the temperature dependence of chemical reactions. It is therefore inadequate to use the MKT concept to evaluate physical effects of low temperature and high temperatures for example freezing or melting of suppositories [**59**].

Formula 1: Arrhenius Equation

$$k = A \cdot e^{\frac{E_a}{RT}}$$

Where:

k	Rate constant of a chemical reaction
A	Pre-exponential factor
E_a	Activation energy
R	Universal gas constant ($8.13144 \cdot 10^{-3}$ kJ mol^{-1} K^{-1})
T	Temperature in K

Formula 2: Haynes Formula

$$MKT = -\frac{E_a}{R} \frac{n}{\sum_{k=1}^{n} e^{\frac{-E_a}{RT_k}}}$$

Where:

MKT	MKT in K
E_a	Activation energy (for most medicinal products between 42 – 125 kJ/mol)
R	Universal gas constant ($8.13144 \cdot 10^{-3}$ kJ mol^{-1} K^{-1})
T	Temperature in K
n	Total number of equal time periods over which data is collected

3.3.2 Climatic zones

In order to stipulate conditions for stability testing of medicinal products and corresponding drug substances the earth was divided in different climatic zones based on historical climate data of temperature and relative humidity / partial water vapour pressure.

From historical climate data the MKT was calculated by setting all monthly average temperatures which are below 19°C to 19°C, as medicinal products are usually stored in

temperate areas, while all monthly average temperatures which are higher than 19°C were taken as such.

The results were four climatic zones: climatic zone I with temperate climate, climatic zone II with subtropical and mediterranean climate, climatic zone III with hot and dry climate and climatic zone IV with hot and humid climate. These are presented in Table 2. For evaluation of temperature excursions during transport it is important to consider that the stipulated stability testing conditions deviate from the calculated testing conditions as a safety margin was included. The safety margin, listed in Table 2 is the difference between the calculated storage condition and the stipulated long term testing condition [**60**].

The ICH guideline Q1A as well as the WHO guideline for stability testing set 25°C / 60% RH as stability testing condition for climatic zones I and II following a worst case approach. 21°C / 45% RH as stability testing condition for climatic zone I is therefore not relevant [**58**] [**61**].

The stability testing conditions for climatic zone IV were under discussion over the last decade. The first approach was to perform testing at 30°C / 70 % RH. Thereafter it was proposed by ICH to change this storage condition to 30°C / 60 % RH in order to harmonise it with the intermediate storage condition for climatic zone II. A compromise resulted in 30°C / 65 % RH as new storage condition for climatic zone IV (second approach). Later the Association of South East Asian Nations (ASEAN) stated that the storage condition 30°C / 65 % RH is not adequate for most of their member countries and therefore stipulated the stability testing conditions for ASEAN countries to 30°C / 75 % RH. This resulted in splitting the climatic zone IV in climatic zone IV_a with hot and humid climate and climatic zone IV_b with hot and very humid climate. The WHO member states of climatic zone IV indicated whether they belong to climatic zone IV_a or IV_b. The results were published by the WHO in Annex 2 to WHO Technical Report Series, No. 953 which lists the stability testing conditions per country. An example for climatic zone IV_a is China and an example for climatic zone IV_b is India [**62**] [**63**].

Table 2: Climatic zones with their calculated storage conditions, stipulated long term stability testing conditions and resulting safety margins for temperature and partial water vapor pressure. Stability testing condition for climatic zone I is not relevant as stability testing for climatic zone I and II are performed at 25°C / 60% RH. For climatic zone IV the formerly used stability testing conditions are also listed. These are marked with the suffix $_{1st}$ for the first approach and suffix $_{2nd}$ for the second approach. Actually climatic zone IV was separated into IV_a and IV_b [60], [62].

Climatic zone	Definition	Calculated storage conditions	Stipulated long term testing conditions	Safety margin
		Temperature / Partial water vapour pressure	*Temperature / Relative Humidity (Partial water vapour pressure)*	*Temperature / Partial water vapour pressure*
I	Temperate climate	19.6°C / 10.3 mbar	21 C / 45 % RH (11.2 mbar)	1.4°C / 0.9 mbar
II	Subtropical and mediterranean climate	21.7°C / 13.6 mbar	25°C / 60 % RH (19.0 mbar)	3.3°C / 5.4 mbar
III	Hot and dry climate	27.8°C / 11.9 mbar	30°C / 35 % RH (14.9 mbar)	2.2°C / 3.0 mbar
IV_{1st}	Hot and humid climate	28°C / 27.2 mbar	30°C / 70 % RH (29.7 mbar)	2.0°C / 2.5 mbar
IV_{2nd}	Hot and humid climate		30°C / 65 % RH (27.6 mbar)	2.0°C / 2.5 mbar
IV_a	Hot and humid climate		30°C / 65 % RH (27.6 mbar)	2.0°C / 0.4 mbar
IV_b	Hot and very humid climate		30°C / 75 % RH (31.8 mbar)	2.0 C / 4.6 mbar

3.3.3 Regulatory Situation Concerning Transport Conditions

Regulatory requirements and guidance on transport conditions of medicinal products are found on international level in WHO guidance documents, on European level in the EC (European Commission)-GMP guide, the *"Guidelines on Good Distribution Practice"* and the CHMP guideline *"Guideline on Declaration of Storage Conditions"* and on national level.

In Germany requirements are defined in the AMWHV. The requirements of the EC-GMP guide and in AMWHV are superficially and of little help in practice. The *"Guidelines on Good Distribution Practice"* (GDP) is currently under revision. The new version which was released for public consultation in July 2011 includes more specific guidelines than the previous version.

More detailed guidance is given in WHO guidance documents, the USP monograph <1079>, the Canadian guideline *"Guidelines for Temperature Control of Drug Products during Storage and Transportation"* and in the guideline of the Irish Medicines Board (IMB) *"Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances"*. The requirements defined in the above mentioned documents are summarized in the following subchapters.

3.3.3.1 WHO

There are several guidance documents issued by the WHO, which are applicable to medicinal products which cover transportation and storage from finished product manufacturers to pharmacies [**64**] [**65**] [**66**].

While the *"WHO guides for storage practice for pharmaceuticals"* [**64**] covers also starting materials and bulk drug products these are out of scope of *"WHO good distribution practice for pharmaceuticals products"* [**66**] but covered by the *"Good trade and distribution practices for pharmaceutical starting materials"* [**65**]. The following provisions are made in the WHO guidance documents which are regarded together due to the high degree of overlapping with regard to transport conditions:

During transportation integrity of the package should be ensured and if special storage conditions are stated on the label of the product these have to be maintained. This means if the expected environmental conditions deviate from the storage conditions defined, transportation should be performed at controlled conditions, which includes checking, monitoring and recording the temperature / humidity conditions with calibrated devices. Storage respectively transport conditions should be established based on the results of stability studies. The storage conditions and labelling statements are defined in the WHO guidance documents as reproduced in Table 3 [**61**] [**64**] [**65**] [**66**]. The labelling statements in the WHO guidance documents deviate between the guidance documents. As the *"WHO guides for storage practice for pharmaceuticals"* is older than the guide on *"Stability testing of active pharmaceutical ingredients and finished pharmaceutical products"* it is assumed that the labelling statements given in the first guide are partially out-dated and are therefore displayed in brackets in Table 3. The designation of labelling statements differs from the approach used in Europe, where a special labelling statement is not required if the stability data at accelerated conditions are within the specification over 6 months of storage.

Table 3: Storage conditions according to WHO guidance documents [64**] [**61**]**

Testing conditions where the product is stable [**61**]	**Required labelling statement** [**61**] [**64**]	**Storage / Transportation Temperature** [**64**]
Not available	Without labelling statement	15°C – 25°C or 15°C – 30°C (depending on the climatic condition)
25°C / 60 % RH (long term) 30°C / 65 % RH or 75 % RH (long term)	"Do not store above 30°C" *("Do not store over 30°C")*	2°C – 30°C
25°C / 60 % RH (long term) 40°C / 75 % RH (accelerated) or 25 °C / 60 % RH (long-term) 30°C / 65 % RH (intermediate, failure of accelerated)	"Do not store above 25°C" *("Do not store over 25°C")*	2°C - 25°C
Not available	*("Do not store over 15°C")*	2°C – 15°C
5°C ± 3°C (long term)	"Store in a refrigerator (2°C to 8°C)" *("Do not store over 8°C")*	2°C to 8°C
Not available	*("Do not store below 8°C")*	8°C to 25°C
-20°C ± 5°C	"Store in freezer"	Not available
Not available	*"Protected from moisture"*	≤ 60 % RH Moisture resistant container
Not available	*"Protected from light"*	Light-resistant container

3.3.3.2 EU

The EC-GMP Guide, Volume 4 Part II defines some requirements for drug substances with regard to storage and transport in paragraphs 10.21 to 10.23. According to that drug substances *"should be transported in a manner that does not adversely affect their quality"*, *"the transport conditions should be stated on the label"* and *"the manufacturer should ensure that the contract acceptor (contractor) for transportation of the drug substance or intermediate knows and follows the appropriate transport and storage conditions"* [**31**].

Analogous information for medicinal products is missing in EC-GMP Guide, Volume 4 Part I [**32**] but is provided in the *"Guidelines on Good Distribution Practice of Medicinal Products for Human Use"* in the paragraphs 20 and 21, which is valid only for finished products but not for bulk drug products [**67**]:

„*Medicinal products should be transported in such a way that their identification is not lost; they do not contaminate, and are not contaminated by, other products or materials; adequate precautions are taken against spillage, breakage or theft; they are secure and not subjected to unacceptable degrees of heat, cold, light, moisture or other adverse influence, nor to attack by microorganisms or pests. Medicinal products requiring controlled temperature storage should also be transported by appropriately specialised means. "*

The guideline will be replaced by a new guideline which was released for public consultation in July 2011. The requirements on transportation of finished medicinal products are much more detailed as in the current guideline. The following provisions are made in the new guideline in relation to temperature and humidity conditions during transport [**68**]:

- If special storage conditions are required during transport, these should be followed.
- Deviations from defined transport conditions are to be reported to the concerned parties i.e. distributor and recipient and procedures for handling temperature excursions should be established.
- Validation of temperature control systems should be performed for products which require transport at controlled conditions.
- If refrigerated transport vehicles are used temperature mapping should be performed considering seasonal temperature variations.
- If cool packs are used direct contact with the product should be prevented.
- The vehicles used for transport should be suitable for their use. This is the responsibility of the distributor. He has to take care about procedure for operation and maintenance of transport vehicles. When possible dedicated vehicles should be used for the transport of medicinal products. If non-dedicated vehicles are used, procedures should be in place to ensure that the quality of the medicinal product is not affected by the use of non-dedicated vehicles. The drivers should be adequately trained for transport of medicinal products.
- Temperature monitoring equipment has to be maintained in regular intervals not exceeding one year.
- The residence time at hubs is limited to 24 hours. If 24 hours are exceeded, it is to be regarded as storage.
- Places were unloading and reloading is performed should be audited.

The CHMP guideline *"Declaration of Storage Conditions"* defines labelling statements which have to be applied depending on the results of stability testing. The labelling statements given in Table 4 have to be used for finished products while the same principles should be applied for drug substances [**69**].

The labelling statements as such are not sufficient to define humidity and temperature ranges for storage areas. For this purpose the temperature definition given in Ph. Eur. General Notices and reproduced in Table 4 can be taken into account [**70**]. The current labelling statements are strictly spoken valid for storage only i.e. not for transport with the exception of *"Store and transport in refrigerator"* and *"Store and transport frozen"*. The labelling statements which indicate storage below 25°C and below 30°C are therefore strictly not applicable during transport. This might make sense for climate zones I and II and for transports which are finished within a short time frame as short time excursions in temperature can be justified under consideration of the MKT but in the light of globalisation with transports through different climatic zones and shipping overseas with transport times of several weeks this seems to be inadequate. In this context transport should be considered as a *"mobile form of storage"* as stated in the *"Concept paper on storage conditions during transport"* which targets in closing the gap of clear guidance for storage conditions during transport by a risk based approach [**71**].

Table 4: Storage conditions, labelling statements and testing conditions in the Europe

Testing conditions where the product is stable	Required labelling statement	Ph. Eur.
25°C/60 % RH (long term) 40°C/75 % RH (accelerated) or 30°C/65 % RH (long term) 40°C/75 % RH (accelerated)	This medicinal product does not require any special storage conditions.	---
25°C/60 % RH (long term) 30°C/60 or 65 % RH (intermediate) or 30°C/65 % RH (long term)	Do not store above 30°C or Store below 30°C	---
25°C/60 % RH (long term)	Do not store above 25°C or Store below 25°C	Room temperature: 15-25°C
5°C ± 3°C (long term)	Store in a refrigerator or Store and transport in refrigerator	In a refrigerator: 2°C to 8°C
< -15°C	Store in a freezer or Store and transport frozen	In a deep freeze: < -15°C

3.3.3.3 Germany

According to the AMWHV the following requirements have to be fulfilled for transport:

Starting materials, intermediates and final products have to be stored in a manner that their quality is not adversely affected. Critical parameters of storage and transport have to be controlled and recorded. The procedures for storage and transport have to be laid down in writing. If transport and storage conditions may impact the quality of the product their suitability should be demonstrated [**34**].

3.3.3.4 Ireland

The Irish Medicines Board has issued a detailed guideline on control and monitoring of storage and transportation temperature conditions for medicinal products and drug substances. It distinguishes requirements for cold storage and cold chain i.e. for products requiring storage and transportation refrigerated or frozen and for storage and transport at controlled temperature i.e. below 25°C or below 30°C.

Irrespective of the transport conditions, procedures should be in place on how to proceed with product transported outside the defined temperature ranges.

Cold chain transportation in insulated containers with ice packs is described for small volume transports. It is stated that direct contact with the ice packs should be avoided by using compartments or baffles in order to avoid damage due to freezing. Transport validation is required for transportation in insulated containers taking into account the expected worst case

scenarios with regard to seasonal temperature variability and maximum transport time. During transport validation both temperature extremes should be evaluated. The conditioning time for ice packs should be determined during validation and the maximum possible transport time should be evaluated.

For large volume transport requiring cold chain conditions refrigerated transport vehicles or transport containers should be used and temperature monitoring during transport is required. The data loggers used should be calibrated and single use monitoring devices should be qualified. Transport validation is required for transport vehicles or containers. Validation should include temperature mapping in order to determine cold / hot spots in the vehicle or container considering worst case conditions with regard to the loading capacity and extremes in environmental temperature.

For transportation under controlled temperature the method and duration of transportation, the amount of product to be transported, the environmental temperatures and the nature of the product should be considered when temperature control measures are laid down for the product [**59**].

3.3.3.5 USA

The General Notices chapter in the USP gives several possible labelling statements which are reproduced in Table 5 [**72**]. The labelling statements should be based on stability data. The interpretation of stability data and establishing the labelling statement differs from Europe as a labelling statement is also required if stability data at accelerated conditions (e.g. 40°C / 75 % RH) are available. Data gained at accelerated storage conditions might be taken into consideration for interpretation of transient temperature spikes which exceed the temperature excursion range of controlled room temperature.

Table 5: Storage conditions and labelling statements according to USP [72**] [**73**]**

Labelling statements	Storage Conditions
Freezer	-25°C to – 10°C
Refrigerator	Usually 2°C to 8°C Excursions between 0 – 15°C are acceptable, if the MKT is less than 8°C. Short term spikes of up to 25°C for maximum 24 hours are allowed if permitted by the manufacturer. For excursions exceeding 24 hours transient spikes have to be supported by stability data.
Cool place	8°C to 15°C
Controlled room temperature	Usually 20 – 25°C Excursions between 15 – 30°C are acceptable, if the MKT is less than 25°C. Short term spikes of up to 40°C not exceeding 24 hours are allowed if permitted by the manufacturer. Short term spikes of more than 40°C have to be supported by stability data.

The USP monograph <1079> *"Good Storage and Shipping Practice"* gives requirements for storage, distribution and shipping of medicinal products. Concerning transport of medicinal products the following provisions are made:

During transportation as a general rule extreme temperature conditions such as excessive heat or freezing should be avoided. Temperature measuring devices which are used have to be calibrated.

Shipping vehicles for articles which require controlled room temperature storage are to be equipped in a manner which ensures that the temperature excursions keep in the range of 15°C to 30°C with a MKT not exceeding 25°C. The vehicles should be qualified considering the load configurations and expected environmental extremes. Qualification should include temperature mapping over a 24 hours period on a hot summer day, a typical day and a cold winter day.

In order to evaluate the influence of multiple short-term excursions, temperature cycling studies should be performed for products which require special storage conditions. Temperature cycling studies mean stability studies where sequential cycling between lower and higher temperatures is performed.

For products requiring cold chain management temperature mapping has to be performed [**73**].

3.3.3.6 Canada

The *"Guidelines for Temperature Control of Drug Products during Storage and Transportation*" issued by the Health Products and Food Branch Inspectorate is applicable for drug products from manufacture to the final distribution point. It does not explicitly include drug substances or bulk drug product. The guideline in detail defines requirements for transport and storage of drug products. Transport is to be conducted under defined conditions which are based on stability data and stated on the label. Short time temperature excursions may be accepted with sound justification. Detailed information to which extent temperature excursions are acceptable is not given. If transportation has to be performed under controlled storage conditions, temperature monitoring and recording have to be performed using calibrated devices or qualified single use devices. The shipping containers or vehicles used for transport should be qualified. There should be written agreements in place between the sender and transport provider and the procedures for handling temperature excursions should be laid down in writing [**74**].

3.3.4 Bulk Stability Studies

Due to globalisation situations occur where bulk drug products are stored for longer durations. This might be based on supply chain considerations or due to regulatory circumstances. For example if a company plans to market a product in a South American country this is only possible if a manufacturing step e.g. packaging is performed in this country.

The EU variation classification guideline requires for a change of the bulk manufacturer or primary packaging manufacturer that conditions of transport and bulk storage should be specified and validated, but further guidance what should concretely be performed in order to validate the conditions of bulk storage and transport is currently missing [**36**].

The EMA has therefore issued a Questions & Answers documents dealing with this topic. It emphasises that bulk stability studies should be performed when bulk product storage exceeds 30 days concerning oral dosage forms or 24 hours concerning sterile dosage forms. It further states that stability studies on the bulk drug product should be performed on a minimum of two pilot scale batches covering at least the maximum storage interval for the bulk drug product [**75**].

3.4 Complex Supply Chains

Globalisation of medicinal product manufacture leads to more complex supply chains. This increases the potential that falsified medicines infiltrate legal supply chains.

The large amount of falsified medicines involved the generation of a European Directive with the objective to define measures preventing falsified medicinal products to get into the legal supply chain. In the fight against falsified medicines one country cannot be successful alone. Therefore global cooperation is absolutely necessary [**46**].

Further information on falsified medicines is not provided in this thesis.

3.5 Product Transfer

Due to globalisation transfer of a medicinal product from one production site to another is an increasingly relevant topic. Reasons for transfer of production sites can be cost saving considerations, optimisation of capacity utilisations or access to new markets which require several production steps to be performed by domestic firms.

In pharmaceutical environment the allocation of production must be properly planned in order to assure that the quality of the medicinal product is not negatively impacted. Certainly the site change has to be handled as a variation to the marketing authorisation.

This section discusses the requirement for a transfer of production sites from a regulatory point of view and beyond.

3.5.1 EU-Variations Related to a Site Change

In the EU-Variation Classification Guideline the transfer of a production site is covered by variation no. B.II.b.1 *"Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product"*. The guideline distinguishes changes in the primary and secondary packaging site, site changes for biological or immunological medicinal products, site changes which require initial product specific GMP-inspection and site changes for bulk manufacture of non-sterile medicinal products and for bulk manufacture including primary packaging for sterile medicinal products manufactured by aseptic methods [**36**].

3.5.1.1 Change of the packaging site

The changes of the primary and secondary packaging sites are classified as a minor variation type IA with immediate notification (i.e. IA_{IN}). The principle of Type IA_{IN} notifications is *"Tell & Do",* which means that the competent authority has to be notified without any delay about the change, accompanied by the documentation defined in the EU variation classification guideline [**76**]. For implementation of a type IA notification an approval of the authority is not required.

For a change of the secondary packaging site a manufacturing authorisation has to be submitted for sites located in the EEA (European Economic Area) and for sites outside the EEA a GMP certificate needs to be provided. Certainly the relevant dossier sections need to be updated and the present and proposed manufacturers need to be clearly stated in the variation application form.

For a change of the primary packaging site additionally the numbers of validation batches need to be stated for specific types of products i.e. emulsions or suspensions and if relevant the approved release and shelf-life specifications should be provided. It is important to consider that conditions of bulk storage and transport need to be addressed for site changes which lead to different locations of bulk manufacturing and primary packaging site. This change indirectly requires the conduct of bulk stability studies and the determination of transport conditions based on these data as described in section 3.3.4 [**36**].

Generally the allocation of a packaging site is rather easy doing. Nevertheless there are considerations to be taken apart from the requirements resulting from the variation classification guideline.

These include supplier qualification of the proposed packaging site, the conclusion of technical agreements (contractual agreements for delimitation of responsibility) and the assurance that the correct packaging materials are used i.e. usually dossier compliant primary packaging material except a change of the primary packaging material is intended to be performed in parallel to the site change. A change of the quality of the primary packaging material would require performing stability studies and consequently would delay the site change and cause additional costs.

3.5.1.2 Site change of bulk manufacture

The change of the bulk manufacture is classified as a variation type IB in the variation classification guideline. Type IB variations follow the principle *"Tell, Wait and Do".* This means that the competent authorities have to be notified about the change; subsequently the applicant has to wait 30 days starting from *"acknowledgement of receipt of a valid notification"*. If he has not received a negative opinion, the change can be implemented [**76**]. In addition to the requirements which need to be fulfilled for the change of the packaging site the batch number of validation batches, *"batch analysis data on one production batch and two pilot-scale batches simulating the production process (or two production batches) and comparative data on the last three batches from the previous site; batch data on the next two production batches should be available on request or reported if outside specifications (with proposed action)"* and a QP declaration stating the GMP compliance of the drug substance manufacturer need to be provided (refer to section 3.1.3 for further information on the QP declaration) [**36**].
As can be concluded from the requirements in the variation guideline a change of the bulk manufacturing site is more complex than a change of the packaging site.

The bulk manufacturer must be selected based on its capability to produce the product and its GMP compliance. The need for supplier qualification and contractual agreements as mentioned for the packaging site change is also relevant for bulk manufacture.

It must be assessed whether the site change entails further changes i.e. a change in the manufacturing process of the finished product (B.II.b.3), which usually requires the conduct of stability studies or a change in the batch size of the finished product (B.II.b.4) [**36**]. Both are very likely related to a site change of the bulk manufacture i.e. as different manufacturing equipment at the proposed site might require adaption of process parameters such as mixing times.

Certainly it would be beneficial if a transfer of manufacturing know-how could be performed from the old site to the new site to facilitate a smooth production start at the proposed site. But this is not always possible i.e. if the present manufacturing site is not willing to cooperate.

For a change of the bulk manufacturing site the time scheduling is very important. This is because the variation can only be performed after two pilot batches and one production batch have successfully been produced and tested, but can be marketed only after the type IB variation procedure is finalized. It should therefore be assured that enough product is available from the current production site also considering some time for validation of the variation and possible clock-stop i.e. about 3 to 4 months from the day of submission.

In connection with the change of the bulk manufacturer it is likely that also quality testing and / or batch release sites are changed. This is change B.II.b.2 of the variation classification guideline. A change of the batch control site is classified as a minor variation of type IA, which has to be notified within 12 months after implementation. A change of the batch release site is classified as a type IA_{IN} notification.

As already described for the change of the packaging site the manufacturer who performs quality control and / or batch release has to be adequately authorised, i.e. a manufacturing authorisation or a GMP certificate has to be submitted accompanied by a QP-declaration, the updated sections of the dossier and naming of the present and proposed manufacturers in the application form. Companies performing batch release must be located in the EEA. In order to change the quality control site of a medicinal product, the analytical method transfer has to be finalized [**36**].

The method transfer is required in order to assure that the receiving laboratory finds the same results as the transferring laboratory, considering the experimental error of the analytical methods and thus can be regarded as valid also at the receiving laboratory. Method transfer is performed by a set a analytical testing i.e. testing of the same sample in the transferring and receiving laboratory and comparing the results based on predefined acceptance criteria. In situations where the former testing site is not involved in the transfer partial revalidation of single validation parameters can also be performed [**77**].

3.5.1.3 Site changes for biological or immunological medicinal products

A site change of bulk manufacture, quality control and release testing for biological or immunological medicinal product is classified as a major variation i.e. type II, which means that an approval of the variation by the competent authority is required before the change can be implemented [**36**] [**76**].The classification as a type II variation is due to the fact that the quality of biological medicinal products is highly dependent on their complex biological manufacturing process, sophisticated analytical methods have to be used for control and that the impact of changes to the manufacturing process is difficult to predict [**78**].

4 Cooperation and Harmonisation of Authorities and Organisations in the Light of Globalisation

The focus of the previous chapter was laid mainly on the challenges of globalisation for a drug product manufacturer. The current chapter deals with another fundamental topic in the context of globalisation, the cooperation and harmonisation initiatives of authorities and organisations. As medicinal products are marketed world-wide, cooperation and harmonisation are the best way to handle the challenges of globalisation.

Various authorities cooperate with one another to cope with the challenges of globalisation. In the light of globalisation big efforts are made in order to harmonise requirements for medicinal products to achieve reduction of duplicate testing and to accelerate drug registration and consequently speed up the access to medicines for the patient. This section presents those organisations which are engaged in harmonisation efforts and depicts cooperation initiatives of authorities.

4.1 Harmonisation within Europe

Europe is a good example for successful harmonisation of regulatory procedures and requirements across countries. After the European Economic Community (EEC) was created by the Treaty of Rome in 1957 with the aim to create a common market in the member countries [**79**], harmonisation activities started also in the field of medicinal products. Having in mind the Contergan tragedy of the 1960ies, the European pharmaceutical legislation also focussed on improving requirements for quality, safety and efficacy.

4.1.1 European Pharmaceutical Legislation

The harmonisation of drug legislation in Europe was initiated with Directive 65/65/EEC. According to the recitals of the directive the reason for its creation was *"to safeguard public health [...] by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community"* [**80**]. Until directive 65/65/EC each EEC country had its own requirements for medicinal products which did not include detailed requirements on quality, safety and efficacy. In Germany, for instance, drug products were registered in the *"Arzneimittelspezialitätenregister"*. For this registration an assessment of quality, safety or efficacy data was no prerequisite [**81**]. Directive 65/65/EEC made marketing authorisations for medicinal products to an obligatory requirement. In order to obtain a marketing authorisation, applicants had to submit data on quality, safety and efficacy and upon assessment of the data a marketing authorisation was granted by the respective national competent authorities [**80**]. The provisions of Directive 65/65/EEC had to be transformed into the national law of each member state which was done in Germany in the "*Gesetz zur Neuordnung des Arzneimittelrechts"* from 1976 [**82**].

Following the directive 65/65/EEC numerous further directives were established and amended which were consolidated in directive 2001/83/EC known as *"Community code relating to medicinal products for human use"* [**30**].

Further milestones in harmonisation were reached after directive 65/65/EC. Worth mentioning is the development of pan-European marketing authorisation application procedures i.e. the decentralised and centralised procedures and their forerunners as well as the establishment of the Committee for Proprietary Medicinal Products (CPMP) and the European Medicines Agency as well as the elaboration of a European Pharmacopoeia.

4.1.2 Committee for Proprietary Medicinal Products (CPMP)

The Committee for Proprietary Medicinal Products was set up by directive 75/319/EEC in order to "*facilitate the adoption of a common position by the Member States regarding marketing authorizations".* It is composed by representatives of the member states and the European Commission.

The CPMP had published numerous of scientific guidelines in the fields of quality, safety and efficacy. Furthermore the CPMP played a major role in the new pan-European procedures for Marketing Authorisation Applications [**83**].

With the establishment of the European Medicines Evaluation Agency (EMEA), later renamed to EMA based on regulation 2309/93/EEC the CPMP was organised as a committee within the EMEA.

The CPMP was replaced by the CHMP as per regulation 726/2004/EC [**84**].

4.1.3 Pan-European Marketing Authorisation Application Procedures

Today Pan-European Marketing Authorisations i.e. the Mutual Recognition Procedure, the Decentralised Procedure and the Centralised Procedure are well-established marketing authorisation application procedures for medicinal products which are deemed to be authorised in more than one member states of the European Union. The development of those procedures already began in the 1975.

4.1.3.1 Mutual Recognition Procedure (MRP) and Decentralised Procedure (DCP)

The forerunner of the current Mutual Recognition Procedure and Decentralised Procedure was the Multi-State Procedure. It was established by directive 75/319/EEC. After approval of a marketing authorisation in one member state the applicant could choose to submit his dossier in further member states which should grant their marketing authorisations subsequently within a time frame of 120 days based on the marketing authorisation granted in one member state. In case of objections these should be discussed with the member state, which already granted the marketing authorisation and if no agreement could be achieved the CPMP was asked for its opinion. The success of the Multi-State Procedure was really unsatisfying [**85**] and it often lead to divergent decisions within the participating countries. From its start in 1975 to its end in 1995 about 400 products ran through the Multi-State Procedure [**83**]. The current procedures are much more successful. In 2010 535 MRPs and 1452 DCPs have been finalised [**86**].

4.1.3.2 Centralised Procedure (CP)

The current Centralised Procedure according to regulation 726/2004/EC [**84**] was created based on the previous Concertation Procedure which was fixed in directive 87/22/EEC. The scope of the Concertation Procedure was high technology products especially those obtained

by biotechnological means [**87**]. The procedure was mandatory for biotechnological products. In the Concertation Procedure one member state operates as rapporteur. After detailed assessment of the dossier, the rapporteur sends an assessment report including its opinion to the remaining member states. Subsequently the comments of all member states were forwarded to the applicant for response. In the majority of cases a harmonised Summary of medicinal Product Characteristics (SmPC) could be achieved. Compared to the Centralised Procedure the marketing authorisations achieved by the Concertation Procedure were national Marketing Authorisation in each member state. The Concertation Procedure was used about 70 times in the time from 1987 to 1995. In 1995 it was followed by the Centralised Procedure and the establishment of the EMEA based on regulation 2309/93/EC [**88**]. The Concertation procedure was more successful than the Multi-State Procedure [**83**]. 54 marketing authorisations applications were finalised in 2010 following the CP [**89**].

4.1.4 European Pharmacopoeia (Ph. Eur.)

With the Convention on the Elaboration of a European Pharmacopoeia from 1964 the decision to create the Ph. Eur. was taken under consideration of the objective for free movement of goods within Europe. The development of the Ph. Eur. was put in the hands of the Council of Europe [**90**]. In 1975 the Ph. Eur. monographs became mandatory requirements in the EEC with directive 75/318/EEC. Since 1994 the conformity of drug substances with the Ph. Eur. can be demonstrated by using the procedure for the Certificate of Suitability to the Monographs of the European Pharmacopoeia [**91**]. Actually the Ph. Eur. includes more than 2000 monographs and more than 300 general methods, which are mandatory in all 35 member states of the European Pharmacopeia Convention and the EU [**45**]. Further 21 countries as well as the WHO are taking part in the work on the Ph. Eur. as observers [**92**].

4.2 International Conference on Harmonisation (ICH)

The International Conference on Harmonisation of Technical Requirements was founded in 1990 with the aim to harmonise regulatory requirements for the registration of new drug products. Representatives from industry and authorities of the regions Europe, Japan and the United States work together in ICH towards this objective [**93**].

The governing body of the ICH is the Steering Committee. The Steering Committee consists of two representatives of each of the involved authorities (EU, FDA and MHLW) and two representatives of each of the involved pharmaceutical industry associations (EFPIA, PhRMA and JPMA). The three observers which are part of the Steering Committee are the WHO, Health Canada and the European Free Trade Association (EFTA) [**94**].

Detailed elaboration of guidelines and corresponding discussions are taking place in the ICH working groups.

ICH has established numerous guidelines in the field of quality, safety and efficacy and also multidisciplinary guidelines.

In the field of quality one merit of ICH was the establishment of harmonised stability testing criteria for the ICH regions. The ICH guidelines on stability Q1A to Q1E define the stability testing conditions for new drug substances and new drug products with respect to

temperature, relative humidity and photostability, the minimum data set which should be available at submission and gives guidance how stability data should be evaluated and to which extend extrapolation of stability data is possible [**58**] [**95**] [**96**] [**97**]. With the models for bracketing and matrixing the ICH stability guidelines offer the opportunity to reduce testing and consequently safe costs for stability testing [**98**]. The main parts of the ICH guidelines have been adopted for existent drug substances and drug products too [**99**]. The stability guidelines are hence a good example for the influence of the ICH work also on existent drug substances and drug products i.e. generics.

Perhaps more impressive examples for that are those guidelines which found their way in the European Pharmacopoeia and consequently changed their value from a guide to obligatory requirements. The ICH residual solvents guideline Q3C is included in Ph. Eur. 5.4 *"Residual Solvents"* and the impurity thresholds of ICH guideline Q3A were taken over in Ph. Eur. 5.10 *"Control of Impurities in Substances for Pharmaceutical Use"* [**47**] [**48**] [**54**].

Quality guidelines on the following topics were developed by the ICH [**100**]:

- Stability
- Analytical Validation
- Impurities
- Pharmacopoeias
- Quality of Biotechnological Products
- Specifications
- Good Manufacturing Practices
- Pharmaceutical development
- Quality Risk Management
- Pharmaceutical Quality System
- Development and Manufacture of Drug Substances

One further milestone of ICH work was the development of the Common Technical Document (CTD) as a consistent format for submission of marketing authorisation applications for the three ICH regions. The CTD reduces reformatting work for industry for submissions in more than one of the ICH regions. It furthermore facilitates the review of submissions due to a standardised structure of submitted data and promotes the information exchange of authorities. Furthermore the CTD was the base for development of the electronic Common Technical Document (eCTD). The CTD was not only adopted as the required format for marketing authorisation applications in Japan, Europe and the United States. Various other countries like Canada adopted the CTD format as well. The same is true for various quality, safety and efficacy guidelines established by ICH [**93**].

As a consequence of globalisation of drug development and a growing interest of non-ICH countries in ICH guidelines the ICH has implemented the Global Cooperation Group (GCG) as a part of the ICH Steering Committee in 1999 with the mission *"to promote a mutual understanding of regional harmonisation initiatives in order to facilitate the harmonization process related to ICH Guidelines regionally and globally, and to facilitate the capacity of drug regulatory authorities and industry to utilise them"* [**101**]. The five regional harmonisation initiatives Asia-Pacific Economic Cooperation (APEC), the Association of the Southeast Asian

Nations, (ASEAN), the Gulf Cooperation Council (GCC), the Pan American Network for Drug Regulatory Harmonisation (PANDRH), and the Southern African Development Community (SADC) as well as representatives from authorities of countries who are either major source of drug substances or of clinical trial data were invited to participate on ICH work through the GCG [**100**] [**93**].

4.3 Pharmacopoeial Discussion Group (PDG)

In the Pharmacopoeial Discussion Group which was founded in 1989 representatives of the EDQM, the United States Pharmacopoeia Discussion Group (USPC) and the Pharmaceutical and Medical Device Agency (PMDA), which is responsible for the Japanese Pharmacopoeia (JP), work on the harmonisation of pharmacopoeial monographs. The PDG does not work completely uncoupled from other harmonisation initiatives as the WHO is observer of the PDG and PDG representatives participate as observers on several discussions of ICH working groups [**102**].

The harmonisation of monographs is performed in a six-stage process which is outlined below:

1. Identification of monographs to be harmonised and assignment of a coordinating pharmacopoeia.
2. Preparation of a draft monograph by the coordinating pharmacopoeia under consideration of the existing monographs of the three pharmacopoeias.
3. Review of the draft monograph by the expert committees of each pharmacopeia and review of the experts comments by the coordinating pharmacopoeia resulting in a harmonised document.
4. Publication in the forums of each pharmacopoeia. Commenting by the stakeholders to their respective pharmacopoeia secretariat and preparation of a harmonised document after review of the comments received.
5. Review of the document by the non-coordinating pharmacopoeias. Either consensus is reached or a new draft is prepared by the coordinating pharmacopoeia.
6. Implementation of the monograph is performed in the three pharmacopoeias. The times of implementation are not harmonised and depend upon the specific procedures of each pharmacopoeia.

The harmonisation of excipient monographs has already reached an admissible extend. An overview is provided in Table 6. Furthermore harmonisation of general chapters is well advanced as can be seen in Table 7.

Table 6: Extend of harmonisation of excipient monographs. Some of the harmonised monographs have already undergone a revision [103**].**

Harmonisation stage	1	2	3	4	5	6
Number of Excipient monographs	0	2	7	17	3	32

Table 7: Harmonised General Chapters between Ph. Eur. / USP / JP [104**]**

Ph. Eur.	JP	USP
2.2.31 Electrophoresis	*23. SDS-Polyacrylamide Gel Electrophoresis*	*<1056> Biotechnology Derived Articles - Polyacrylamide Gel Electrophoresis*
2.2.47 Capillary electrophoresis	*4. Capillary Electrophoresis*	*<1053> Biotechnology Derived Articles - Capillary Electrophoresis*
2.2.54 Isoelectric focusing	*9. Isoelectric Focusing*	*<1054> Biotechnology Derived Articles - Isoelectric Focusing*
2.2.55 Peptide mapping	*15. Peptide Mapping*	*<1055> Biotechnology Derived Articles - Peptide Mapping*
2.2.56 Amino acid analysis	*1. Amino Acid Analysis*	*<1052> Biotechnology Derived Articles - Amino Acid Analysis*
2.4.14 Sulphated Ash	*2.44 Residue on Ignition Test*	*<281> Residue on Ignition*
2.6.1 Sterility	*4.06 Sterility Test*	*<71> Sterility Tests*
2.6.12 Microbiological examination of non-sterile products: microbial enumeration tests	*4.05 Microbiological Examination of Non-sterile Products: II. Microbiological Examination of Non-sterile Products - Microbial Enumeration Tests*	*<61> Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests*
2.6.13 Microbiological examination of non-sterile products: tests for specified micro-organisms	*4.05 Microbiological Examination of Non-sterile Products: I. Microbiological Examination of Non-sterile Products - Tests for Specified Micro-organisms*	*<62> Microbiological Examination of Non-sterile Products: Tests for Specified Micro-organisms*
2.9.1 Disintegration of Tablets and Capsules	*6.09 Disintegration Test*	*<701> Disintegration*
2.9.7 Friability of uncoated tablets	*26. Tablet Friability Test*	*<1216> Tablet Friability*
2.9.17 Test for extractable volume of parenteral preparations	*6.05 Tests for Extractable Volume of Parenteral Preparations*	*<1> Injections*
2.9.19 Particulate contamination: sub-visible Particles	*6.07 Insoluble Particulate Matter Test for Injections*	*<788> Particulate Matter in Injections*
2.9.26 Specific surface area by gas adsorption	*3.02 Specific Surface Area by Gas Adsorption*	*<846> Specific Surface Area*
2.9.36 Powder flow	*18. Powder Flow*	*<1174> Powder Flow*
2.9.37 Optical microscopy	*3.04 Particle Size Determination*	*<776> Optical Microscopy*
2.9.38 Particle-Size distribution estimation by analytical sieving	*3.04 Particle Size Determination*	*<786> Particle-Size Distribution Determination by Analytical Sieving*
5.1.4 Microbiological Quality of non sterile pharmaceutical preparations and substances for pharmaceutical use	*12. Microbiological Attributes of Non-sterile Pharmaceutical Products*	*<1111> Microbiological Attributes of Non-Sterile Pharmaceutical Products*

When full harmonisation of monograph is not possible due to differing standpoints, partial harmonisation is performed.

In order to avoid that monographs that once have been harmonised are drifting apart over time, the pharmacopoeias agreed not to revise harmonised monographs in a solo attempt [**105**].

The PDG focussed on harmonisation of general chapters and excipient monographs but did not consider the harmonisation of drug substance monographs. Following industry wishes, EDQM and USPC started a pilot project to harmonise drug substance monographs prospectively. The PMDA acts as an observer in this project. Four harmonised drug substance monographs have been published in Pharmeuropa and Pharmacopoeial Forum in 2010 [**45**] [**106**]. Two of those monographs, Montelukast Sodium and Rizatripan Benzoate, have already been published in Ph. Eur. supplement 7.3. [**107**] and the monograph Rizatripan Benzoate was published in USP 34 [**108**].

4.4 Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S)

The Pharmaceutical Inspection Convention (PIC) and Pharmaceutical Inspection Co-operation Scheme are two institutions which operate together in the field of GMP.

The Pharmaceutical Inspection Convention is the older institution. It was founded in 1979 by the EFTA with the aims of harmonisation of GMP requirements, consistent inspection systems, training of inspectors, exchange of information and mutual confidence in order to achieve mutual recognition of inspections by a formal treaty between countries. After it has been recognised that European PIC member countries must not sign agreements with countries that would like to accede PIC, the PIC Scheme was formed in 1995 as cooperation between health authorities on an informal basis. Currently PIC/S has 39 member countries. In January 2011 the US and Ukraine joined PIC/S. PIC/S countries are not bound to mutually accept inspection results of other PIC/S countries.

The PIC/S scheme has established GMP guidelines and guidelines for preparation of a site master file for industry as well as procedures for inspectorates with respect to quality system requirements, rapid alerts and recalls due to quality defects and a standardised inspection report format and aide memoires for inspectors. The EC-GMP Guide (Eudralex volume 4) and the PIC/S GMP Guide are equally as regards content [**29**].

4.5 Mutual Recognition Agreements (MRA)

The EC has established Mutual Recognition Agreements with some countries with the aim to reduce trade barriers while safeguarding public health by mutually acceptance of various documents and exchange of information. If a MRA is available, this means that comparable GMP standards are prevalent in the corresponding countries.

The EC has fully operational MRA in place with Australia, Switzerland and New Zealand. The MRA with Canada does not include preapproval inspections and medicinal product derived

from plasma [**109**] and the MRA with Japan has only limited scope. The transitional period for the MRA with the US ended in November 2001. Therefore no MRA with the US is in operation. Nevertheless an alert system between EC and US exists [**110**].

The documents which are mutually recognised for countries with full operational MRAs are the manufacturing authorisations, inspection outcomes and the batch certification of the manufacturer. This prevents authorities to perform inspections in the countries with which MRAs are in place. Nevertheless authorities may perform inspections if deemed necessary due to public health reasons. Qualified persons can waive retesting of batches if a MRA is available with the exporting country [**109**].

4.6 World Health Organization (WHO)

The World Health Organization is the health authority in the United Nations system. It was founded in 1948 and comprises 193 member countries and two associate members.

According to the WHO constitution *"the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition"* [**111**]. Consequently WHO is mainly engaged to improve the health standards in developing countries. Main objectives of the WHO are to improve the access to medicines and to ensure the safety of medicines. To name only one example, WHO has started a prequalification programme in 2001 with the objective to improve the availability of qualitative medicines for the treatments of HIV / AIDS, tuberculosis and malaria. For medicines which are included in the WHOs *"Invitation for Expression of Interest"* manufacturers can provide a dossier including data on quality, safety and efficacy. Following an assessment of the dossier and an inspection of production site the product is included on the prequalified products list, which serves primarily the United Nations procurement agencies as an overview for medicines meeting acceptable standards. It is further used by the countries and aid organisations for reference [**112**].

One area of WHOs work is the quality and safety of medicines. In this context various recommendations, guidelines and reports were developed on the following topics:

- Blood Product and Related Biologicals
- Counterfeit Medicines
- Internationally Nonproprietary Names
- Quality Assurance
- Regulatory Support
- Safety and Efficacy
- The International Pharmacopoeia

Upon other, the GMP and GDP as well as the stability guidelines of the WHO are important documents in the field of quality [**113**].

Of further importance with regard to cooperation of authorities in order to facilitate the access to medicines over the world is the WHO Certification Scheme. The key document is the Certificate for a Pharmaceutical Product (CPP), which is issued by the authority of the exporting country and mainly states information on the licensing and marketing status of the

product in the exporting country. The CPP is used in some countries which have less sophisticated drug regulatory agencies to substitute several parts of the submission dossier [**114**].

4.7 International Cooperation of the European Medicines Agency (EMA)

The EMA cooperates with various organisations and countries on an international level e.g. ICH, the Codex Alimentarius, WHO, FDA, MHLW, Health Canada and Therapeutic Goods Administration (TGA) and other non-ICH regulatory authorities. These cooperations are commonly based on MRAs or confidentiality agreements. An intensive cooperation is present between EMA and FDA.

4.7.1 Cooperation between EMA and FDA

EMA and FDA have a confidentiality agreement in place since 2003, which was updated in 2010. Several collaboration projects exist between EMA and FDA. On areas of mutual interest, entitled as "*clusters",* information is exchanged in regular (i.e. monthly to quarterly) teleconferences. The *"clusters"* include the following topics:

- Oncology
- Orphan medicinal products
- Paediatrics
- Advanced Therapy Medicinal Products
- Pharmacogenomics
- Vaccines
- Veterinary medicinal products
- Blood Products
- Biosimilars

Information exchange on other products is also performed on an ad hoc basis. Furthermore regular teleconferences are performed in the area of pharmacovigilance and safety on a bimonthly basis [**115**] [**116**].

Another collaboration initiative of EMA and FDA is the option for parallel scientific advice for products within the scope of the *"clusters"*. A parallel scientific advice is usually performed in request of the applicant. It is limited to breakthrough medicinal products, due to limited resources in the agencies. Within the procedure for parallel scientific advice a joint discussion is performed between EMA and FDA. Nevertheless each agency gives independent advice to the applicant i.e. the advices may differ [**117**].

Another field of cooperation between EMA and FDA are inspections. Collaborations exist in the field of Good Clinical Practice (GCP) and GMP.

The "*Pilot EMA-FDA GCP Initiative"* started in September 2009 with the objective to exchange information on the interpretation of GCP, GCP inspections and to perform collaborative GCP inspections (i.e. joint inspections and observed inspections) for sites mostly located in the EU

and US. The programme was deemed successful and will be continued with widened scope for joint inspections also in third countries [**118**].

Regulatory authorities from the US (FDA), Australia (TGA) and Europe (EMA, EDQM, France (AFSSAPS), Germany (ZLG), Ireland (IMB), Italy (AIFA), United Kingdom (MHRA) participated in the *"International API inspection Pilot Programme"* from December 2008 to December 2010. Precondition for the participating countries were comparable GMP standards i.e. ICH Q7A and the availability of confidentiality agreements. The programme was focused on GMP inspections of drug substance manufacturers in third countries. The objectives of the programme were to decrease duplicate inspections i.e. inspections at the same site performed from more than one of the participants within a short time interval, to increase the total number of inspections with value for more than one participant and to increase the overall coverage of drug substance manufacturing sites inspected. These objectives were reached by exchange of information on planned inspections, by exchange of inspections reports and by joint inspections. Due to the positive result of the programme, this collaboration will be continued under inclusion of all EEA members. As a long term vision further agencies with comparable GMP standards and perhaps the WHO could be involved in order to create an efficient global inspection programme for drug substance manufacturers [**119**].

5 How to Deal with Globalisation Challenges in a Mid-Sized Pharmaceutical Company

As one representative for all globalisation challenges described in section 3, an approach for selecting adequate temperature conditions during transport is developed in the following chapter using cause and effect analysis and decision analysis. The use of science and risk based approaches can certainly equally be applied to further challenges evoked by globalisation.

5.1 Transportation

As discussed in section 3.3 the extent to which medicinal products are transported is increasing due to globalisation. Maintaining the quality of medicinal products during transportation is a challenge also for mid-sized pharmaceutical companies. In the following an approach is proposed, how the quality of medicinal products is maintained during transportation of solid oral dosage forms for a mid-sized pharmaceutical company.

5.1.1 Scenario

The fictious mid-sized pharmaceutical company named Virtual Pharma was founded more than 60 years ago and comprises one site which is located in Germany near Gießen. The site includes a production facility for solid oral dosage forms, a quality control unit as well as marketing and distribution. The product portfolio of Virtual Pharma includes mainly generics and a few original preparations. All products marketed by Virtual Pharma are solid oral dosage forms. The company has focussed purely on the German market in the past and products were mainly produced in the facilities of Virtual Pharma.

But in the recent years the situation changed:

Marketing of products is expanded to an European level and it is planned to enter some non-European countries in the future. Due to in-licencing activities with contract obligations which bind to a manufacturer or due to cost considerations about 30 % of production shifted to contract manufacturers. The contract manufacturers are situated in European and non-European countries.

The changes in marketing focus and production sites affect the extent to which medicinal products are transported. Therefore an approach is needed for decision making which transports of solid oral dosage forms need to be performed under controlled conditions at 15°C to 25°C and which transports can be performed under uncontrolled conditions using risk management facilitation methods.

Generally the majority of solid oral dosage forms do not require storage in a refrigerator or a freezer. As Virtual Pharma markets no products which require cold-temperature storage or storage in a freezer these storage conditions are disregarded in the following approach.

5.1.2 Influence Factors on Quality of Medicinal Products during Transport

There are several factors which might have an effect on the quality of the medicinal product during transport. In order to identify and structure these risk factors, a cause and effect diagram was selected as an appropriate tool. It is presented in Figure 6. A discusion of the risk factors which were identified is provided as follows:

The product intrisic properties e.g. the stability of the drug substance with respect to humidity and temperature and the selection of the dosage form are already fixed since the pharmaceutical development of the medicinal product. Changing these factors to minimise the risk during transport would be connected to an immense operating expense and cost intensive. It is therefore not regarded as a regular option to change the product intrinsic properties to improve the behaviour of the drug product during transport. This might only be considered in very exceptional cases. The decision wether transport should be performed under controlled or uncontrolled conditions must therefore be based on the available stability data.

The packaging material has also been fixed during the development of the medicinal product. A change in the packaging material of the medicinal product would at least require the performance of new stability studies. Change of the packaging material i.e. from PVC / aluminium blister packs to aluminium / aluminium blister packs might be an option if the product is intended to be marketed in countries of climatic zone IV and stability studies reveal problems at 30°C / 65 % RH or 40°C / 75 % RH.

The risks associated with measuring and control devices are mainly relevant for controlled transports but can also be of concern for uncontrolled transports if temperature monitoring is performed e.g. for transport validation. If measuring and control devices are defect, not calibrated or deliver no data due to an electrical power failure and consequently data cannot be evaluated it might result in rejection of the product and is therefore equatable with a quality defect during transport.

The risk associated with failure in power supply or defects of the cooling equipment is associated with temperature controlled transports only.

Defects of the transport vehicle itself concern both, uncontrolled transports as well as transports under controlled conditions. They might lead to time delays in transport and would affect uncontrolled transports to a greater extend than controlled transports, provided that the cooling system is not concerned by the defect.

The risks associated with transit and environmental conditions affect uncontrolled transports more than controlled transports.

The main criteria which are needed to stipulate whether transport is performed under controlled conditions are:

1. The properties of the product in its packaging material, which express itself in the stability data of the drug product. Review of relevant stability data is therefore important when establishing transportation conditions for a drug product.
2. The environmental conditions during transport for which the climatic zone could be used as an indicator.
3. The anticipated maximum transportation time which depends on the transport vehicle used i.e. truck, airfreight or seafreight and the infrastructure on the transport route.

Risks associated with measuring and control techniques, transport and equipment might effect the quality of the medicinal product but are not necessary for the principal decision if a given product has to be transported under controlled environmental conditions or not.

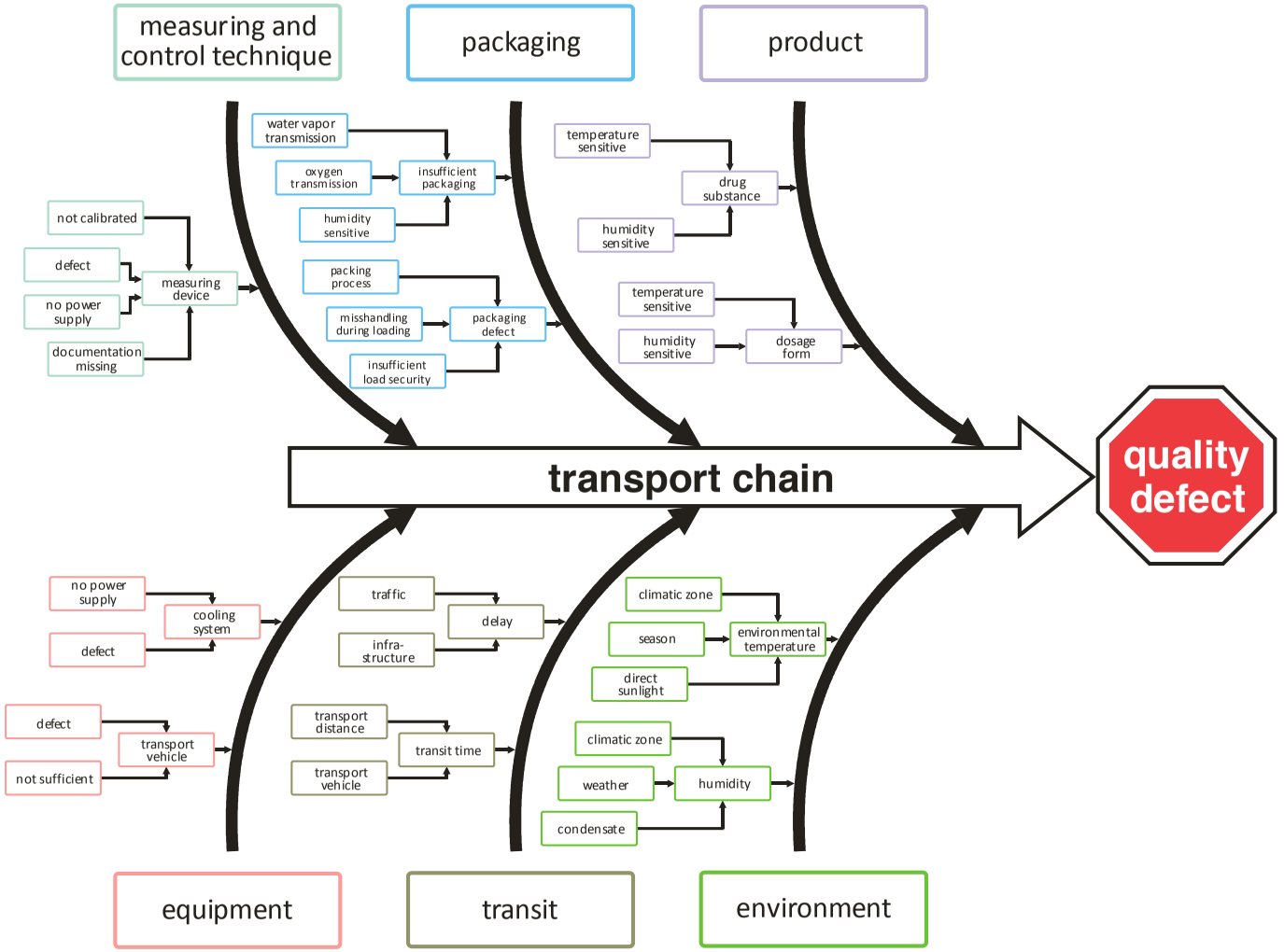

Figure 6: Cause and effect diagram for quality defects during transport.

5.1.3 Controlled Transport or Uncontrolled Transport

The principal decision, whether a controlled transport is required or an uncontrolled transport is sufficient to reduce the risk for quality defects during transport to an acceptable level, should be based on the results of stability data, the environmental conditions and the anticipated maximum transport time.

The environmental conditions on a transportation route are difficult to predict as they vary due to seasonal variations and the actual weather. In order to establish a rather general procedure to decide on whether a controlled transport is needed or not, a worst case scenario assuming an extreme temperature is used.

As an extreme temperature for transports in climatic zones I/II 63°C was selected. This was the maximum temperature achieved in a research project untertaken by the International Safe Transit Assosiation (ISTA). The project aimed in determining extreme temperatures in the interior of a vehicle of Less-Than-Truckload scale and was conducted from August 2001 to September 2001 in the US i.e. climatic zone II. The temperature extremes observed in the study were short time only and it is not realistic that a temperature of more than 60°C will last over long times [**120**]. Therefore the extreme temperature of the study is adequate for the use in a worst case scenario whereas it needs to be emphasized that if a broader and more specific data base is used, the worst case temperature might be reduced to a more realistic value and consequently maximum acceptable transportation times might exceed.

The extreme temperature for climatic zones III/IV was estimated based on the temperature of climatic zone I/II by adding 5°C. The estimated value for climatic zone III/IV is therefore 68°C. If a broader and more specific data base would be used, another worst case transport temperature might be more appropriate but for a first approach the estimation is regarded as adequate.

The stability of the medicinal product as further very important aspect needs to be assessed. Based on the shelf-life stipulated on the long term stability data of the respective climatic zone, on the extreme temperature for transport and on the safety margin of stability testing conditions according to Table 2, a maximum transport time for the product is calculated using the Haynes Formula (Formula 2). The calcualted result is corrected by a safety factor of 0.5 in order to consider further transports with possible temperature excursions e.g. for transports out of the responsibility of the pharmaceutical company e.g. from wholesaler to pharmacy or from pharmacy to the patient. The result is the maximum acceptable transport time.

The maximum acceptable transport times for uncontrolled transports in climatic zones I and II, calculated according to the Haynes formula, are presented in Table 8. The same is presented in Table 9 for climatic zones III and IV.

Further consideration must be given to the physicochemical stability of the dosage form as the use of the Haynes Formula considers chemical reaction kinetic only i.e. degradation of the drug substance. If there is a hint from accelerated stability data that untolerable changes occur in physicochemical properties, transportation should be performed under controlled conditions.

If the worst case approach results in an exceeding of the maximum acceptable transport time, the specific transport needs to be assessed. Two opportunities are present: Either the suitability of uncontrolled conditions is assured by performing a transport validation or transport is conducted under controlled and validated conditions.

In order to improve the overview of this process, it is visualized in a decision tree. Refer to Figure 7.

Table 8: Maximum Acceptable Transport Time for Uncontrolled Transport in Climatic zones I and II. The shelf-life is based on stability data for long term conditions for climatic zone II or more stressful conditions. $T_{storage}$ is the anticipated storage temperature for climatic zone II according to Table 2. In reality the storage temperature is usually lower as the temperature of pharmaceutical warehouses is 15°C to 20°C. $T_{transport}$ is the anticipated worst case temperature for climatic zone II. $t_{transport}$ is the calculated maximum transport time. t_{safety} is the maximum acceptable transport time arising from the maximum transport time multiplied with the safety factor of 0.5.

Shelf-Life	$T_{storage}$	$T_{transport}$	MKT	$t_{transport}$	t_{safety}
24 months	21.7°C	63°C	24.9°C	5 days	2.5 days
36 months			25.0°C	8 days	4 days
48 months			24.9°C	10 days	5 days
60 months			24.9°C	13 days	6.5 days

Table 9: Maximum Acceptable Transport Time for Uncontrolled Transport in Climatic zones III and IV The shelf-life is based on stability data for long term conditions for climatic zone III or IV or more stressful conditions. $T_{storage}$ is the anticipated storage temperature for climatic zone IV according to Table 2. In reality the storage temperature is usually lower as the temperature of pharmaceutical warehouses is 15°C to 20°C. $T_{transport}$ is the estimated worst case temperature for climatic zone III / IV. $t_{transport}$ is the calculated maximum transport time. t_{safety} is the maximum acceptable transport time arising from the maximum transport time multiplied with the safety factor of 0.5.

Shelf-Life	$T_{storage}$	$T_{transport}$	MKT	$t_{transport}$	t_{safety}
24 months	28°C	68°C	29.6°C	3 days	1.5 days
36 months			29.8°C	5 days	2.5 days
48 months			29.9°C	7 days	3.5 days
60 months			29.9°C	9 days	4.5 days

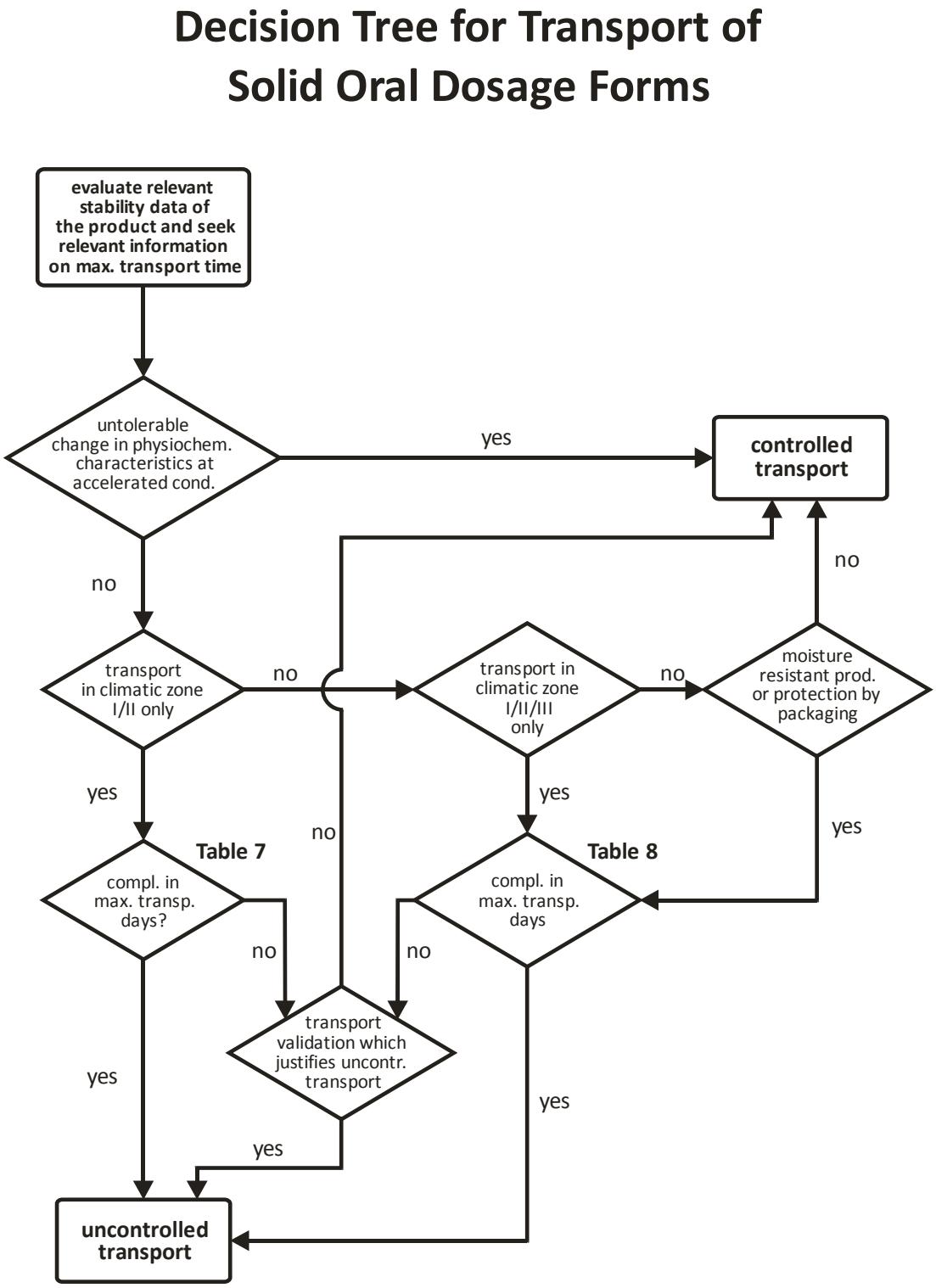

Figure 7: Decision tree for transport of solid oral dosage forms

5.1.4 Decision Analysis

5.1.4.1 Situation Appraisal

The decision tree discussed in section 5.1.3 is used to separate transports which can be performed under uncontrolled conditions as the maximum acceptable transportation time is not exceeded, from transports were this is not possible based on a worst case approach.

Remembering the current situation of Virtual Pharma discussed in section 5.1.1, it can be concluded that most of transports are finished within the maximum acceptable transport time as Virtual Pharma transports most of products within Germany, some within Europe and only a small number of transports are performed from contract manufacturers outside Europe. Whereas the number of the last ones is expected to increase in the future, as further in-licensing of products and access of further markets outside Europe is planned.

For these transports which cannot be performed under uncontrolled conditions based on the worst case approach presented in Figure 7 the following opportunities remain:

1. Transport under uncontrolled conditions after successful performance of a transport validation
2. Transport under controlled conditions after successful performance of a transport validation
3. Combination of controlled and uncontrolled transport

Actually a decision needs to be taken for the transport of the generic medicinal product Virtual Film-Coated Tablets from a manufacturer in India to the site of Virtual Pharma in Germany. The manufacture of Virtual Film-Coated tablets has recently been transferred to the Indian manufacturer which is located in Pune. Virtual Pharma is delighted that they obtained a discount contract with a health insurance company for Virtual Film-Coated Tablets due to the decrease of production costs as a consequence of the site change to India.

Virtual Film-Coated tablets have a shelf-life of 36 months which is based on long-term stability data over 36 months at 30°C / 65 % RH and accelerated stability data at 40°C / 75 % RH over 6 months. The stability data show little increase of impurities over time which is more distinctive at accelerated conditions. All physicochemical characteristics show only small variability without any trend. No information is available what might happen to Virtual Film-Coated Tablets when frozen. Virtual Film-Coated Tablets are packed in Aluminium / Aluminium blister packs and therefore are very well protected from humidity.

In order to safe costs air-freight is not taken into consideration as the maximum acceptable transportation time according to the worst case approach of 2.5 days would be exceeded. Transport is planned to be performed by truck from the manufacturing site in Pune to Mumbai harbour, further by container ship from Mumbai harbour to Hamburg harbour and again by truck to Virtual Pharma in Gießen. The overall transport time is about 6 to 8 weeks and therefore clearly exceeds the maximum acceptable transport time of 2.5 days according to the worst case approach.

Table 10: Transport details for sea-freight from Pune to Gießen. All values are a rough estimate only.

Stage	Starting Point→Destination	Transport vehicle	Estimated Transportation Time
1	Pune → Mumbai	Truck	about 4 hours (+ additional 1 day for reloading)
2	Mumbai → Hamburg	Container ship	About 6 to 8 weeks
3	Hamburg → Gießen	Truck	7 hours (+ additional 1 day for reloading)

As the situation demands a decision between several alternatives, decision analysis is the method of choice to handle the problem.

The decision process needs to involve various functions of Virtual Pharma. Therefore a project team should be established comprising a representative of the quality assurance, logistics, purchasing, quality control and regulatory affairs.

The representative of quality assurance is needed as transport validation is typically the responsibility of quality assurance.

The representative of logistics and purchasing are needed in respect of costs and estimated transport times.

The representative of quality control and regulatory affairs can contribute their knowledge on the stability of the medicinal product.

5.1.4.2 STEP 1 - Decision Statement

As a first step in the decision analysis the decision statement is to be verbalised. The decision statement for the problem described is the following:

Select the best transportation method for Virtual Film-Coated Tablets by sea freight

5.1.4.3 STEP 2 – List Objectives / Criteria and STEP 3 – Classify Objectives / Criteria

The next step of the decision analysis is selecting the criteria which are relevant to take the decision. The criteria which are deemed relevant are included in Table 11.

Table 11: List of objectives / criteria and their classification. MUST criteria were transferred to WANT criteria. This is symbolized with ↳.

Item	Objectives / Criteria	Classification
A	Mean Kinetic Temperature less than 30°C	MUST
	↳ Temperature variability as low as possible	WANT
B	Costs as low as possible	WANT
C	Operational expenditures for data evaluation as low as possible	WANT
D	Time under uncontrolled conditions as low as possible	WANT
E	Flexibility as high as possible	WANT

5.1.4.4 STEP 4 – Assign Weights

The decision analysis proceeds with the assignment of weights to the criteria which were selected in the previous step. As the members of the project team were not able to agree

about the weights by discussion, a preference matrix was used to assign the weights. By using the preference matrix each criterion combats all other criteria. The preference matrix is displayed in Figure 8 and the resulting weight assignment is summarized in Table 12.

In the following justification is provided for the weighing of each criterion:

A versus B: The temperature variability (A) is an important influence factor on the quality of a medicinal product during transport. If the temperature variability is too high it might jeopardise the success of the transport validation and could result in quality defects during transport. This is extremely important for the transport of Virtual Film-Coated Tablets having in mind the long transport time of about 6 to 8 weeks. The costs (B) are enormous important considering the severe competition in the generic market. Nevertheless maintaining the quality of the product during transport and success of the transport validation is regarded as more important. Therefore **A** beats B.

A versus C: As detailed above the temperature variability (A) is of big concern for Virtual Film-Coated Tablets. The operational expenditures (C), e.g. for evaluation of temperature data gained during routine transport or during transport validation, binds manpower and is under consideration of the competition in generic pharmaceutical business also an important factor. Nevertheless **A** is considered more important as the quality of the medicinal product and the success of transport validation should not be compromised.

A versus D: The transport time under uncontrolled environment (D) is regarded as important as keeping the temperature variability (A) as low as possible (i.e. the whole transportation time for uncontrolled transports and the reloading times for controlled transport). Therefore **A** and **D** are considered as equally important.

A versus E: The flexibility of transports organisation (E), e.g. use of alternative carriers, preliminary lead time needed for organisation of the transport, can facilitate the planning of transports but it is no major influence factor. Therefore **A** beats E.

B versus C: The costs (**B**) and the operational expenditures (**C**) are considered equally important.

B versus D: Quality might be affected if the time of the product at increased temperatures is prolonged. Costs (B) are therefore considered less important than the time under uncontrolled conditions (**D**).

B versus E: The flexibility of transports organisation (E) can facilitate the planning of transports but it is no major influence factor. Therefore **B** beats E.

C versus D: The operational expenditure (C) is regarded as less important compared to the time under uncontrolled conditions (**D**) as the quality of the Virtual Film-Coated Tablets might be compromised if exposed longer times to uncontrolled conditions.

C versus E and D versus E: The flexibility of transports organisation (E) can ease transport scheduling but it is no major influence factor. Therefore **C** and **D** beat E.

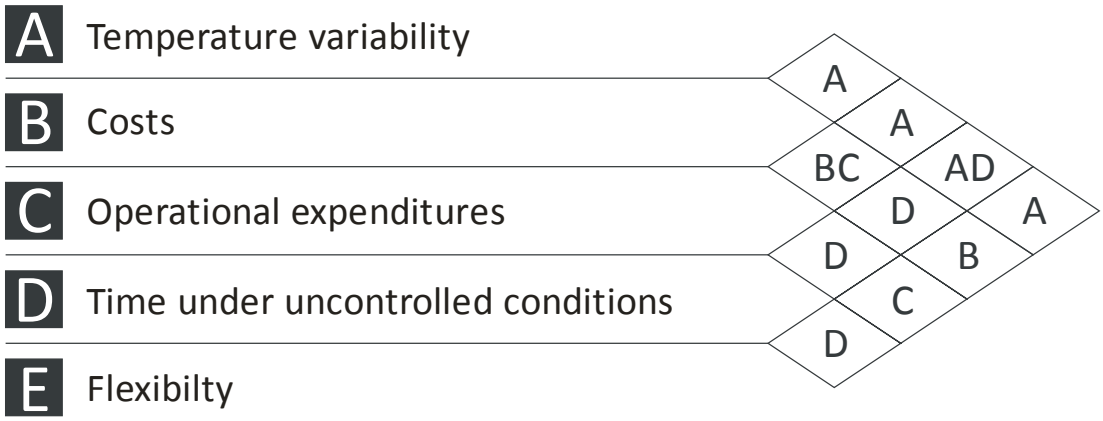

Figure 8: Preference matrix for assignment of weights

Table 12: Weights for the criteria achieved by counting the number of incidences in the preference matrix added by one.

Criterion	A	B	C	D	E
Weighing	5	3	3	5	1

5.1.4.5 STEP 5 – List Alternatives

The next step of decision analysis is to list the alternatives. The alternatives result from the decision tree in Table 13 and are further limited by the exclusion of air-freight due to cost considerations.

The first alternative is performing an uncontrolled transport by sea-freight and assuring the quality of the medicinal product by transport validation. This alternative is the most cost-saving alternative but imposes the biggest risks for quality defects during transport.

The second alternative uses a controlled transport in the temperature range from 15°C to 25°C instead for all three transport stages. This alternative is the most expensive of the alternatives but a cost-saving alternative if compared to air-freight.

The third and fourth alternative are combinations of alternatives I and II.

In alternative III the longest transportation stage, i.e. the time on the container ship, is performed in an temperature controlled reefer.

In alternative IV the transportation stages performed in the truck i.e. stages I and III are performed at temperature controlled conditions. An ISTA study dealing with temperature and humidity in ocean containers revealed that the temperature variability before and after the time on the ship is higher than the temperature variability on the ocean [**121**]. Therefore stage I and III are deemed to impose the medicinal product to the greatest temperature variability.

Table 13 describes the alternatives considering their conformance to the relevant criteria. Ranking factors between 1 and 4 were assigned. The ranking factor “4” indicates best concordance with the criterion and the ranking factor “1” low concordance with the criterion.

Table 13: Alternatives and their ranking factors for the relevant criteria

Criterion		Alternative I controlled transport		Alternative II uncontrolled transport		Alternative III ship controlled – truck uncontrolled		Alternative IV truck controlled – ship uncontrolled	
		description	***rank***	***description***	***rank***	***description***	***rank***	***description***	***rank***
A	Temperature variability	Temperature is controlled (15°C - 25°C) at all stages	**4**	Temperature variability depends on the environment	**1**	Temperature is controlled (15°C - 25°C) at stage 2 only; higher variability as for alternative IV	**2**	Temperature is controlled (15°C - 25°C) at stages 1 & 3 only; lower variability as for alternative III.	**3**
B	Costs	Higher costs as special equipments and energy are needed	**1**	Lower costs as no special equipments and energy are needed	**4**	Medium costs as special a reefer is required for step 2	**2**	Medium cost (lower than for alternative III) as temperate truck is needed.	**3**
C	Operational expenditures	Operational expenditures for data evaluation during transport validation and routine transports	**1**	Operational expenditures for data evaluation during transport validation	**3**	Operational expenditures for data evaluation during transport validation and routine transports (stage 2 only)	**2**	Operational expenditures for data evaluation during transport validation and routine transports (stage 1 & 3 only)	**2**
D	Time under uncontrolled conditions	Low, only during loading or in case of failures	**4**	As temperature is uncontrolled, time delays may induce quality defects	**1**	Longest transport stage 2 is performed under controlled conditions	**3**	Shorter transport stages 1 & 3 are performed under controlled conditions	**2**
E	Flexibility	Controlled transport reduces the number of carriers and needs more preliminary lead time	**1**	A huge number of carriers are available and preliminary lead time is reduced	**3**	As transport is partly controlled and partly uncontrolled medium ranking.	**2**	As transport is partly controlled and partly uncontrolled medium ranking	**2**

5.1.4.6 STEP 6 – Compare Alternatives against Objectives

MUST - Criteria

The only MUST criterion, mean kinetic temperature, is certainly fulfilled for alternative I. For alternative II to IV temperature excursions which bring the MKT above 30°C might occur. Finally transport validation will reveal the truth.

For now GO is given to all alternatives whereas the risk associated with alternative II to IV should be kept in mind for performance of a potential problem analysis concerning this issue if alternative II, III or IV seem to be superior.

WANT- Criteria

The comparision of WANT-Criteria against the objectives is performed by multiplicating the weighing factor with the ranking. The results are displayed in Table 14.

Table 14: Scoring of the Alternatives by multiplication of weighing factor and ranking

Criterion		Weight	Alternative I		Alternative II		Alternative III		Alternative IV	
			rank	*weight x rank*	*rank*	*weight x rank*	*rank*	*weight x rank*	*rank*	*weight x rank*
A	Temperature variability	5	4	**20**	1	**5**	2	**10**	3	**15**
B	Costs	3	1	**3**	4	**12**	2	**6**	3	**9**
C	Operational expenditures	3	1	**3**	3	**9**	2	**6**	2	**6**
D	Time uncontrolled	5	4	**20**	1	**5**	3	**15**	2	**10**
E	Flexibility	1	1	**1**	3	**3**	2	**2**	2	**2**
$\sum$				**47**		**34**		**39**		**42**

The scores for all alternatives are quite close to each other. Alternative I seems to be the best alternative whereas the distance to alternatives II, III and IV is not very clear. The alternatives which include at least one transportation stage at controlled conditions i.e. alternatives I, III and IV are more favourable than the option for uncontrolled transport. In order to find the

best balanced choice the inherent risks of alternative I are discussed in the following section. Alternatives II, III and IV are also regarded.

5.1.4.7 STEP 7 – Risks / Adverse Consequences

Inherent Risks of all Alternatives and Risk Minimizing Measures

All Alternatives share the risks which are special for sea-freight i.e. quite long transport times. In extreme situations this might lead to stock out of Virtual Film-Coated Tablets which would result in financial damage as Virtual Pharma has a discount contract for Virtual Film-Coated Tablets with a health insurance company and is therefore constrained to be deliverable. Stock out situation could be avoided by using air-freight as transport method for very urgent transports. Such urgent transports are usually avoided by foresighted planning. The probability for such situation is therefore regarded as low.

Table 15: Inherent risks of all alternatives with their probability, seriousness and risk minimizing measures. ➲indicates the reduction of probability or seriousness due to risk minimizing measures.

Risk	Probability	Seriousness	Risk Minimizing Measures
Stock-out due to long transport times	Low ➲ Very Low	High	Air-freight as back-up option

Inherent Risks Alternative I only and Risk Minimizing Measures

Alternative I comprises the most expensive solution but on the other hand the risk for quality defects during transport is relatively low.

Temperature excursions might occur during loading processes or in case of failures e.g. if the energy supply of the reefer or transport vehicle cannot be assured.

The loading times should therefore be reduced as far as possible. In order to reach this, good coordination and communication between the Indian manufacturer, the carriers and the receiving party Virtual Pharma must be assured. The procedures and maximum times for loading should be fixed in writing. Auditing of the carriers is important in order to check if they know about the time and temperature sensibility of medicinal products and have procedures in place which reduce the risk for quality defects to an acceptable level.

The carrier responsibility for maintaining the transport temperature of 15°C-25°C should be fixed in a contractual agreement in order to allow for damage compensation in case of failure to meet the agreed temperature range.

The risks that higher transport costs for controlled transport impair the competitiveness of Virtual Pharma is regarded as low, as costs for Virtual Film-Coated Tablets were already reduced by changing the manufacturing site to India and preferring sea-freight as transport method. Nevertheless transportation cost could be further reduced by bundling multiple transports.

Table 16: Inherent risks of alternative I with its probability, seriousness and risk minimizing measures ➲indicates the reduction of probability or seriousness due to risk minimizing measures.

Risk	Probability	Seriousness	Risk Minimizing Measures
Costs impair the competitiveness of Virtual Pharma	Low ➲ Very Low	High	Combining multiple transports to one transport
Prolonged loading times at uncontrolled temperature affect quality	Medium ➲ Very Low	High	Agreeing maximal loading times with Indian manufacturer and carrier. Auditing Carrier and Manufacturer
Failures in temperature control affect quality	Low ➲ Very Low	High ➲ Low	Assessing the maintenance schedule of the carriers during audit. Contractual agreement which allows for damage compensation in case of temperature excursions

Inherent Risks Alternative II, III, and IV only and Risk Minimizing Measures

Alternatives II, III and IV all include uncontrolled transport stages. Temperature excursions might bring the Mean Kinetic Temperature above 30°C. The success of the transport validation might be jeopardized and quality defects could be triggered. The most extreme temperature excursions are expected during loading processes. Therefore maximum loading times should be agreed. Furthermore maximum transport times should be agreed with the carriers. Further reduction of risk is not possible as transport is (partially) performed under uncontrolled conditions and can therefore not be influenced.

Nothing is known about the effect of freezing to the physicochemical characteristics of Virtual Film-Coated Tablets. If uncontrolled transport is considered as transport method for Virtual Film-Coated Tablets, the effect of freezing should be evaluated. If freezing has an influence, adequate precautions have to be taken, i.e. controlled transport in winter.

Table 17: Inherent risks of alternatives II, III and IV with its probability, seriousness and risk minimizing measures ➲indicates the reduction of probability or seriousness due to risk minimizing measures.

Risk	Probability	Seriousness	Risk Minimizing Measures
Temperature excursions might affect quality	Medium ➲ Low	High	Agreeing maximum loading times and maximum transport times with Indian manufacturer and carrier. Auditing Carrier and Manufacturer
Freezing	Medium ➲ Low	Unknown	Risk of freezing and its impact on medicinal product should be assessed during transport validation

5.1.4.8 STEP 8 – Best Balanced Choice

The risk minimizing measures for alternative I reduce the risk to an acceptable level. The risks associated with alternative II, III, and IV are little higher. Therefore alternative I is considered as the best balanced choice.

Virtual Film-Coated tables will therefore be transported using a controlled transport at 15°C to 25°C by sea-freight and in exceptional cases, i.e. very urgent deliveries by air-freight.

The outcome of the decision analysis showed that quality of medicinal products must not be compromised by cost saving consideration.

6 Conclusions and Outlook

As various incidents with substandard quality medicinal products show, assuring the quality of medicinal products is essential in order to protect the health of patients. Even though the competition in the pharmaceutical sector, especially in the generic business are actually very hard and austerity measures of policy induce further decline in prices, quality issues should not be compromised by cost saving considerations.

Nevertheless it is assumed that the extent of drug substances and medicinal products which are sourced from lower cost countries will further grow in future. Thus the challenges which are evoked by globalisation of development and manufacture of medicinal product need to be adequately addressed.

Inspections of drug substance manufacturers, which were focussed on lower cost countries in India and China, revealed an astonishing high number of drug substance manufacturer that are not manufacturing fully in accordance with GMP requirements. Consequently drug product manufacturers will legally be obliged to perform audits of drug substance manufacturers from 2013 on.

Thus drug product manufacturers should review their procedures for supplier qualification and use risk-based approaches for prioritisation of audits. If contract manufacturers are used, who are responsible for drug substance supply, their procedures for supplier qualification should be assessed and sharing of audit reports should be agreed.

Whether the legal obligation of drug product manufacturers to audit drug substance manufacturers will reduce the number of sites which prove to have insufficient GMP standards in place remains to be seen. Making inspections of drug substance manufacturers to an obligatory requirement could be a further measure for assurance of drug substance manufacturers GMP compliance. This certainly would result in a number of manufacturing sites to be inspected which hardly can be accomplished by one authority alone. Cooperation initiatives of authorities in the context of GMP inspections would be required. The *"International API inspection Pilot Programme"* was one step in this direction.

With regard to analytical methods for purity and identity testing of medicinal products the trend will maybe lead to the inclusion of more sophisticated methods which are able to detect also those impurities which are not expected due to the route of manufacture. The future will show whether such methods will routinely be used or only in cases with a reason for concern. Irrespectively of the analytical methods used to control medicinal products, criminal minds probably always will find a way to defraud and they are perhaps always one step ahead. Thus quality control cannot be the only measure to combat against substandard medicinal product. The selection of trustworthy suppliers, thorough supplier qualification, supplier evaluation and auditing, the knowledge of the supply chain and supply chain security are also essential measures in order to reduce the risk for medicinal products with substandard quality.

The requirements for the transport of drug substances and medicinal products will certainly increase in Europe, after the guidelines which are currently under revision are finalised. In how

far the proposal for dealing with transports in a mid-sized pharmaceutical company, which was developed in this thesis, will satisfy these requirements is not yet clear. If the statement in the *"Concept paper on storage conditions during transport"* to regard transports as a *"mobile form of storage",* will be interpreted in a strict sense, the worst case approach, which does not foresee temperature monitoring and control for short-term transports, would not suffice. As this would mean that all provisions for storage, e.g. temperature monitoring, temperature mapping and temperature control need also to be fulfilled for all transports irrespectively of their duration. In this case the worst case approach might be used as a tool for prioritisation of transport validations. Those products where the maximum acceptable transport time is exceeded the most, would receive the highest priority and those where the maximum acceptable transport time is not exceeded would be assigned with the lowest priority.

The approach for transportation of medicinal products developed in this master thesis used cause and effect analysis and decision making techniques. The same tools can equally be used for other challenges evoked by globalisation. Thus the use of science and risk based approaches and decision making techniques have impressively proven to be valuable tools to deal with these complex challenges.

With the progress of globalisation, harmonisation initiatives are supposed to proceed as well. The establishment of the GCG within ICH was one step towards involvement of non-ICH countries into the harmonisation efforts of ICH.

International valid requirements for format and content of dossiers for marketing authorisation and a Pharmacopoeia which is valid internationally could be a future vision. But to be realistic, it is not regarded as very likely that this vision will ever be achieved. Each partial step which goes into the direction of further harmonisation of requirements should be regarded as a success.

Abbreviations

AFSSAPS	Agence française de sécurité sanitaire des produits de santé (France)
AIFA	Agenzia Italiana del Farmaco (Italy)
AMG	Arzneimittelgesetz
AMWHV	Verordnung über die Anwendung der Guten Herstellungspraxis bei der Herstellung von Arzneimitteln und Wirkstoffen und über die Anwendung der Guten fachlichen Praxis bei der Herstellung von Produkten menschlicher Herkunft (Arzneimittel – und Wirkstoffherstellungsverordnung)
ASEAN	Association of South East Asian Nations
APEC	Asia Pacific Economic Cooperation
API	Active Pharmaceutical Ingredient (= Drug Substance)
ASMF	Active Substance Master File
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CE	Capillary Elecrophoresis
CEP	Certificates of Suitability to the Monographs of the European Pharmacopoeia
CFR	Code of Federal Regulations
CHMP	Committee For Medicinal Products For Human Use
CPMP	Committee for Proprietary Medicinal Products
CTD	Common Technical Document
EC	European Commission
EDQM	European Directorate of the Quality of Medicines & Health Care
EEA	European Economic Area
EEC	European Economic Community
eCTD	electronic Common Technical Document
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFTA	European Free Trade Association
EMA	European Medicines Agency
EMEA	European Medicines Agency (former abbreviation)
EMS	Eosinophilia-myalgia syndrome
EU	European Union
FDA	Food and Drug Administration (USA)
GCC	Gulf Cooperation Council
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
HPLC	High Performance Liquid Chromatographie
ICH	International Conference on Harmonisation
IMB	Irish Medicines Board (Ireland)
ISO	International Standardisation Organisation
ISTA	International Safe Transit Association

JP	Japanese Pharmacopoeia
JPMA	Japan Pharmaceutical Manufacturers Association
MHLW	Ministry of Health, Labor and Welfare (Japan)
MKT	Mean Kinetic Temperature
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
MS	Mass Spectrometrie
NMR	Nucelar Magnetic Resonance Spectroscopy
OECD	Organisation for Economic Co-operation and Development
OSCS	Oversulfated chondroitin sulfate
PANDRH	Pan American Network for Drug Regulatory Harmonization
PDE	Permitted Daily Exposure
PIC	Pharmaceutical Inspecition Convention
PIC/S	Pharmaceutical Inspecition Convention and Pharmaceutical Inspection Co-operation Scheme
PhRMA	Pharmaceutical Manufacturers Association (USA)
Ph.Eur.	European Pharmacopeoia
PMDA	Pharmaceutical and Medical Device Agency (Japan)
QP	Qualified Person
RH	Relative Humidity
SADC	Southern African Development Community
SFDA	Chinese State Food and Drug Administration
SmPC	Summary of Medicinal Product Characteristics
TGA	Therapeutic Goods Administration (Australia)
USP	United States Pharmacopoeia
USPC	United States Pharmacopoeia Convention
WHO	World Health Organization
ZLG	Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten (Germany)

Bibliography

[1] Europe Economics Chancery House, "Policies to Combat Counterfeit Medicines - Contribution to Impact Assessment," 2008.

[2] EMA, Position Paper on Control of Impurities of Pharmaceutical Substances: Compliance with the European Pharmacopoeia General Monograph "Substances for Pharmaceutical Use" and General Monograph "Control of Impurities in Substances for Pharmaceutical Use", October 2003.

[3] ISO, ISO 9000:2005 Quality management system - Fundamentals and vocabulary, 2005.

[4] ICH, Specification: Test Procedures and Acceptance Criteria For New Drug Substances and New Drug Products: Chemical Substances, 1999.

[5] ICH, Pharmaceutical Development Q8 (R2), 1999.

[6] J. Leo Schep, J. Robin Slaughter, A. Wayne Temple, and D. Michael G. Beasley, "Diethylene glycol poisoning," *Clinical Toxicology*, vol. 47, pp. 525-535, 2009.

[7] Frank Studt, "Ökonomische Auditierung von asiatischen Wirkstofflieferanten," *Pharmind*, vol. 72, no. 11, 2010.

[8] Gerald J. Gleich Arthur N. Mayeno, "Eosinophilia-myalgia syndrome and trptophan production: a cautionary tale," *TIBTECH*, vol. 12, 1994.

[9] Antwort der Bundesregierung auf die Kleine Anfrage der Abgeordneten Frau Rust und der Fraktion DIE GRÜNEN / Bündnis 90, 1990.

[10] Ulrike Holzgrabe, "Erkennung und Vermeidung von Arzneimittelfälschungen durch Verwendung adäquater Wirk- und Hilfsstoffe," *Pharmind*, vol. 71, no. 12, pp. 2102-2108, 2009.

[11] Holzgrabe Ulrike, "Erkennung und Vermeidung von Arzneimittelfälschungen durch Verwendung adäquater Wirk-und Hilfsstoffe," vol. 71, no. 12, 2009.

[12] Beyer Tanja et al., "Composition of OSCS-contaminated heparin occurring in 2008 in batches on the German market," *European Journal of Pharmaceutical Sciences*, vol. 40, no. 4, 2010.

[13] EDQM, USP, and NSBSC, "Summary of workshop sessions, 2nd workshop on the charactersation of Heparin products," 19.-20.06.2008.

[14] "Heparin: Rücknahmen auch in der Schweiz, Italien, Dänemark und Frankreich," *Ärzteblatt*, no. 26. März 2008, 2008.

[15] Alban Susanne, "Lehren aus dem Heparin-Skandal," *Pharmazeutische Zeitung*, no. 01, 2010.

[16] Stephan Knott and Mona Tawab, "Praxisnahne Analytik und Hintergrundinformationen im Pharma-Alltag - Heparin Analysen," *Pharmind*, vol. 72, no. 10.

[17] Mona Tawab and Manfred Schubert-Zsilavecz, "Heparin Skandal - Wie es dazu kommen konnte und die Lehren daraus," *Pharmazeutische Zeitung*, vol. 20, 2008.

[18] OECD, Glossary of Statistical Terms, 2007.

[19] Peter Boegh Nielsen (Statistics Denmark), Samuli Rikama and Johanna Sisto (Statistics Finland) Pekka Alajääskö (Eurostat), Global value chains - international sourcing to China and India, 2011.

[20] Christian Zeller, *Globalisierungstrategien - Der Weg von Novartis*.: Springer, 2001.

[21] Gerhard Dubois and Christopher Haeger, ""Operational Excellence" in der pharmazeutischen Industrie," *Pharmind*, vol. 63, no. 6, 2001.

[22] Herwig Mittermayer and Joachim Teubner, "Strategische Bewertung von Outsourcing Partnern," *Pharmind*, vol. 73, no. 3, 2011.

[23] EDQM, Annual Report 2009, 2009.

[24] Heinrich Prinz Dr. and Christian Schulz Dr., "Vergleich des EG-GMP-Leitfadens Teil I mit der SFDA-GMP-Guideline für chinesische Firmen," *Pharmind*, 2008.

[25] COMMISSION DIRECTIVE 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.

[26] WHO, WHO good manufacturing practices: main principles for pharmaceutical products, Annex 3, WHO

Technical Report Series 961, 2011.

[27] WHO, WHO good manufacturing practices for active pharmaceutical ingredients, Annex 2, WHO Technical Report Series, No. 957, 2010.

[28] ICH, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7A, 2000.

[29] http://www.picscheme.org, 01.08.2011.

[30] DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use.

[31] EC, The Rules Governing Medicinal Product in the European Union Volume 4 - Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use - Part II: Basic Requirements for Active Substances used as Starting Materials, 2010.

[32] EC, The Rules Governing Medicinal Product in the European Union Volume 4 - Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use - Part II: Basic Requirements for Medicinal Products.

[33] Gesetz über den Verkehr mit Arzneimittel (Arzneimittelgesetz -AMG).

[34] Arzneimittel- und Wirkstoffherstellungsverordnung-AMWHV, 2006.

[35] EC, Notice to Applicants, Volume 2B, Module 1: Administrative information, Application form, May 2008.

[36] EC, Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (2010/C17/01), Jan. 22, 2010.

[37] EMA, Template for the Qualified Person´s declaration concerning GMP compliance of the active substance used as starting material and verification of its supply chain "The QP declaration template", Draft, 6 December 2010.

[38] http://www.edqm.eu/en/The-Inspection-Programme-159.html, 01.08.2011.

[39] Code of Federal Regulations (CFR), Title 21 Food and Drugs, April 2010.

[40] Dr., Michael Schäfer, "Anforderungen an die Qualifizierung von Wirkstofflieferanten," *Pharmind*, 2007.

[41] Dr., Elke Podpetschnig-Fopp, "Aktuelle Entwicklungen im Bereich der Qualitätssicherung in Europa und den USA," *Pharmind*, 2009.

[42] Dr., Wolfgang Heisig, "Auditierung / Qualifizierung von Wirkstoffherstellern durch akkreditierte Stellen," *Pharmind*, 2008.

[43] EMA, "Compilation of Community Procedures on Inspections and Exchange of Information, EMA/INS/GMP/459921/2010 Rev 12," 25 February 2011.

[44] Viola Hieble-Gerhard, Risk-based Management of GMP Audits, 2010.

[45] EDQM, EDQM Annual Report 2010, 2011.

[46] Directive. 2011/62/EU of 8 June 2011 the European Parliament and of the Council of amending Directive 2001/83/EC.

[47] ICH, Impurities in new Drug Substances, Q3A (R2), 2006.

[48] ICH, Impurities: Guideline for Residual Solvents Q3C (R5), 2011.

[49] EMEA, Annex to: CPMP/ICH/283/95: Guideline for Residual Solvents & CVMP/VICH/520/99 Guideline on Impurities: Residual Solvents Annex I: Specifications for Class 1 and Class 2 Residual Solvents in Active Substances, 2005.

[50] EMEA, EMEA/CHMP/SWP/4446/2000 - Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents, 2008.

[51] ICH, Final Concept Paper Q3D: Impurities: Guideline for Metal Impurities, 2009.

[52] EMEA, CPMP/SWP/5199/02; EMEA/CHMP/QWP/251344/2006 - Guideline On The Limits Of Genotoxic Impurities, 2006.

[53] EDQM, Certification of suitability of Monographs of the European Pharmacopeia - Content of the dossier for chemical purity and microbiological quality, 2007.

[54] EDQM, European Pharmacopoeia Edition 7.0.

[55] EMEA, CPMP/QWP/227/02 Rev 01 - Guideline on Active Substance Master File Procedure, April 15, 2005.

[56] EMEA, Position Paper on: Control of Impurities of Pharmacopoeial Substances: Compliance with the European Pharmacopoeia General Monograph "Substances For Pharmaceutical Use" and General Chapter "Control of Impurities In Substances For Pharmaceutical Use", 2004.

[57] EDQM, "EDQM conference proceedings - Quality of medicines in a globalised world: dreams and reality," , Prague, Czech Republic, 14.-15. October 2010.

[58] ICH, Stability Testing of New Drug Substances and Products - Q1A(R2), 2003.

[59] IMB, Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances, 2006.

[60] Wolfgang Grimm, Goetz Harnischfeger, and Martin Tegtmeier, *Stabilitätsprüfung in der Pharmazie*, 2nd ed.: ECV Editio Cantor Verlag, 2004.

[61] WHO, Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: WHO Expert Committee on Specifications For Pharmaceutical Preparations,Forty-third report, Annex 2 (WHO Technical Report Series No. 953), 2009.

[62] Sabine Kopp Dr., "Stability Testing of Pharmaceutical Products in a Global Environment," *RAJ Pharma*, May 2006.

[63] WHO, Table 2 of Annex 2 to WHO Technical Report Series, No 953: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products, December 1, 2010.

[64] WHO, WHO guide to good storage practice for pharmaceuticals In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report, Annex 9 (WHO Technical Report Series, No. 908), 2003.

[65] WHO, Good trade and distribution practices for pharmaceutical starting materials. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eight report, Annex 2 (WHO Technical Report Series, No. 917)., 2003.

[66] WHO, WHO good distribution practices for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report, Annex 5 (Technical Report Series, No. 957), 2010.

[67] EC, Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C/63/03), 1994.

[68] EC, Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use, public consultation until 31.12.2011.

[69] EMEA, Guideline on Declaration of Storage Conditions: A: In the Product Information of Medicinal Products B: For Active Substances CPMP/QWP/609/96/Rev2, 2007.

[70] EDQM, Ph.Eur. 7.0, 1. General Notices, 2010.

[71] EMA, Concept paper on storage conditions during transport EMA/INS/GMP/638479/2010, 2010.

[72] USP34, General Notices and Requirements.

[73] USP34, Good Storage and Shipping Practice.

[74] Health Products and Food Branch Inspectorate, Guidelines for Temperature Control of Drug Products during Storage and Transportation GUI-0069, 2011.

[75] EMA, Q&A Stability - Stability issues of pharmaceutical bulk products use in manufacture of the finished product, February 2010.

[76] COMMISSION REGULATION (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.

[77] Frank Böttcher and Timo Krebsbach, "Transfer of Analytical Procedures," *Pharmind*, vol. 73, no. 1, pp. 152-158, 2011.

[78] ICH, "Comparability of Biotechnological / Biological Product Subject to Changes in their Manufacturing Process (Q5E)," 18 November 2004.

[79] http://europa.eu/abc/12lessons/lesson_2/index_de.htm, 06.08.2011.

[80] Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products, (As amended by Directives 66/454/EEC, 75/319/EEC, 83/570/EEC, 87/21/EEC, 89/341/EEC, 89/342/EEC, 89/343/EEC, 92/27/EEC, 92/73/EEC et

93/39/EEC).

[81] Bettina Geng, Die Nachzulassung - Gesetzliche Bestimmung und Anforderungen an die pharmazeutische Qualität von Arzneimitteln von der "78'er-Anmeldung" bis heute (Master Thesis) , 2008.

[82] Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz-AMG), in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S.3394) zuletzt geändert durch das Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften vom 12. Juli 2009 (BGBl. I S. 1900).

[83] David B. Jefferys, "The new pharmaceutical regulatory procedures for Europe," *Trends in Pharmacological Sciences*, vol. 16, no. 7, pp. 226-231, July 1995.

[84] Regulation No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down the Community procedures for the authorisation and supervision of medicinal products for human and veterinary use establishing a European Medicines Agency.

[85] D. B. Jefferys and K. H. Jones, "Emea and the new pharmaceutical procedures for Europe," *European Journal of Clinical Pharmacology*, vol. 47, no. 6, pp. 471-476, 1995.

[86] CMDh, "CMDh Summary of Activities 2010 (Doc. Ref. CMDh/199/2011)," January 2011.

[87] "Council Directive 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology," *Official Journal L 015 , 17/01/1987 P. 0038 - 0041*.

[88] "Council Regulation 2309/93/EEC of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products," 22 July 1993.

[89] EMA, "Monthly statistics report: May 2011 (EMA/535520/2011)," 5 July 2011.

[90] Council of Europe, Convention on the Elaboration of a European Pharmacopoeia.

[91] EDQM, "European Directorate for the Quality of Medicines," 04/2005.

[92] "http://www.edqm.eu/en/List-of-PhEur-Members-Observers-1023.html," 09.08.2011.

[93] ICH, The Value and Benefits of ICH to Drug Regulatory Authorities - Advancing Harmonisation for Better Health, 2010.

[94] http://www.ich.org/about/organisation-of-ich.html, 02.08.2011.

[95] ICH, Stability Testing For New Dosage Forms Q1C, 1996.

[96] ICH, Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products (Q1D), 2002.

[97] ICH, Evaluation of Stability Data Q1E, 2003.

[98] ICH, Stability Testing: Photostability Testing of New Drug Substances and Products Q1B, 1996.

[99] EMEA, Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products, 2003.

[100] http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html, 02.08.2011.

[101] http://www.ich.org/about/vision.html, 02.08.2011.

[102] "International Harmonisation, Pharmaceutical Discussion Group Statement of Harmonisation Policy (November 2003)," *Pharmeuropa*, July 2004.

[103] USP 34, "Pharmacopoeial Harmonization".

[104] EDQM, "European Pharmacopoeia Supplement 7.1".

[105] "Working Procedures of the Pharmacopoeial Discussion Group (PDG), Revised Version (June 2010)," *Pharmeuropa*, October 2010.

[106] Mark J. Wiggins, Philip M. Travis, and Rebecca A. Fitzgerald, "Ph. Eur. / USP Prospective Harmonisation - API Pilot Project: Industry Perspective," *Pharmacopoeial Forum*, Vol. 36(6) [Nov.–Dec. 2010].

[107] EDQM, "European Pharmacopoeia Supplement 7.3".

[108] USP 34,.

[109] EMEA, "Mutual Recognition Agreements Between the EU and the respective Parties Australia, Canada, New

Zealand and Switzerland (EMEA/MRA/22/03 Final)," *5 May 2003*.

[110] "http://www.ema.europa.eu," *5.8.2011*.

[111] WHO, Constitution of the World Health Organization.

[112] http://apps.who.int/prequal/, 06.08.2011.

[113] http://www.who.int/medicines/en/, 06.08.2011.

[114] http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/en/, 06.08.2011.

[115] EMA, "Interactions between the European Medicines Agency and U.S. Food and Drug Administration September 2009-September 2010 (EMA/705027/2010)," June 2011.

[116] "http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/06/news_detail_001282.jsp&mid=WC0b01ac058004d5c1&murl=menus/news_and_events/news_and_events.jsp," 10.08.2011.

[117] EMEA, "General Principles EMEA- FDA Parallel Scientific Advice (EMEA/24517/2009)," 22 July 2009.

[118] EMA, "Report on the Pilot EMA-FDA GCP Initiative - September 2009 — March 2011 (EXT/INS/GCP/56289/2011)," 18 July 2011.

[119] EMA, "Final report on the International API inspection Pilot Programme (EMA/453741/2011)," 16 June 2011.

[120] Dennis Young and ISTA, ISTA Temperature Project - Data Summary, 2002.

[121] David Leinberger and ISTA, Ocean Container Temperature and Humidity Study, 2006.

Declaration - Erklärung

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

Hattersheim den 12. September 2011

Acknowledgement - Danksagung

An erster Stelle möchte ich mich bei den Menschen bedanken, die mich zum Bewältigen eines Masterstudiums neben dem Beruf ermutig und bei dieser Herausforderung unterstützt haben.

Für die Betreuung meiner Arbeit bedanke ich mich bei den Herren Dr. Josef Hofer und Herbert A. Jopp.

Meinem Arbeitgeber Hennig Arzneimittel GmbH & Co. KG möchte ich dafür danken, das mir die Teilnahme am Masterstudium ermöglicht wurde.

Für die anregenden Diskussionen und wertvolle Unterstützung möchte ich Herrn Dr. Wilhelm Großebüter danken.

Von ganzem Herzen möchte ich Marc danken, der mich ertragen, aufgemuntert und auf andere Gedanken gebracht hat.

Meiner Familie und meinen Freunden danke ich dafür, dass sie während dieser Zeit immer für mich da waren.