Development of an adequate strategy for a global change in the primary container closure system of a parenteral herbal drug

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List of Abbreviations

acc. to	according to
AIMDs	active implantable medical devices
AMG	Arzneimittelgesetz
ANDA	Abbreviated New Drug Application
ANDS	Abbreviated New Drug Submission
ASTM	American Society for Testing and Materials
BPA	bisphenol A
CAD	canadian dollars
CDER	Center for Drug Evaluation and Research
CDRH	Center for device and radiological health
CE	"Conformité Eurospéene"
CFR	Code of federal regulation
CFU	Colony forming units
COC	Cycloolefin Copolymere
COP	Cycloolefin Polymers
CPMP	Committee for Proprietary Medicinal Products
CPSC	Consumer Product Safety Commission
CTD	Common Technical Document
CVMP	Committee for Medicinal Products for Veterinary Use
DEHP	Diethylhexylphthalat
DIN	Deutsches Institut für Normung (German Institute for Standardisation)
DMF	Drug Master File
e. g.	exempli gratia
EA	extension application
EC/EG	European Community
EMEA/EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GMP	Good Manufacturing Practice
HCM	Hyaluron Contract Manufacturing
HEPA	high-efficiency particulate air
ICH	International Conference on Harmonisation
IR spectroscopy	infrared spectroscopy
ISO	International Organization for Standardization
IVDDs	In-vitro diagnostic devices
kGy	kilogray
LAL	limulus amebocyte lysate
M	mol
MAH	marketing authorization holder
max.	maximum

MEDDEV	MEDICAL DEVICES : Guidance document
mg	Milligram
min.	Minimum
mL	Milliliter
MPG	Medizinproduktegesetz (medicinal products act)
MPKPV	Medizinproduktekostenverordnung (medical devices fee ordinance)
MPSV	Medizinproduktesicherheitsverordnung (medical devices safety ordinance)
MPV	Medizinprodukteverordnung (Medical Devices Ordinance)
NDA	new drug application
NDS	new drug submission
NMT	not more than
NOC	Post Notice of Compliance Change
NtA	Notice to Applicants
OPC	one-point-cut
PAS	Prior Approval Supplement
PDA	Parenteral Drug Association
PET	polyetylene terephthalate
Ph. Eur.	Pharmacopeia Europeia
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PIL	package information leaflet
ppm	parts per million
QOS	Quality Overall Summary
QWP	Quality Working Party
SKNR	Strukturnummer (structural number)
SmPC	Summary of Product Characteristics
TSE	transmissible spongiforme enzephalopathie
USA	United States of America
USP/NF	United States Pharmacopeia / National Formulary
UV	ultraviolet
Vol.	volume
µg	microgram
Wfl	water for injection

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1. Introduction

The aim of this master thesis is to develop a suitable strategy for a global change in the primary packaging of a parenteral herbal drug in the EU (especially Germany), USA and Canada. This herbal drug is an aqueous solution for injection for subcutaneous administration at cancer. The drug substance is an aqueous herbal extract which consists of a mixture of different herbal ingredients. The main components are carbohydrates, proteins, phenylpropanglycosides and flavonoids. At the moment the primary container closure system is a one-point-cut (OPC) glass ampoule.

This primary packaging, however, shows some problems regarding the handling by the patient. In the last time some occurrence at the opening of the OPC-ampoules are reported from some patients especially from oversea. The foreign distributors received information about problems with the opening of the ampoules. In some cases the patient got percutaneous injuries after breaking the ampoules.

Therefore the production department wants to find a primary packaging, which is more appropriate compared to the current OPC-ampoules regarding patient-friendliness and the safety aspect.

For the selecting of a new suitable primary packaging an important aspect of this herbal medicinal drug should be considered. A special feature of the proteins in this herbal extract is the high-binding affinity to different surfaces such as plastic and other polymers.

In an internal meeting the production department and the upper management ask the responsible regulatory affairs manager for the evaluation of the regulatory requirements for a change of the primary packaging. Which kinds of other primary packaging systems are available and could be an improvement of the current packaging system? Furthermore the upper management wants to know a realistic time line and the cost of this global change in the USA, Canada and Germany.

The plan for the regulatory affairs manager and the production department is to search and collect facts regarding the different container closure systems. The collected information will be analyzed via a decision analysis and presented at the next meeting with the upper management in three months.

2. General definitions for the container closure system

At the moment no harmonized ICH guideline of packaging material for medicinal drugs is available. There are a lot of guidelines and regulations for packaging material. For the ICH countries Germany and USA and for Canada following sources of information regarding the pharmaceutical packaging material are helpful:

Source of information	EU	USA	Canada
Pharmacopeia	Ph. Eur. (1)	USP (2)	USP (2)
Regulations	EU directives e. g. 2001/83/EC (3)	Relevant CRF articles	Food and Drug Regulations, CRC, c 870 (4)
Guidelines	e. g. GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERI-ALS, London, 19 May 2005,CPMP/QWP/4359/03, EMEA/CVMP/205/04 (5)	FDA guidance for industry "Container Closure Systems for Packaging Human Drugs and Biologics" (6)	e. g. DRAFT GUIDANCE FOR INDUSTRY Quality Guidance: Applications for Drug Identification Numbers (DINAs) for Pharmaceuticals 2003/06/11 (7) Good Manufacturing Practices (GMP) Guidelines – 2009 Edition, Version 2 GUI-0001, Date of implementation March 4, 2011 (8)
Technical standards	DIN/ISO	DIN/ISO, ASTM	DIN/ISO, ASTM

Table 1: Overview of guidelines and regulations for packaging material in EU, USA, Canada

In the regulatory environment there are a lot of different definitions available for the term "container closure system". For a correct understanding of container closure system and its corresponding parts for pharmaceutical drugs an adequate definition is important. Therefore some examples of definitions are presented for this term.

In the FDA guidance for industry "Container Closure Systems for Packaging Human Drugs and Biologics" (6) the following definition for the container closure system is described:

"*A container closure system refers to the* ***sum of packaging components that together contain and protect the dosage form****. This includes* ***primary packaging components and secondary packaging components****, if the latter are intended to*

provide additional protection to the drug product. A packaging system is equivalent to a container closure system."

In the EMA guideline "Guideline on plastic immediate packaging materials" (CPMP/QWP/4359/03 and EMEA/CVMP/205/04, 2005) [(5)] the definition for a container closure system is given as follows:

"*Container closure system is the* ***sum of packaging components that together contain and protect the active substance or the dosage form****. This includes* ***immediate packaging components and secondary packaging components****, if the latter are intended to provide additional protection to the active substance or to the drug product*."

Both definitions of the container closure system are very similar with two slight deviations. In the FDA guidance the container closure system includes only the protection of the dosage form and in the EMA guideline also the protection of active substance is enclosed. Furthermore in the EMA guideline the primary packaging components are defined as immediate packaging components.

3. Definition of primary and secondary packaging

Based on these definitions it is also necessary to know, what is meant with the terms "primary packaging" and "secondary packaging". For both terms there are also different definitions available.

For example in the FDA guidance for industry "Container Closure Systems for Packaging Human Drugs and Biologics" [(6)] the following explanation for the "primary and secondary packaging" is given:

"*A* ***primary packaging component*** *means a packaging component that is or may be in direct contact with the dosage form. A* ***secondary packaging component*** *means a packaging component that is not and will not be in direct contact with the dosage form*."

Furthermore in the WHO guideline "Guidelines on packaging for pharmaceutical products, Annex 9" [(9)] the primary and secondary packaging are described as follows:

"The ***primary packaging components*** *(e.g. bottles, vials, closures, blisters) are in direct physical contact with the product, whereas the* ***secondary components are not*** *(e.g. aluminium caps, cardboard boxes)."*

4. Definition of different type of packaging (containers)

In the definitions to primary and secondary packaging also different types of packaging materials are described. Here the term "container" is used for the different packaging materials. A short tabulated overview should demonstrate the different

kinds of packaging material that are used for pharmaceutical drugs. Information to the primary packaging material is available especially in the pharmacopeias like Ph. Eur. [1] and USP [2]. References to regulatory requirements for the secondary and tertiary container can be found for example in the DIRECTIVE 94/62/EC [10] and in the Defect Evaluation List for Folding Boxes, Labels, Pack Inserts and Patient Information Booklets. [11]

Types of packaging material	Short description of definition	Examples
Container	Contains or is intended to contain a product Is, or may be in direct contact with it The closure is a part of the container	Single-dose container, multi-dose container, well-closed container, airtight container, sealed container, tamper-proof container, child-proof container
Primary or immediate container	In direct contact with product Provides the major protection for the drug product against environmental stress	Rubber closures, bottles, vials, ampoules, cartridges, pre-filled syringes
Secondary container	Provides information = printed packaging material Additional protection against light and/or water vapour	Wrapper to contain primary pack Cardboard (Box to contain primary pack) Paper (labels, PIL)
Tertiary container	"logistical" packaging components	Cartons, palettes, shrink wraps

Table 2: Overview of different types of packaging materials

5. Which are the requirements for the ampoule as primary packaging material?

Requirements regarding to packaging specification for glass ampoules as primary packaging material (container) in Germany, USA and Canada are presented in the following table:

EU	USA	Canada
Ph. Eur. Monograph 3.2.1 "glass containers for pharmaceutical use" [1] Commission Directive 94/62/EC <Packaging and packaging waste> [10]	USP <660> glass containers [2]	USP <660> glass containers [2]

Table 3: Requirements regarding to packaging specification for glass ampoules in EU, USA, Canada

In addition following technical standards have been defined for the testing of glass containers:

DIN/ISO Norm	Titel
ISO 9187	Injection equipment for medical use - Part 1: Ampoules for injectables. 2nd ed. 2000 [12]
ISO 720	Glass - Hydrolytic resistance of glass grains at 121 ℃ - Method of test and Classification [13]
ISO 4802-1	Glassware - Hydrolytic resistance of the interior surface of glass containers Part 1: Determination by titrimetric method and classification [14]
ISO 4802-2	Glassware - Hydrolytic resistance of the interior surface of glass containers Part 2: Determination by flame spectrometry and classification [15]

Table 4: Technical standards for glass containers

5.1 Description of the primary packaging material currently used for the drug product

The ampoule, which is used as current primary packaging material for the parenteral herbal drug, is a one-point-cut ampoule (OPC ampoule). The ampoule consists of colorless tubular glass type I.

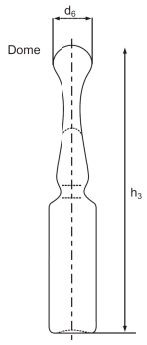


Figure 1: technical drawing of OPC ampoule (Source: [16])

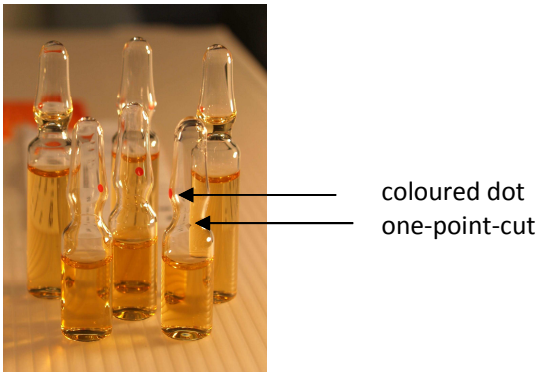


Figure 2: picture of the current used OPC glass ampoule

5.2 Quality specification according to Ph. Eur. and USP

In the following table the specification parameters acc. to Ph. Eur. [1] and USP [2] for glass containers, especially for type I glass containers, are presented.

acc. to Ph. Eur. 3.2.1	USP <660>
Test A: Test of hydrolytic resistance of the inner surfaces of glass containers (surface test)	surface glass test (test of hydrolytic resistance) (powder glass test)
Determination of the filling volume	Determination of the Filling Volume
Test of arsenic release	Test of arsenic release <211>

Table 5: Specification parameters acc. to Ph. Eur. and USP for type I glass containers

5.3 Which testing standard is necessary for the glass ampoule?

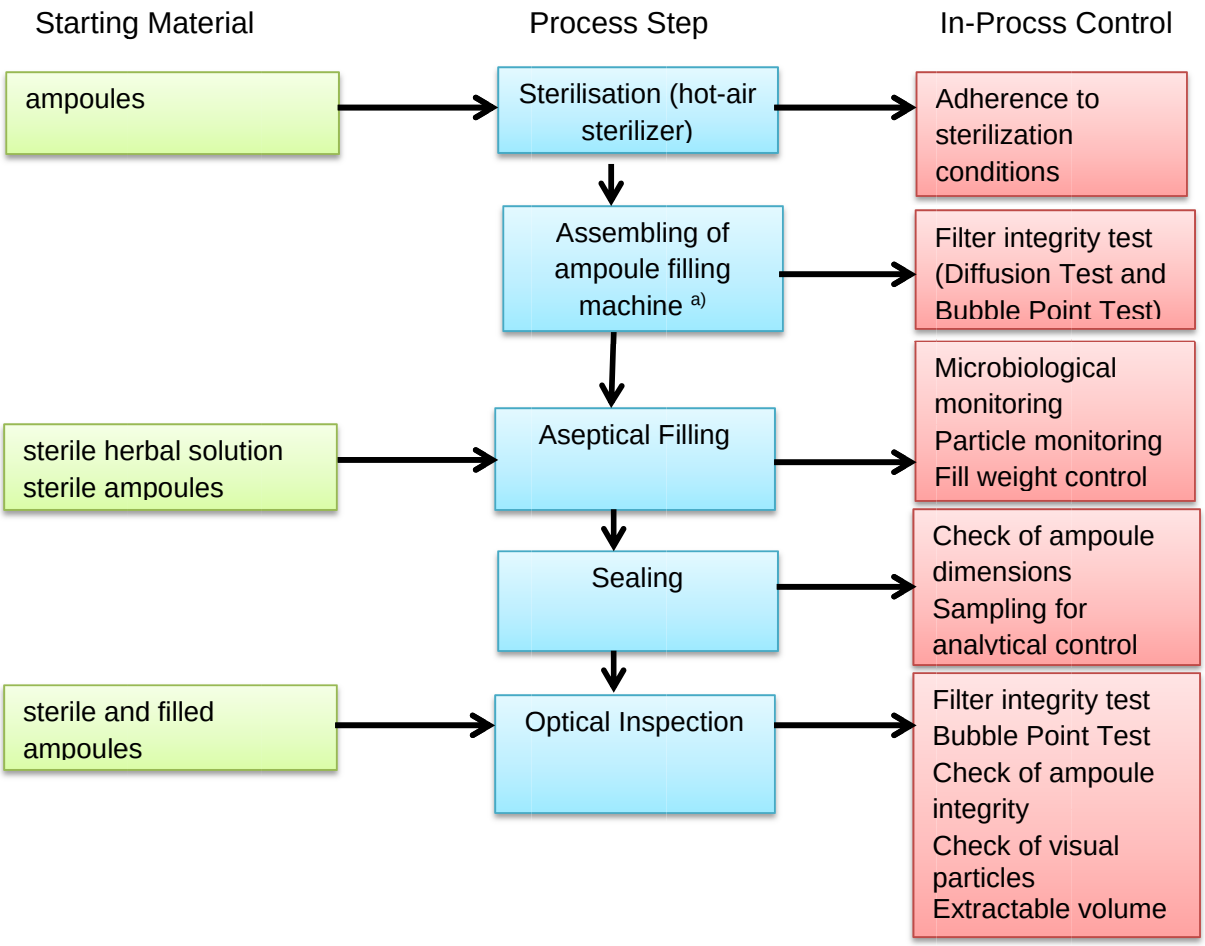
Based on the requirements of the different monographs of Ph. Eur. (1) and USP (2) the testing standard for the current primary packaging material “glass ampoule” is defined as follows:

Specification parameter	Reference	Short description of test performance
Test of dimensional parameters	In-house method	Determination of height and diameter with a sliding caliper acc. to supplier specification
Test of exterior properties (appearance)	In-house method	Visual inspection of contamination, flaws, melt down parts of glass, etc.
Test of breaking point	In-house method	Every ampoule must show a red breaking point.
Test of breaking force	In-house method	The ampoule must break up easily; stronger splintering or breaking of the ampoule may not appear. The number of the ampoules which cannot be broken up or unusually hard is to be documented in the protocol.
Determination of the filling volume	Ph. Eur. 3.2.1 and USP<660>	For ampoules it is the volume up to the height of the shoulder. Determination of filling volume by weighing
Test of hydrolytic resistance for glass type I containers	Ph. Eur. 3.2.1 and USP<660>	See Ph. Eur. Test A See USP powder glass test
Test for arsenic release	Ph. Eur. 2.2.23 and USP<221>	This test is performed acc. to hydride generation atomic absorption spectrometry 2.2.23 method I, Ph. Eur. and <211> USP method I, spectrophotometry

Table 6: Tabulated overview of a testing standard for a glass ampoule

5.4 Description of manufacturing process for ampoule filling

The current manufacturing process for the "ampoule filling” consists of following process steps:



a) A filter is installed into the machine at the assembling of ampoule filling machine.

5.5 Which process validation parameters should be tested for this primary packaging?

For a correct performance of process validation following current laws, guidelines, recommendations and regulations should be considered:

- EU-guideline of good manufacture practice, Chap. 5.18 – 5.24 (17)
- EU GMP guideline Annex 15, "Qualification and Validation" (18)
- EU GMP guideline Annex 1, "Manufacturing of sterile medicinal products" (19)
- PIC/S documents (GUIDE TO GOOD MANUFACTURING PRACTICE OF MEDICINAL PRODUCTS ANNEXES, PE 009-10, 1-2 October 2012) (20)
- ICH-Q7A Guideline (Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, chapter 12.43) (21)
- White paper, FDA Guidance Update: Process Validation: General Principles and Practices (November 2008) (22)

- Guide Process Validation: Moist Heat Sterilization for Pharmaceuticals Supersedes, May 1, 2001 [23]
- Good Manufacturing Practices (GMP) Guidelines – 2009 Edition, Version 2 GUI-0001 Supersedes: 2009 Edition, March 4 2011 [24]
- EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines. [17]
- ICH Q9 guideline “Quality Risk Management”, EMA/INS/GMP/79766/ 2011 [25]

The process validation should cover all critical parameter of risk analysis. For the production step “ampoule filling” following validation parameter are tested according to the results of risk analysis:

Validation parameter	Background for evaluation of the validation parameter
Sterile filter selection	The correct selection of sterile filter is essential for this manufacturing of the drug product regarding the sterility and the conformity of ingredients (see also chemical interaction).
Diffusion test	This test is performed for investigation of integrity of filter.
Bubble point test	This test is performed for investigation of integrity of filter.
Rinse amount of WfI	The correct rinse amount of WfI is important for the optimal washing process of glass ampoules before sterilization
Temperature of autoclave	20 min at 121 ℃ acc. to P h. Eur. 5.1.1 and USP <1211>
Killing of bioindicators	Integrity test for the autoclave acc. to Ph. Eur. 5.1.2 and USP <1035>
Scrap amount of ampoules (Yield I)	A clean form of ampoule head is important for the transport stability and tightness of the ampoules. A documentation of the scrap amount of ampoules can give a hint to problems of material quality of the ampoules.
Filling volume (Fill weight check)	acc. to Ph. Eur. 3.2.1 and USP <660>
Optical control (total yield II)	The optical control is important for check of macroscopic damages of ampoules which can occur during the ampoule filling. The amount of damaged ampoules should be not more than 5 %.
Sub-visible particles	acc. to Ph. Eur. 2.9.19 and USP <788>
Bacterial endotoxins	acc. to Ph. Eur. 2.6.14 and USP <85>
Sterility	acc. to. Ph. Eur. 2.6.1 and USP <71>
Extractable volume	acc. to Ph. Eur. 2.9.17 and USP <1>
pH value	acc. to Ph. Eur. 2.2.3 and USP <791>
Colour	acc. to Ph. Eur. 2.2.2 and USP <631>

Table 7: Critical process parameter of ampoule filling

5.6 Which are the costs for one ampoule?

The current cost for one glass ampoule is ca. 10 - 30 cent.

5.7 Which improvements are possible for this primary packaging regarding to user application?

The problem of contamination of ampoule contents with glass particles is common known upon the opening of some types of ampoules. Such small glass fragments may be injected through several administration routes. [26]

Furthermore the glass particles may also carry some metals used in their manufacture [27], [28]. A safety problem occurring from glass ampoules is the contamination by these tiny particles, which can lead to injuries. In animal studies, it could be shown that infusion of glass microparticles resulted in pulmonary silicosis and nodular fibrosis of the liver, spleen, and the small bowel. [29]

Another problem of the glass ampoules are sharp edges after opening of the ampoule. These edges can lead to subcutaneous injuries especially by patients with physical limitations.

Such problems can be avoided by the use of an ampoule opener. A lot of different variants are on the market. One example is given in figure 3.

Figure 3: Example of an ampoule opener (Source: [30])

For an addition of an ampoule opener into the current marketing authorisation the manufacturing authorisation holder (MAH) must test the ampoule opener according to the current regulations for medical devices in the EU, USA and Canada and also according to technical standards e. g. ISO norm 13485 [31]. In general the MAH can make a contract with a manufacturer for such ampoule opener, who has the required information to the manufacture, the quality system and certificates acc. to medical device regulations.

Regulatory requirements for this extension of current marketing authorisation are as follows:

For USA

If you want to put the ampoule opener together with the glass ampoule in one secondary package such as a folding box then the proposed change can be classified as a moderate change = “Supplement-Changes Being Effected” in 30 days acc. to the Guidance for Industry - “Change to an approved NDA or ANDA”. [32]

In the section of changes for packaging material is written:

"a change to or in a container closure system, except as otherwise provided for in this guidance, that does not affect the quality of the drug product"

The costs for this type of change are integrated in the annual fees of the medicinal product and not separated listed compared to fee regulation of national health authority in Germany.

In Canada the addition of an ampoule breaker to the glass ampoule in one secondary package is classified as an annual notification. The annually fees are ca. 1.020 $ (Canadian Dollars) = 766 Euros at the moment.

In the EU the change from the ampoule to a combination of ampoule with an ampoule breaker would be a variation type IA_{IN} acc. to the classification guideline [33]. In this guideline conditions and documents are relevant for such packaging change:

B.IV.1 Change of a measuring or administration device	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Addition or replacement of a device which is not an integrated part of the primary packaging			
1. Device with CE marking	**1, 2, 3**	**1, 2, 4**	**IA_{IN}**

Conditions
1. The proposed measuring device must accurately deliver the required dose for the product concerned in line with the approved posology and results of such studies should be available.
2. The new device is compatible with the medicinal product.
3. The change should not lead to substantial amendments of the product information.

Documentation
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including description, detailed drawing and composition of the device material and supplier where appropriate, and including revised product information as appropriate.
2. Proof of CE marking
4. Samples of the new device where applicable (see NTA, Requirements for samples in the Member States).

Figure 4: Overview of conditions and documentation to a change from the ampoule to a combination of an ampoule with an ampoule breaker acc. to European classification guideline [33]

In Germany this change is classified below the SKNR number 0833 “Applikationshilfe / Applikator (ohne Vorliegen der Bedingung von SKNR 5551, 5595 o. 5606)” (see change catalog of BfArM) [34].

The costs for such change in the EU are depended on national fee requirements. For example in Germany the fees for this change are ca. 310 - 410 Euros.

6. Which are the requirements for a pre-filled syringe as primary packaging material?

A second possibility for a primary packaging system for the herbal drug is the pre-filled syringe. Advantages of this container closure system compared to the ampoule are an improvement of the closing accuracy, the safety aspect for the patient, the quality of life. An important aspect for the use of pre-filled syringe is also the reduction of patient time in the clinic and at home. For the application of the glass ampoule up to 8 steps are required. But for an administration of a pre-filled syringe only 3 or 4 steps are needed. [35]

Furthermore the change from an ampoule to a pre-filled syringe is also a strategic decision based on the wishes of physicians and patient, which are looking for easier modes of administration. [36]

Another point of view is that a change from the ampoule to a pre-filled syringe can support the differentiation of the medicinal product compared to other competing drugs in the same therapeutic category. This differentiation aspect can increase the market share of this medicinal product. [36]

A further economic aspect is that the marketing authorization holder can demand for the optimized product presentation a premium price compared to the current primary packaging. The increase of attractiveness of this medicinal product for the physicians and patient can lead to an increase of sale. [37]

From regulatory point of view it is necessary to know the correct regulatory classification of the pre-filled syringe in USA, Canada and EU.

6.1 Classification of pre-filled syringe in USA

According to 21 CFR 3.2 (e) the pre-filled syringes belong to the combination products. The definition of a combination product is described as follows: [38]

*“A combination product is a product composed of **any combination of a drug and a device**; a biological product and a device; a drug and a biological product; or a drug, device and a biological product”*

This definition includes following combinations:

1. A product ***comprised of two or more regulated components*** *(i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic)* ***that are physically, chemically, or otherwise combined or mixed and produced as a single entity****;*
2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labelling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labelling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose); or

4. Any investigational drug, device, or biological product packaged separately that according to its proposed labelling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Examples for the combination products under point 1 are as follows:

- *Monoclonal antibody combined with a therapeutic drug*
- *Device coated or impregnated with a drug or biologic*
    - *Drug-eluting stent; pacing lead with steroid-coated tip; catheter with antimicrobial coating; condom with spermicide*
    - *Skin substitutes with cellular components; orthopedic implant with growth factors*
- ***Pre-filled syringes,*** *insulin injector pens, metered dose inhalers, transdermal patches*

6.2 Classification of pre-filled syringe in Canada

Health Canada describes in the “Policy on Drug/Medical Device Combination Products, October 20, 1998” the classification of a combination product as drug or a medical device as follows: [(39)]

1. *A combination product will be subject to either the Medical Devices Regulations or the Food and Drug Regulations according to the principal mechanism of action by which the claimed effect or purpose is achieved.*

2. *Where the principal mechanism of* ***action by which the claimed effect or purpose is achieved by pharmacological, immunological, or metabolic means, the combination product will be subject to the Food and Drug***

Regulations**, unless that **action occurs in vitro, without reintroducing a modified cellular substance to the patient, in which case the product will be subject to the Medical Devices Regulations.

3. *Where the **principal mechanism of action** by which the claimed effect or purpose **is not achieved by pharmacological, immunological, or metabolic means,** but may be assisted in that **effect or purpose by pharmacological, immunological, or metabolic means, the combination product will be subject to the Medical Devices Regulations.***

Examples for combination product that are classified as drugs are as follow:

- ***pre-filled syringes***
- *patches for transdermal drug delivery*
- *implants whose primary purpose is to release a drug*
- *wound dressings whose primary purpose is to deliver a drug*
- *dental products impregnated with a drug whose primary purpose is to deliver a drug*
- *red blood cell processing solutions*
- *contrast media*
- *peritoneal dialysis solutions*
- *alcohol swabs*

6.3 Classification of pre-filled syringe in Europe

Acc. to the Council Directive 93/42/EEC of 14 June 1993 [(40)] concerning medical devices the pre-filled syringe belongs to the combination products (medical device + medicinal product). Furthermore the classification of such combination products is made acc. to the *Primary Mode of Action* as follows:

Variant 1

*"Is the **medicinal product form a single integral product** which is intended **exclusively for use in the given combination and which is not reusable**, then the single product shall be governed by Directive 65/64/EEC.* " Furthermore the requirements of Annex I to the Directive 93/94/EEC [(40)] regarding safety and performance related medical device features are concerned.

An example for the variant 1 is the pre-filled syringe. Here the Primary Mode of Action **is as a drug**.

Variant 2

*"Where a device incorporates, as an **integral part, a substance which, if used separately,** may be considered to be a medicinal product within the meaning of Article 1 of Directive 65/65/EEC and **which is liable to act upon the body with action ancillary to that of the device**, that **device must be assessed and authorized in accordance with this Directive."***

An example for variant 2 is a heparin coated catheter. Here the **medicinal drug** is verified **as drug** acc. the Directive 2001/83/EC. [3] But the **catheter** is classified as **medical device of class III**.

For the pre-filled syringes following guidelines and guidance documents for USA, Canada and EU are relevant.

EU	USA	Canada
Guideline on Plastic Immediate Packaging Materials [5] CPMP/QWP/4359/03; EMEA/CVMP/205/04 EU-Directive 2002/72/EC Plastic materials and articles intended to come into contact with foodstuffs [41] EMEA/410/01 <Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal> [42] Commission Directive 94/62/EC <Packaging and packaging waste> [43]	Guidance for Industry-Container Closure Systems for Packaging of Human Drugs and Biologics (FDA) [6] Guidance for Industry – Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products (February 2008) [44] 21 CFR 3.2 (e) [38] 21 CRF 210, 211 16 CFR 1700	Information Requirements For Food Packaging Submissions - Health Canada [45] Process Validation: Terminal Sterilization Processes for Pharmaceutical Products (GUIDE-0074) [46] Good Manufacturing Practices (GMP) Guidelines - 2009 Edition, Version 2 (GUI-0001) [8] Notice - Revision of the Procedure on the issuance of Drug Identification Numbers (DINs) for Unit Dose Pre-filled Syringes [47] Policy on Drug/Medical Device Combination Products – Decisions [48] DRAFT GUIDANCE FOR INDUSTRY "Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) (2001-07-18) [49]

Table 8: Overview of relevant guidelines and guidance documents for pre-filled syringes in EU, USA and Canada

6.4 Which are the technical requirements that should be fulfilled by a pre-filled syringe? Which parts of the CTD are concerned?

For the USA the Guidance for Industry "*Container Closure Systems for Packaging Human Drugs and Biologics*" from May 1999 [6] is relevant. In this guidance all information to the technical, quality and regulatory requirements for packaging components of Human Drugs and Biologics are described.

- The Quality standards for the pre-filled syringe acc. to this guidance are the current good manufacturing practice (CGMP) requirements for the control of drug product containers and closures (see 21 CFR Parts 210 and 211)
- The FDA requirements for tamper-resistant closures (see 21 CFR 211.132)

- The Consumer Product Safety Commission (CPSC) requirements for child-resistant closures (see 16 CFR 1700)
- The requirements for product containers (see drug monographs of USP/NF)

In the USP the general requirements for containers are defined in the chapter "General Notices and Requirements" (Preservation, Packaging, Storage and Labelling). Information on the different material of the containers is available in the "General Chapters" of USP e. g. in USP <381> and USP29-NF24. [(2)]

Furthermore the information regarding to the manufacturing and processing of the drug product, which includes also the details to the packaging material, should be described in Module 3.2.P.2, 3.2.P.3 of the CTD or in a DMF.

For the container closure system the suitability for the "Intended Use" should be demonstrated regarding following aspects:

- Protection
- Compatibility
- Safety
- Performance of packaging components and/or system

Protection

The container closure system should be an adequate protection of the dosage form against environmental factors such as temperature and light which lead to degradation of the drug product. Common aspects that can induce degradation are the exposure to light, the loss of solvent, the exposure to reactive gases, the absorption of water vapour and microbial contamination. Based on these facts following tests should be performed to investigate the suitability of pre-filled syringe regarding its protection features. In general these parameters are tested in the long term stability studies (see P.8.3 of the CTD).

Stress factor	Test method
Exposure to light	USP test for light transmission USP <661>
The loss of solvent	e. g. by a polyethylene container wall Note: this aspect is not so relevant for the pre-filled syringe
Water vapour or reactive gases (e.g. oxygen)	Only relevant for plastic containers and not for glass containers
Protection from microbial contamination	Performance of an adequate container closure integrity test (see section 3.2.P.2.5)

Table 9: Overview of stress factors and corresponding compendial test methods

Compatibility

The separate packaging components should be tested regarding their compatibility with the drug product, because an interaction with the dosage form can be caused to a change in the quality of the drug product or of one of the packaging components.

Interactions between the packaging components and the dosage form could be as follow:

- Loss of potency due to absorption or adsorption of the drug substance induce by leaching of a chemical substance from a packaging component
- Loss of concentration of an excipient based on absorption
- Change of pH value in the drug product
- Discoloration of dosage form or the packaging component
- Increase of brittleness of packaging components

In general most of these aspects are investigated in the stability studies but for the investigation of extractables and leachabels separate tests are necessary. These special development studies are normally described in the 3.2.P.2 section of the CTD.

Extractables can be defined as compounds that can be extracted from packaging materials in the presence of a solvent and under certain specified conditions. (50)

Leachables are chemical substances in the packaging material which can contaminate a drug formulation under normal use conditions e.g. by interaction with the drug substance. (50)

Performance of extraction studies

These studies should be made under controlled conditions. For the performance of an extraction study several different solvents should be tested such as methanol, ethanol, hexane, acetone, dichloromethane, ethyl acetate, iso-propanol, t-butyl methyl ether, toluene, water, buffers, or matrix-matched buffers. Storage conditions acc. to Soxhlet extraction at 60°C for 21 days or other extraction schedules, that are scientifically accepted, should be used. (50)

Appropriate analysis methods for such studies are HPLC or gas chromatography. These methods are suitable to detect the qualitative or quantitative extraction profile of volatile or non-volatile extractables. For extractable studies the packaging material should be tested both in the drug product solution and in a stronger extracting solvent than the drug product to obtain a qualitative reference extraction profile compared to the extraction profile of the drug product. (50)

In general the extractable level profiles demonstrate the worst-case scenario. Therefore the extractable profile should always be higher than the leachables profile, which is obtained under normal use conditions, i.e., with product in the syringe over time.

Performance of leachable studies (50)

The leachables studies are controlled extraction studies. With special analytical methods the limits of quantification of the leachables are investigated acc. to the concept of safety concern threshold (SCT). The SCT is the dose in µg/day below

which a leachable would present negligible concern for adverse carcinogenic and noncarcinogenic effects. [51]

Safety

The safety aspect plays a large role in the development of suitable packaging material. The packaging components should not consist of material that leaches out harmful and undesirable amounts of substances that can harm the patient. Therefore it is necessary to test the packaging components which have direct contact with the dosage form on leachable substances. Additionally substances that can migrate into the dosage form such as inks or adhesive should be also investigated in the leachable tests. The tests are the same as described under the section "compatibility".

For injectable drug product comprehensive studies that consist of two parts are necessary:
Part 1: extraction study (see attachment C of FDA guidance [6])
Part 2: toxicological evaluation of the extracted substances for determination of safe level

For injectable drug products tests performed acc. to USP Biological Reactivity Tests (USP <87> and <88>) and USP Elastomeric Closures for Injections tests (USP <381>) are suitable methods for the evidence of material safety. [2]

Performance

Another important aspect for the assessment of container closure system suitability is the performance test. Two major points should be considered:

a) the container closure system functionality
b) the drug delivery

For the assessment of **"container closure system functionality"** following points regarding the container design should be considered:

- improvement of patient compliance
- minimisation of waste
- improvement of case of use

Attributes of a good syringe design could be as follows: [52]

- intuitive and transparent mechanism
- needle stick safety
- provides added leverage to the user
- affords multiple plunging postures
- affords multiple injection postures/sites
- provides good visibility to label and drug

- is comfortable to use
- it is packaged intelligently to avoid inadvertent activation

All these design attributes should be tested during the design development of the pre-filled syringe. For the routine quality control the optical inspection (good visibility to label and rug) and the comfortable use are relevant points for testing of container closure system functionality. Here the parameters “static and sliding friction” of the plunger rod and plunger stopper should be investigated at the pre-filled syringe.

Child resistance requirements are also relevant aspects for the packaging in the USA. They are described in the Consumer Product Safety Commission (CPSC) requirements for child-resistant closures and included in 16 CFR 1700.1-20. In the § 1700.3 “Establishment of standards for special packaging” is written as follows: (6)

“(1) That the degree or nature of the hazard to children in the availability of such substance, by reason of its packaging, is such that special packaging is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting such substance…”

Performance standards and test methods if a packaging system is child-resistant and adult-use-effective are described under 16 CFR 1700.15 and 16 CFR 1700.20. (6)

In the FDA guidance “Container Closure Systems for Packaging Human Drugs and Biologics” (6) the application of the child-resistant requirements for human drugs is written as follows:

*“… the **manufacturer** or packager **is responsible for child-resistant packaging** if the drug product is intended to be **dispensed to the consumer as packaged without repackaging by the pharmacists** (16 CFR 1701.1). However, any **prescriptions dispensed to patients** upon their release for **their use at home** would be **subject to the PPPA packaging requirements**….”*

It should be keep in mind that child-resistant closures are more relevant for oral medicinal products and not for injectable medicinal products, because they are normally administered from the parents or medical staff.

The second point **“drug delivery”** plays a relevant role for the container closure system “pre-filled syringe”. Two aspects are important. The first point is the “functionality” that can be measured by the test parameters: static and sliding friction. The second point is the “delivered dose” of the pre-filled syringe, which is described in the package insert. This parameter is essential for the correct use of this combination product.

For Canada

In Canada the pre-filled syringe belongs to the combination products. According to the *Policy on Drug/Medical Device Combination Products, October 20, 1998* [39] the pre-filled syringe as combination product is classified as drug. Therefore the regulatory requirements for drugs are also valid for this combination product. Furthermore Health Canada orientates itself on technical requirements and regulations of USA and Europe, such as USP [2] and ISO norms.

In the *DRAFT GUIDANCE FOR INDUSTRY "Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) (2001-07-18)"* [49] also information to correct presentation of the container closure system for the drug product acc. to the requirements of CTD structure is available. The description is very similar to the requirements of the container closure system in Europe, which are described for the drugs in the notices to applicants (NtA Vol. 2B) and also in the Guidance for Industry "*Container Closure Systems for Packaging Human Drugs and Biologics*" from May 1999 [6].

For example in section **P.2.4 "Container Closure System"** the suitability of the container closure system should be described. Here information from the drug product development should be included. Following aspect should be discussed:

- the choice of material for the presented container closure system
- The protection from moisture and light
- The compatibility of the materials with the dosage form (see sorption to container and leaching)
- The safety of the used materials (TSE conformity)
- The performance of the container closure system regarding to reproducibility of dose delivery from the device when it is presented as part of the drug product

In section **P.2.5 the "Microbiological Attributes"** of the dosage form should be discussed. Furthermore for sterile products a test of container closure integrity should be performed. According to the ICH's Q1A guidance document [53] one primary stability batch of the drug product should be used for antimicrobial preservative effectiveness.

In section **P.2.6** compatibility studies should be presented. The studies should cover the storage conditions of the drug product which are described in the labeling, e. g. 24 h at room temperature or 72 h under refrigeration. The compatibility of the drug product with reconstitution diluents or dosage devices (e. g. precipitation of drug substance in solution, sorption on injection vessels) should be investigated with respect to following test parameters:

- pH value
- assay
- levels of individual and total degradation products

- sub-visible particulate matter
- extractables from packaging components such as glass, PVC, polyolefin containers

Furthermore in **section P.7** a description of the whole container closure system should be given. Here the materials of each packaging component and its specification should be presented. The specifications should include the description, the dimensions and the drawings of the packaging components acc. to the accepted monographs of pharmacopeia such as USP/NF [(2)] or Ph. Eur. [(1)]. Non-compendial methods should be validated. Furthermore a short description of non-functional secondary packaging components and functional secondary packaging components should be provided.

In the following table a short overview about the content of specifications documents for the container closure systems of sterile products is presented. [(49)]

Sterile products
Specifications for routine testing
Name, physical description, dimensions (e.g. thickness, etc.)
Specific identification tests (e. g. IR) for components with direct product contact
Qualification of components
Composition and drawings of all packaging components
Description of any additional treatments* sterilization and depyrogenation of the components
USP <661> Containers includes USP <87> / <88> tests
USP <671> Containers – Permeation
USP <381> Elastomeric Closures for Injections includes USP <87> / <88> tests

Table 10: Overview about the specifications of container closure system for sterile products. * e. g. coating of tubes, siliconization of rubber stoppers, sulphur treatment of ampoules/vials

Additionally to information based on *DRAFT GUIDANCE FOR INDUSTRY "Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) (2001-07-18)"* [(49)] the applicant can find also information to requirements on packaging material and the container closure system for the medicinal product in the draft guidance document Drug Master Files (DMF) [(54)]. In this document information and requirements to the type II Drug master file (packaging materials) are included.

For Europe

In Europe no consolidated container closure guideline compared to FDA exists. Compared to the USA in Europe the child-resistant packaging is not necessary at the moment. The few existing child-resistance requirements are not valid for all EU member states. Furthermore these requirements enclose only a very limited list of medicinal products. [(55)]

For combination products such as a pre-filled syringe following regulation and guideline are relevant in Europe:

- 93/94/EEC Annex I (14 June 1993) regarding the information to safety and performance [40]
- MEDDEV 2.1/3 rev. 3 [56]
- Directive 2001/83/EC as amend by 202/98/EC and 2004/27/EC [3]
- Notice to Applicants Vol. 2 B especially 3.2.P.2., 3.2.P.3, 3.2.P.7 and 3.2.P.8 [57]
- EUROPEAN PARLIAMENT AND COUNCIL DIRECTIVE 94/62/EC of 20 December 1994 on packaging and packaging waste [10]
- Ph. Eur. Monographs for specific containers and materials [1]
- CPMP/QWP/4359/03, May 2005_Guideline on Plastic Immediate Packaging Materials [5]
- ISO norms like ISO 13485:2003 [31] and 9001:2008 [58]

In Annex I of Council Directive 93/94/EEC [40] general requirements in part I and requirements regarding design and construction of medical devices are described. The content of both parts is very similar to the information which is included in the Guidance for Industry "*Container Closure Systems for Packaging Human Drugs and Biologics*" from May 1999. [6] Therefore a detailed description of the content of Annex I of Council Directive 93/94/EEC [40] is not presented here.

Another important regulatory document for pre-filled syringes, which consist of plastic material such as a plastic barrel, is the Guideline on Plastic Immediate Packaging Material CPMP/QWP/4349/03 (May 2005) [5]. In this guideline special information for the specification and testing of plastic material of immediate packaging is given.

Especially in section 3.2.P.2.4 of the CTD information of plastic material in relation to stability, integrity, compatibility of medicinal product regarding to the method of administration and sterilisation should be presented.

Furthermore compatibility studies like extraction and interaction studies and/or toxicological studies to special materials should be shown in this section. The definition of extraction studies are described in this guideline as follows:

"For extraction studies appropriate solvent system under stress condition should be used. The used solvent should have the same properties to extract substances as the active substance/ dosage form. The nature and the amount of extract substances should be listed in the specification of the packaging material."

The definition of **interaction studies** is as follows:
These studies evaluate the critical functional characteristics of the container/delivery system. The interaction studies includes following study types: migration studies and sorption studies.
With **migration studies** leaching substances from the plastic material can be monitored. They should be performed on at least one batch of active substance/medicinal product.
With the **sorption studies** a possible loss of drug quality based on adsorption or sorption effects can be evaluated.

If the applicant does not have developmental migration studies, he can monitor the leachables during stability studies, which are conducted under normal and accelerated storage conditions.

Additionally the photostability of the plastic material should be presented, if it is known that degradation products caused by impact of light have a significant impact on the compatibility of the container.

In section 3.2.P.7 of CTD information to container closure system should be provided, which should include following points:

- a description of container closure system and all components of the plastic material
- general information on the plastic material for each packaging component
- specifications for each plastic material

Following general information is relevant:

- Chemical name, chemical name of any monomer used
- The name of material supplier
- The complete qualitative composition of plastic material acc. to special Ph. Eur. monograph [(1)]

For the specification the established specification of plastic material acc. to an appropriated Ph. Eur. monograph [(1)] or another pharmacopeia monograph of a member state in the EU or an in-house monograph can be used.

6.5 Description of different type of pre-filled syringes

According to the 21 CFR 3.2 (e) [(38)] (for USA), the Policy on Drug/Medical Device Combination Products [(39)] (for Canada) and the Council Directive 93/42/EEC + (for Europe) the pre-filled syringe is a combination product which is classified as drug. Therefore it acts as primary container for the drug product like the ampoule. Based on this the primary container should be tested according to seal integrity, compatibility and drug stability through the whole shelf life of the drug product. According to the requirements of USP [(2)], Ph. Eur. [(1)] as well as ISO standards the

pre-filled syringe should be a clear, transparent, low extractable, low particle, and sterile container closure system. (35)

Today a lot different types of pre-filled syringes are available. The manufacturer can select between **glass-based** or **plastic-based systems**.

The **glass-based system of pre-filled syringes** consists of a glass barrel and complementing elastomeric compounds such as plunger stoppers, tip caps and needle shields.

The **advantage of the glass-based system** is the long history of glass products as packaging components in the pharmaceutical industry. Furthermore the majority of pre-filled syringes are glass-based systems and there are multiple proven suppliers for this system available. (59)

The **disadvantages** of the glass-based system are:

- Breakage
- Dimensional variation e. g. at glass barrel tip
- Potential surface reactivity between the glass wall and the drug substance
- Particulate contamination
- Adhesive or other potential leachables
- Inconsistent application of silicone oil

At the glass-based system of pre-filled syringe there are also different types available. The manufacturer can choose between **oily siliconised syringes** and **baked-on silicone syringes.**

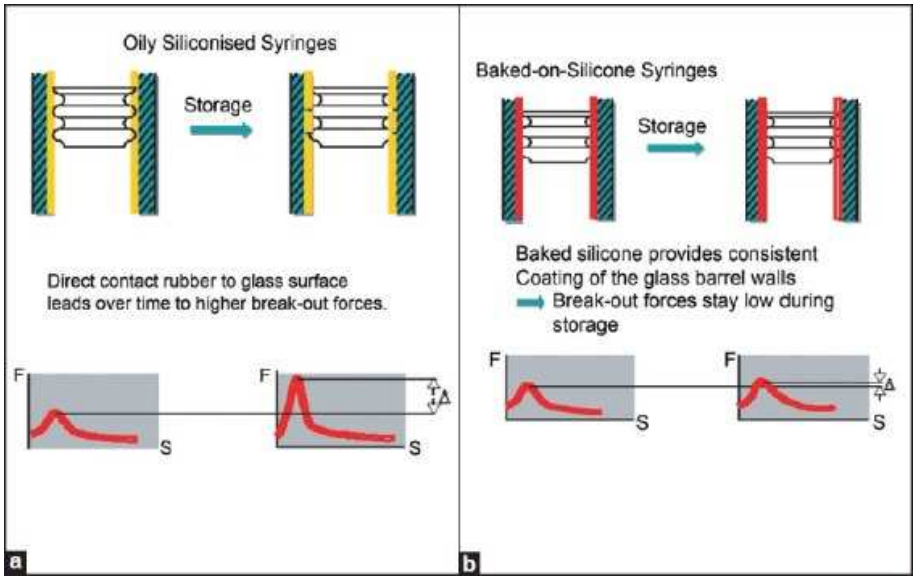


Figure 5: Overview about the break-out-forces before and during the storage of oily siliconised syringes and baked on silicone syringes. (60)

At the **oily siliconised syringes** leads the direct contact of rubber to glass surface to higher break out forces and can induce a contamination of the drug product.
The **advantage of baked-on-silicone syringe** is the consistent coating of the glass barrel walls. Based on this fact the break-out forces stay low during storage. (61)

Another known problem of the glass-based system is the pH shift. The change of pH value occurs at glass type I which consists of borosilicate glass. In the manufacturing around the beginning of cooling phase at 580 ℃ the sodium oxide is formed and remains in the glass. During the storage time the sodium ions are released into the water for injection and induce an increase of the concentration of hydroxide ions. This can also induce an increase of alkalinity (= pH shift) of the drug product. (60)

The **second variant for pre-filled syringes is the plastic-based systems**. In the last time this system has been gaining further acceptance based on the benefits compared to the traditional glass-based systems. Additionally the Japanese market has transitioned over 50 % of its syringes to plastic because of its superior performance. (62)

The most widely used plastic system for pre-filled syringes are manufactured from cycloolefin polymer (COP) or cycloolefin copolymer (COC) resin. The advantages of the plastic-based systems are:

- high break resistance
- design flexibility
- decreased surface reactivity
- less absorption / adsorption of the drug substance
- good compatibility with high or low pH value

Today two main types of materials for plastic-based systems for pre-filled syringes are used. (63)

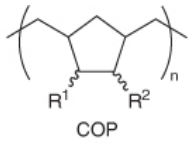


Figure 6: structure formula of cycloolefin polymer (COP) (64)

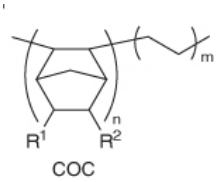


Figure 7: structure formula of cycloolefin co-polymer (COC) (64)

Major properties of COP	Major properties of COC
Low water absorbance	Is a clear amorphous copolymer based on cyclic and linear olefins
High transparency	High transparency
Low specific gravity	Low density
High heat resistance	Excellent moisture barrier capability
Low impurities	has a very low energy and nonreactive surface and therefore a good Resistance to aqueous and polar organic media

Table 11: Comparison of the properties between COP and COC-polymers. (64)

An example for the use of “COP” as material for pre-filled syringes is the Daikyo Crystal Zenith insert needle syringe. This syringe consists of the break resistant cycloolefin polymer (COP) and has many advantageous properties such as glass-like transparency, highly break resistant and an excellent moisture barrier. Furthermore this material ensures extremely low particulate levels. Another important aspect is the elimination of silicone oil and the use of tungsten pins that are commonly used in forming glass syringe barrels. (65)

An example for the use of “COC“ as material for pre-filled syringes is the Topas® COC pre-filled syringe, which consists of TOPAS 6013 COC resin. This material is also used for pre-filled syringe needleless injectors and other drug delivery systems such insulins pumps. (66)

Additionally to the different materials for the pre-filled syringes the manufacturer should be also thinking about another design aspect, namely the needle. Here also different possibilities are available. Closure systems for pre-filled syringes could be as follows: (67)

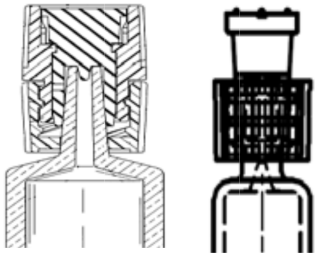
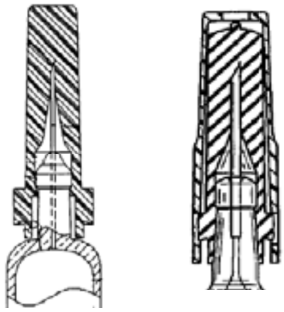
Luer conical fittings acc. to ISO 594-1	Conical lock fittings (luer lock) acc. to ISO 594-2	With cannula + needle shield cover
		

Figure 8: Overview about the different closure system of pre-filled syringes acc. to ISO-norm. (67)

In general the pre-filled syringe consists of following components:

Components of pre-filled syringes with pre-stage needle	Components of pre-filled syringes without pre-stage needle	Material of the component
plunger rod/piston	plunger rod/piston	plastic
plunger stopper	plunger stopper	elastomer
barrel	barrel	glass or plastic
needle	-----	stainless steel or elastomer
needle shield cover	-----	plastic
------	tip cap	elastomer
------	luer lock adapter	plastic
lubricant	lubricant	silicone oil

Table 12: Comparison between components of pre-filled syringes with and without pre-stage needle

In figure 9 the composition of a pre-filled syringe with a pre-staged needle and in figure 10 without a pre-staged needle is demonstrated.

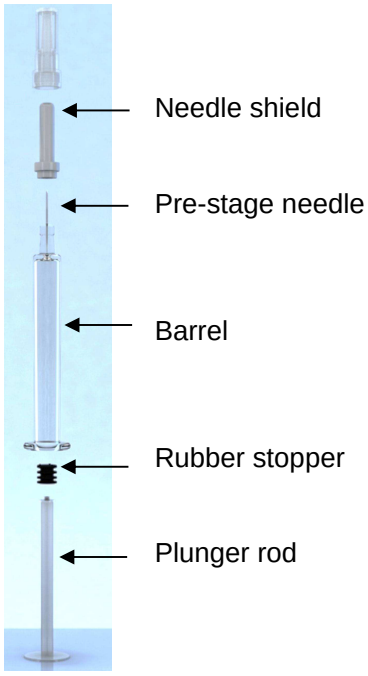


Figure 9: pre-filled syringe with pre-stage needle (Source: [68])

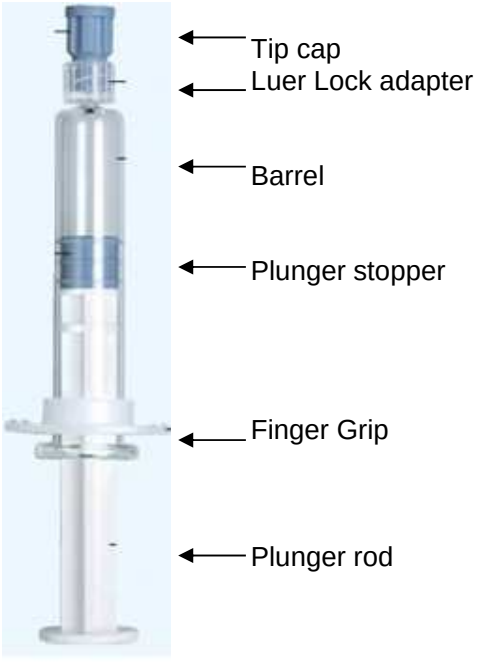


Figure 10: pre-filled syringe without pre-stage needle (Source: [69])

6.6 Specification of separate components of pre-filled syringe

The pre-filled syringe consists of separate components with different materials such as plastic, glass, elastomer and silicone. Therefore for all these components special monographs of Ph. Eur. [1] and USP [2] should be considered. Based on the different

requirements for the separate component of the pre-filled syringe the specification are described for each component.

6.6.1 Specification for the barrel of pre-filled syringe

6.6.1.1 Specification for the glass barrel of pre-filled syringe

For the **glass barrel** the requirements for the glass container as primary packaging material (container) for the ICH regions EU, USA and Canada are valid. In the following table the specification parameters acc. to Ph. Eur. [1] and USP [2] for glass containers, especially for colourless tubular glass of hydrolytic class type I, are presented.

Ph. Eur.	USP
Identification test C: test of surface treatment (etching test) acc. to Ph. Eur. 3.2.1	Identification with surface glass test acc. to USP <660> CONTAINERS—GLASS

Table 13: Specification parameters for tubular glass containers acc. to Ph. Eur. and USP

Furthermore physical test acc. to “defect evaluation list for “containers made of tubular glass” (vol. 19, Editio Cantor) should be performed on the glass barrel. In the defect list following test parameters are described for the evaluation of glass barrels: [70]

- Detection of germ content,
- Content of particles,
- Test on inner surface siliconization,
- Detection of glass particles,
- Detection of the influence of cooling on the glass barrel,
- Detection of deviation in the dimension,
- Test of colour adhesion on the glass barrel

6.6.1.2 Specification for the plastic barrel of pre-filled syringe

For the **plastic barrel** there are a lot of different monographs in the USP [2] and Ph. Eur. [1]. For USA and Canada the monograph USP <661> is relevant.

In the **USP monograph <661> CONTAINERS-PLASTICS** [2] the specification parameters and test method and limits for following plastic materials are described:

- Polyethylene high density
- Polyethylene low density
- Polypropylene
- polyetylene terephthalate (PET) bottles and polyetylene terephthalate G containers

Following specification parameters should be evaluated for parenteral preparations:

Specification paramters	Test methods and limits
Identity test	IR spectroscopy
Thermal analysis	Differential scanning calorimetry
Biological tests	Biological reactivity test in vitro acc. to USP <87> Biological reactivity test in vivo acc. to USP <88>
Physicochemical tests	Nonvolatile residue
	Residue on ignition acc. to USP <281>
	Heavy metals acc. to USP <231>

Table 14: Specification parameters for parenteral preparations acc. to USP [2]

In the Ph. Eur. [1] different monographs for the different plastic materials are available. Following monograph could be relevant for the plastic-based systems:

Ph. Eur. monograph	Titel
3.1.3	Polyolefines
3.1.4	Polyethylene without additives for containers for parenteral preparations and for ophthalmic preparations
3.1.5	Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations
3.1.6	Polypropylene for containers for parenteral preparations and for ophthalmic preparations
3.2.2 3.2.2.1	Plastic containers and closures for pharmaceutical use Plastic containers for aqueous solutions for infusion
3.2.8	Sterile single-use plastic syringes

Table 15: Overview of relevant Ph. Eur. monographs for plastic-based systems

For example for a plastic barrel that consists of the “COP”, the material should be evaluated acc. to the polyolefine monographs of Ph. Eur 3.1.3. Following specification parameters should be tested acc. to monograph Ph. Eur. 3.1.3: [1]

Specification parameter	Test method	Acceptance criterion
Appearance of solution S1	Ph. Eur. 2.2.1, Ph. Eur. 2.2.2	Complies
Acidity or alkality	Ph. Eur. 3.1.3	NMT 1 ml of 0.01 HCl is required for colour change from yellow to orange
Absorbance	Ph. Eur. 2.2.25	maximum 0.2
Reducing substances	Ph. Eur. 3.1.3	the difference of titration volume should be NMT 3.0 ml
Substances soluble in hexane	Ph. Eur. 3.1.3	does not exceed 5 %

Specification parameter	Test method	Acceptance criterion
Extractable aluminium	Ph. Eur. 3.1.3	max. 1 ppm
Extractable titanium	Ph. Eur. 3.1.3	max. 1 ppm
Extractable zinc	Ph. Eur. 3.1.3	max. 1 ppm
Extractable heavy metals	Ph. Eur. 2.4.8	max. 2.5 ppm
Sulfated ash	Ph. Eur. 2.4.14	max. 1.0 %

Table 16: Specification paramters acc. to polyolefine monographs of Ph. Eur 3.1.3

6.6.2 Specification for plunger rod, luer lock adapter and needle shield cover

In general the plunger rod, luer lock adapter and the needle shield cover consist of plastic such as polycarbonate. Normally these syringe components have no direct product contact and therefore a detailed testing compared to other plastic components like the plastic barrel are not performed routinely. But for the first production batches the plunger rod can be evaluated acc. to the requirements of defect evaluation list for “injection moulded parts made of plastic, closures, sealing disks and dosage aids” vol. 22 Editio Cantor. (71)

6.6.3 Specification for Plunger stopper (piston) and tip cap

The plunger stopper (piston) is typically made from butyl bared rubber and can be coated with a fluropolymer film like FluorTec® barrier film. The coating of the plunger stopper serves as a barrier between the drug and the elastomer. (72) Ready- to -use (RU) plunger stoppers should be preferred for pre-filled syringes concerning the aspect of particle reduction. Here the stoppers are washed and sterilized before the delivery to the drug manufacturer.

The tip cap consists also of elastomers e. g. chlorobutyl rubber. Both syringe components have direct product contact. Therefore a detailed evaluation of these components acc. to the specific material monographs of USP (2) and Ph. Eur. (1) is necessary.

According to the **USP monograph <381> “Elastomeric closures for injections”** the elastomeric closures can be differed between type I and type II closures.
Type I is especially for aqueous solutions and type II is typically intended for non-aqueous preparations.

Characteristics of elastomeric closures are as follows:

- are translucent or opaque
- have no characteristic colour
- are homogeneous
- are particle-free from flash and adventitious materials

In the following table an overview about the specification parameters for type I closures are presented.

Specification parameters	Test methods	Acceptance criteria
Identification	IR spectrophotometry acc. to standard	complies with reference standard
Biological test	USP <87> Test of Biological Reactivity in-vitro and USP <88> in-vivo	complies
Physicochemical tests		
Appearance of solution	Determination of turbidity/opalescence Determination of colour.	solution S not more than intensely colored than color standard
Acidity or Alkalinity	USP <381>	NMT 0.8 ml of 0.01 N HCl for yellow color change or NMT 0.3 ml of 0.01 N NaOH for blue color change
Absorbance	USP <381>	does not exceed 0.2 for type I closure
Reducing substances	USP <381>	differences between titration volumes is not greater than 0.3 ml for type I closures
Heavy metals	USP <231>	NMT 2 ppm heavy metals as lead
Extractable zinc	USP <381>	NMT 5 ppm of extractable zinc
Ammonium	USP <381>	NMT 2 ppm of NH_4
Volatile sulfides	USP <381>	any black stain on the paper produced by test solution is not more intense than produced by control substance

Table 17: Specification parameters for type I closures acc. to USP monograph <381>

The required functionally tests, such as penetrability, fragmentation and self-sealing, are only for closures intended to be pierced by a hypodermic needle.

According to the Ph. Eur. monograph 3.2.9 “RUBBER CLOSURES FOR CONTAINERS FOR AQUEOUS PARENTERAL PREPARATIONS, FOR POWDERS AND FOR FREEZE-DRIED POWDERS” [(1)] the closures are also classified in two types. For the type I closures stricter requirements are necessary compared to type II closures. Type II closures have special mechanical properties and are suitable for special uses such as piercings etc.

In the following table a short overview about the specific parameters for closures type I is described. A lot of the described specification parameters are equal to the USP monograph <381>.

Specification parameters	Test methods	Acceptance criteria
Identification	Test A: stretching test	complies
	Test B: IR spectrophotometry acc. to Ph. Eur. 2.2.24	complies with reference chromatogram
	Test C: total ash acc. to Ph. Eur. 2.4.16	total ash is within ± 10 % of the result obtained with the type sample
Appearance of solution	Clarity acc. to Ph. Eur. 2.2.1 for type I closures and color acc. to Ph. Eur. 2.2.2 method II	complies NMT coloured than GY_5
Acidity or alkalinity	Ph. Eur. 3.2.9	colour change to blue or yellow
Absorbance	Ph. Eur. 3.2.9	does not exceed 0.2 for type I closures
Reducing substances	Ph. Eur. 3.2.9	differences between titration volumes not greater than 3.0 ml for type I closures
Ammonium	Ph. Eur. 2.4.1	max. 2 ppm
Extractable zinc	Ph. Eur. 3.2.9	max. 5 µg of extractable zinc per ml of solutions
Extractable heavy metals	Ph. Eur. 2.4.8	max. 2 ppm
Residue on evaporation	Ph. Eur. 3.2.9	residue weighs NMT 2.0 mg for type I rubber
Volatile sulfides	Ph. Eur. 3.2.9	any black stain on the paper is not more intense than of a standard

Table 18: Specification parameters for type I closures acc. to Ph. Eur monograph 3.2.9

The functionally tests, such as penetrability, fragmentation and self-sealing, are only for closures which intended to be pierced by a hypodermic needle.

Furthermore physical tests shall be made acc. to the defect evaluation list for “rubber parts” vol. 20, Editio Cantor [(73)]. Based on this defect list following analysis parameter should be evaluated:

- Delivery, labeling of packaging
- The particle test
- Function of sealing lamellas with glass cartridge
- Foreign bodies and spots
- Form or production defects
- Visual examination of other defects

6.6.4 Specification for needle (cannula)

The cannula shall be fixed acc. to ISO 7864:193, 13.1. [74] For fixing cannula inside the glass cone an adhesive such as UV hardening adhesive acc. to USP class VI shall be used. The test on retention (steadiness) force shall be made acc. to ISO 7864. [74] The cannula steel shall meet the requirements of ISO 9626. [75]

6.6.5 Specification for lubricants

At the lubricants a distinction between silicone oil emulsion and silicone oil can be made. Examples for silicone oil emulsion are the silicone oil emulsion 355 NF and the silicone oil NF 35 % emulsion. Representatives for silicone oils are the silicone oil 1000 cs Dow Corning 360 or the fluid Dimethicone NF.

For the different lubricants following monographs of USP-NF [2] and Ph. Eur. [1] could be relevant:

- USP-NF monograph for “Dimethicone”
- Ph. Eur. monograph for “Dimeticone”
- and the Ph. Eur. monograph 3.1.8 “Silicone oil used as a lubricant”

Acc. to the USP-NF monograph for “Dimethicone” following specification parameters, test methods and limits should be used for the evaluation of the silicone oils such as the silicone oil 1000 cs Dow Corning or the fluid Dimethicone NF.

Specification Parameter	**Test method**	**Acceptance criteria**
Identification	IR spectrophotometry	complies with reference chromatogram
Specific gravity	USP <841>	e. g. 0.973
Viscosity	USP <911>	nominal viscosity less than 1000 centistokes at 25 ℃ ± 0.1 (with capillary viscosimeter) nominal viscosity of 1000 centstokes or greater at 25 ℃ ± 0.1 (with rotational viscosimeter)
Refractive index	USP <831>	e.g. 1.4046
Acidity	USP-NF <Dimethicone>	color change to blue, use not more than 0.10 mL of 0.050 N alcoholic KOH
Loss on heating	USP-NF <Dimethicone>	it loses not more than the max. % of its weight
Heavy metals	USP <231>	any red color in test solution is not more intense than that in standard solution (5 µg per g)
Bacterial endotoxins	USP <85>	it contains not more than 1.0 USP Endotoxin Unit per mL ≙ NMT 10 EU/mL
Residual solvents	USP <467>	complies
Assay	See IR spectrophotometry	complies with reference chromatogram

Table 19: Specification parameters for lubricants acc. to the USP-NF monograph for “Dimethicone”

The specification parameters that are described in the Ph. Eur. monograph for "Dimeticone" [1] are different compared to the USP-NF monograph [2]. In the following table a short overview about the specification of Dimeticone acc. to Ph. Eur. monograph are presented.

Specification parameter	**Test methods**	**Acceptance criteria**
Appearance	Ph. Eur. <Dimeticone>	clear, colourless liquid of various viscosities
Solubility	Ph. Eur. <Dimeticone>	practically insoluble in water, very slightly soluble or practically insoluble in anhydrous ethanol, miscible with ethyl acetate, methyl ketone, toluene
Identification		
Test A	Kinematic viscosity at 25 ℃	product-specific
Test B	IR spectrophoto-metry acc. to Ph. Eur. 2.2.24	complies with reference chromatogram
Test C	Colour test	colour change to violet
Test D	Sulfated ash acc. to Ph. Eur. 2.4.14	residue is a white powder and gives a reaction of silicates acc. to Ph. Eur. 2.3.1
Acidity	Ph. Eur. <Dimeticone>	colour change to blue with 0.01 M NaOH
Viscosity	Ph. Eur. 2.2.9	90 – 110 % of nominal kinematic viscosity at 25 ℃ that is described on the label of reference standard
Mineral oils	Ph. Eur. <Dimeticone>	UV-assay at 365 nm fluorescence is not more intense that a solution containing 0.1 ppm quinine sulfate in 0.005 M sulfuric acid
Phenylated compounds	Absorbance acc. to Ph. Eur. 2.2.25	not greater than 0.2
Heavy metals	Ph. Eur. <Dimeticone>	max. 5 ppm, any red color in test solution is not more intense than that in reference solution
Volatile matter	Ph. Eur. <Dimeticone>	max. 0.3 per cent

Table 20: Specification paramters for lubricants acc. to Ph. Eur. monograph for "Dimeticone"

Additionally to the specific monograph for "Dimeticone" in the general Ph. Eur. monograph 3.1.8 "Silicone oil used as lubricant" [1] the specification parameters, test methods and acceptance criteria are described for other type of silicone oils and silicone emulsions. In the following table a short overview about the content of this monograph is described.

Specification parameter	Test method	Acceptance criteria
Characters		
Appearance	Ph. Eur. 3.1.8	clear, colorless liquid or various viscosities
Solubility	Ph. Eur. 3.1.8	practically insoluble in water, very slightly soluble or practically insoluble in anhydrous ethanol, miscible with ethyl acetate, methyl ketone, toluene
Identification		
Test A	Kinematic viscosity at 25 ℃	complies
Test B	IR spectrophoto-metry acc. to Ph. Eur. 2.2.24, standard: silicone oil CRS	complies with reference standard
Test C	Colour test	colour change to violet
Test D	Sulfated ash acc. to Ph. Eur. 2.4.14	residue is a white powder and gives a reaction of silicates acc. to Ph. Eur. 2.3.1
Acidity	Ph. Eur. 3.8.1	NMT 0.15 mL of 0.01 NaOH for colour change to blue
Viscosity	Ph. Eur. 2.2.10	at 25 ℃, kinematic visc osity is within the range of 95 – 105 % of nominal viscosity
Mineral oils	Ph. Eur. 3.8.1	UV-assay at 365 nm fluorescence is not more intense that a solution containing 0.1 ppm quinine sulfate in 0.005 M sulfuric acid
Phenylated compounds	Refractive index acc. to Ph. Eur. 2.2.6	not greater than 1.410
Heavy metals	Ph. Eur. 3.8.1	max. 5 ppm, any red color in test solution is not more intense than that in reference solution
Volatile mater	Ph. Eur. 3.8.1	max. 2.0 % determined on 2.00 g by heating in an oven at 150 ℃ for 24 h

Table 21: Specification parameters for lubricants acc. to Ph. Eur. monograph 3.1.8 "Silicone oil used as lubricant"

6.7 Which testing standard is necessary for the pre-filled syringe?

A short overview about the separate test methods is given in section 6.2 at the separate description to the different components of pre-filled syringes. A detailed explanation to the different test method for the separate components of pre-filled syringes is not made in this master thesis based on the restricted scope. The detail

description to the performance of the different test methods is available in the separate pharmacopeia monographs of USP-NF [2] and Ph. Eur. [1].

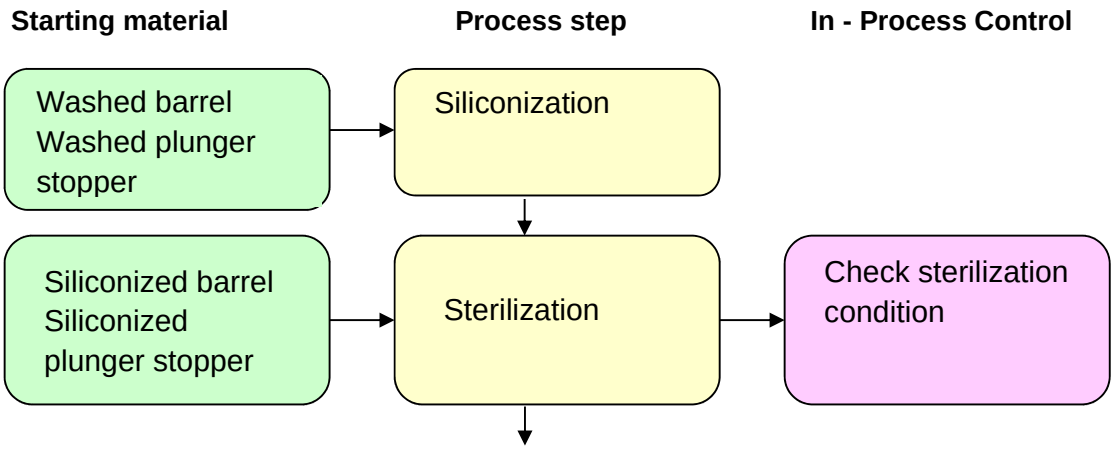
6.8 Which manufacturing steps are needed for the assembling, the filling and packaging of a pre-filled syringe?

Compared to manufacturing steps for the primary packaging “ampoule” additional manufacturing steps as well as other equipment for the manufacturing process of pre-filled syringe is necessary. For a medium-sized enterprise the costs for the establishment of a new filling and packaging production line that includes also new buildings and personnel, are very high. For example the costs for the production line are minimum 1-1.5 million Euros. Therefore it is easier to use the expertise and the equipment of a contract manufacturer.

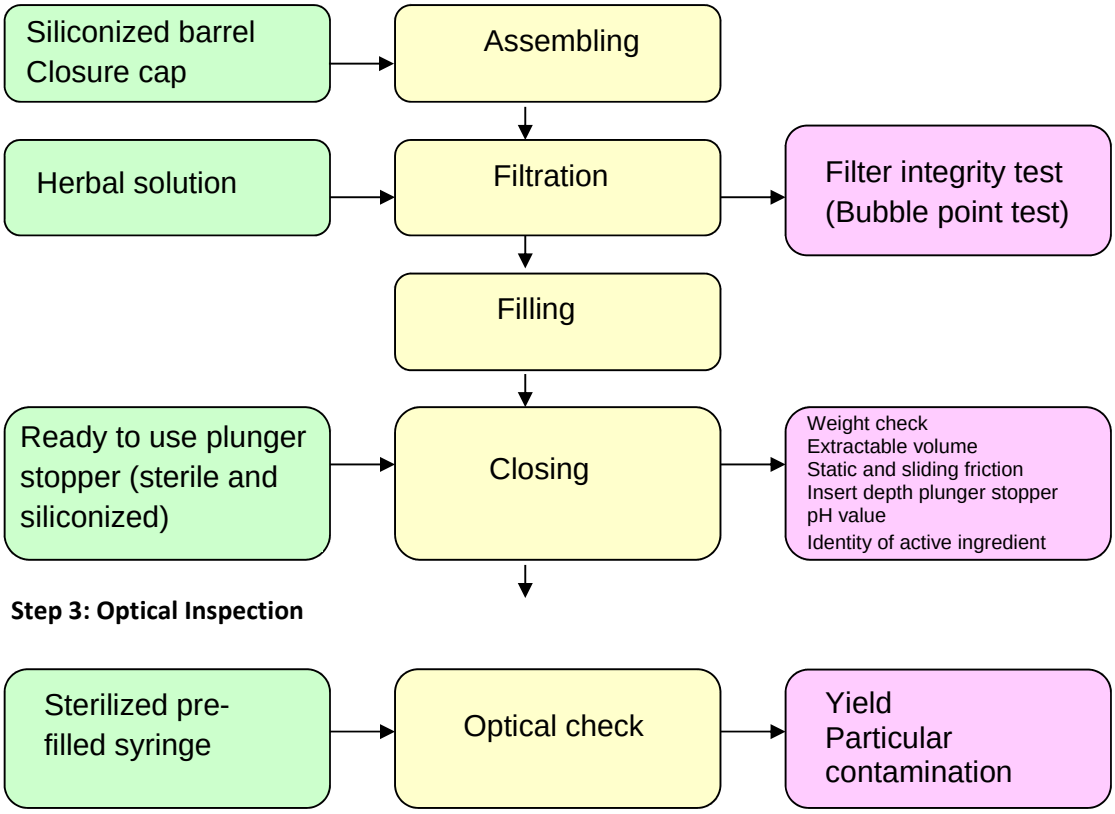
The following example of a flow chart demonstrates the separate production steps that are needed for the assembling, the filling and packaging of the drug into the pre-filled syringe with a luer lock system under aseptic conditions:

Flow chart of manufacturing process of pre-filled syringe under aseptic conditions

Step 1: Preparation of the immediate container (pre-filled syringe)



Step 2: Aseptic Filling of the herbal solution and assembling of pre-filled syringe



The **process steps "filling" and "sterilization"** play a pivotal role in the manufacturing of pre-filled syringes. The traditional filling methods consist of three points: [60]

1. filling of syringe with the solution
2. closing of pre-filled syringe
3. final sterilization

But the disadvantage of the traditional method is that the coating of the plunger stopper can be damage by the placing of this stopper. Newer techniques such as "HCM" (Hyaluron Contract manufacturing) involve online vacuum filling coupled with online vacuum, known as bubble-free filling [60]. The advantage of such technique is the elimination of air bubbles inside the syringe. Furthermore the totally removing of gas bubbles improves the stability of oxygen sensitive compounds. Additionally this new technique is compatible with coated stoppers. [60]

The **other main process step** in the manufacturing of pre-filled syringes is the **sterilization.** Normally the sterilization is performed by autoclaving or ionizing radiation. But the autoclaving procedure is not suitable for all types of pre-filled syringes. The advantage of ionizing radiation is that the syringe plunger remains in its packaging form. For herbal products a terminal sterilization is not suitable because the drug substance is not heat stable. Therefore the manufacturing process must be

performed under aseptic conditions. Here a filtration of the herbal product is the only possibility for the sterilization of the drug product. Based on this an aseptic manufacturing process is needed. In this case only the components of pre-filled syringe such as closure cap, barrel, plunger stopper must be sterilized before use the filling process under aseptic conditions.

6.9 Which process validation parameter should be tested for this primary packaging?

For the process validation a lot of different guidance documents are relevant. Therefore only a short list of the important guidance documents is presented here. Following document could be helpful for the process validation:

- ICH Q6A with the section 3.3.2.3 “Parental Drug Products” [76]
- The guidance document on sterile product filtration process of the Parenteral Drug Association (PDA) and the FDA [77]
- The guidance document on aseptic processing (in the EU) [17]
- The draft guidance on Process Validation (EMA/CHMP/CVMP/QWP/70278/ 2012-Rev1) [78]

In the ICH Q6A [76] is written in section 3.3.2.3 “Parenteral Drug Products” that following validation parameter should be evaluated in a process validation for a parenteral drug:

- The uniformity of dosage units: weight variation; fill volume and uniformity of fill
- pH value
- Sterility: LAL test or pyrogen test
- Particulate matter: visible, sub-visible particles and clarity
- Water content: only for parenterals for reconstitution or non-aqueous parenterals
- Antimicrobial preservative content
- Extractables
- Functionality testing of the delivery system

Additionally to the general validation parameter acc. to ICH Q6A other parameter for a process validation under aseptic environment are relevant. For example an evaluation of environmental factors such as temperature, relative humidity, air velocity, uni-directional air flow, HEPA filtration and pressure differentials between rooms of different classification is necessary. [60]

Therefore following validation parameters should be considered in the process validation under aseptic conditions: [60]

- Direction of air flow
- Air balance
- Air changes per hour
- Air velocity
- Air pressure

If the components of the pre-filled syringe are not delivered as ready-to-use elements, it is essential to validate the washing and sterilization process for example for the plunger stopper, the luer lock adapter, the tip cap the safety cap and the syringe barrel.

For the **validation of washing process** following aspect should be considered. The cleanliness of elastomeric components such as plunger stopper or tip cap is important for the manufacturing process of pre-filled syringe. Generally water for injection is used for the final rinsing of plunger stopper. Additionally highly purified water for the final rinse cycle of the syringe washing machine is used. For this process step validation parameters such as visible, sub-visible particles, bioburden and endotoxins should be tested. The quality of the water is clearly defined in the relevant guidelines of FDA (Parenteral Drug Association Technical Report No. 4 titled, "Design Concepts for the Validation of a “Water for Injection” System.") [79] and EMA (Note for guidance on quality of water for pharmaceutical use, CPMP/QWP/158/01_EMEA/CVMP/115/01). [80] Furthermore the USP monograph “Water for Injectable Products” and the Ph. Eur. monograph “Water for Injections” [1] can also give relevant information for the validation of washing process.

The **validation of the sterilization process** for syringe components is also a challenge in the process validation. For example if the syringe components sterilized with gamma irradiation four validation issues should be evaluated. [60]

1. The determination of the maximum dose of irradiation that is tolerated by the product must be evaluated. For example for a chlorobutyl rubber closures an exposure between 25 and 50 kGy is useful. After this irradiation the integrity of this syringe component should be check.
2. For the selection of suitable sterilizing dose the ISO regulation 11137 [81] can be helpful. In this regulation information relating to sterilization of medical devices is described. For example the average bioburden should be performed from three batches. Furthermore if a sample of 100 syringe plunger is evaluated then no more as two positive tests of 100 should be occurred.
3. The third point of validation should be a determination of dose mapping. That means the irradiation dose which is received in each point of the batch to be sterilized. The dose mapping should be validated from three different loads and involves the distribution of the dosimeter to different measurement points like “cold point” and “hot point”.

4. Last but not least the determination of the expiry date should be validated at this process step. This is made with aging studies to check the packaging integrity and the behavior of the irradiated product.

A pivotal step in the **aseptic process step is the product filtration**. Here the filter must be validated to demonstrate the suitability to remove the bacteria of the bulk solution. The evaluation of filter suitability can be checked with a bioburden test. The filter validation should be carried out under worst case conditions such as the maximum allowed filtration time and maximum pressure.

For the sterile injection product the sterile test acc. to Ph. Eur. 2.6.1 is required. At the sterility test acc. to Ph. Eur. [(1)] or USP [(2)] the absence of antimicrobial activity of the medicinal product is confirmed. This test is performed with 1 – 2 different incubation media and up to six different microorganisms. The incubation time is 14 days. After this a comparison of the growth of microorganisms in the absence and in the present of product is made.

Another point in the **aseptic process validation is the evaluation of media fill**. Here a simulation of manufacturing process using microbial growth medium (media fill) is made. This process simulation includes the formulation, the filtration and the filling with a suitable media. Furthermore the media fill program should enclose the worst case activities. A minimum of 3000 units should be filled.

As **validation parameters for the functionality testing of the delivery system** following aspects can be used:

- Dosage accuracy
- Filling rate
- The duration of the assembling of closure cap
- The sliding and static friction
- The pull-off force and torsion force

Additionally validation parameters based on GMP requirements are also included in the process validation. For example at the **process step "optical inspection"** a 100 % check of the pre-filled syringes for particulate contaminations and other cosmetics such as defects in the closure cap or in the barrel. Furthermore the calculation of the yield after filling, optical inspection and over the entire production process is also a critical check regarding validity of manufacturing process.

6.10 Which changes of secondary packaging and labeling is necessary for this change?

For the change from the glass ampoule to the pre-filled syringe another cardbox based on the different dimension of the pre-filled syringe is necessary. Furthermore the outer labeling on the secondary packaging and also in the SmPC and in the PIL should be changed. In the SmPC the section *6.4 Special precautions for storage* and

6.5 Nature and contents of container should be adapted on the new primary container. For example in section 6.5 the different materials of the syringe components should be described as follows:

Pre-filled syringe

Glass barrel:	colourless glass Type I
Plunger stopper:	chlorobutyl rubber (Type I)
Tip cap:	chlorobutyl rubber
Luer-Lock-Adapter:	Polycarbonate

6.11 Which are the costs for one pre-filled syringe before filling?

The costs are between 1-2 Euros for one pre-filled syringe (before filling).

6.12 Which regulatory points should be considered for a global change from the glass ampoule to the pre-filled syringe?

6.12.1 Regulatory requirements for EU

In the EU the change of ampoule to the pre-filled syringe is classified as extension application acc. to the Guideline on the "Categorisation of extension applications (EA) vs. Variation application (V) of October 2003 (Notes to Applicant Final Rev. 3)" [82].

In this guideline this change is described in the tabulated overview as follows: [33]

Examples	**"Strengh" only for classification as EA / Type II / Type IA/IB**	**Classification as EA / Type II / Type IA/IB**
Parenterals – different containers		
13. Solution for injection from vial to pre-filled syringe (same concentration)		EA*
* EA = extension application		

Table 22: Classification of a change from an ampoule to pre-filled syringe acc. to European classification guideline

Based on this information the applicant must submit following documents:
A cover letter
A completed EU application form
A full CTD module 1
An update of quality overall summary (QOS)
Relevant sections of the CTD module 3 (such as P.2, P.3, P.7 and P.8)
Revised SmPC, PIL and labeling

In the EU application form the section 1.3 and section 1.4 are relevant for the extension application. For this application the point “yes” must be marked and the variant “change or addition of new route of administration” must be ticked.

1.3. **IS THIS AN APPLICATION FOR A CHANGE TO YOUR EXISTING MARKETING AUTHORISATION LEADING TO AN EXTENSION AS REFERRED TO IN ANNEX II OF REGULATIONS (EC) NO 1084/2003 OR 1085/2003, OR ANY NATIONAL LEGISLATION , WHERE APPLICABLE ?**

○ **No** *(complete section 1.4. + 1.6)*

● **Yes** *(complete sections below and also complete section 1.4. + 1.6)*
Please specify:

☐ qualitative change in declared active substance not defined as a new active substance
- ○ replacement by a different salt/ester, complex/derivative (same therapeutic moiety)
- ○ replacement by a different isomer, mixture of isomers, of a mixture by an isolated isomer
- ○ replacement of a biological substance or product of biotechnology
- ○ new ligand or coupling mechanism for a radiopharmaceutical
- ○ change to the extraction solvent or the radio of herbal drug to herbal drug preparation

☐ change of bioavailability
☐ change of pharmacokinetics
☐ change or addition of a new strength / potency
☐ change or addition of a new pharmaceutical form
☒ change or addition of a new route of administration

After this the application must be filled the legal basis of this extension application. In the relevant case the point 1.4.1 article 8(3) application and the point “known active substance” should be marked.

1.4.1. ○ **Article 8(3) application, (i.e. dossier with administrative, quality, pre-clinical and clinical data*)**
○ New active substance
Note: constituent of a product not yet authorised by a competent authority or by the Community (for centralised procedure)

● Known active substance
Note: . constituent of a product already authorised by a competent authority or the Community
. same or different marketing authorisation holder
. for extensions of complete applications, cross references can only be made to pre-clinical and clinical data*

The fees for an extension application can be differing between the separate member states. In Germany the fees for such submission are ca. 19.200 Euros.

6.12.2 Regulatory requirements for USA

According to the Guidance for Industry, Change to an Approved NDA or ANDA, April 2004, Rev. 1 [32] the change of primary container closure is classified as “Major Changes”. Therefore the application type for this change is a Prior Approval Supplement (PAS). The condition for this change is fulfilled based on the information under point 4, where is written as follows:

“For sterile drug products, any change that may affect drug product sterility assurance, such as: A change to a pre-filled syringe dosage form from another container system”

A further important condition for such PAS is that the material of the pre-filled syringe is used also for other CDER-approved products. Is this condition fulfilled then this

application is a supplement application. Further information to current used materials are available on the FDA-homepage “Inactive Ingredient Search for Approved Drug Products: Frequently Asked Questions” [83] and in the database (see screen shot): [84]

Figure 11: Screen Shot of FDA Drug Database for inactive ingredients. **[84]**

Furthermore this change has also an influence to the manufacturing process and the manufacturing site. Therefore the FDA makes an inspection of manufacturing site before start of the new manufacturing process with the new primary container closure system. A detailed description to FDA inspection is presented in the attachment B of the Guidance for Industry, Change to an Approved NDA or ANDA, April 2004, Rev. 1. [32]

According to the CFR Code of Federal Regulations Titel 21, Vol. 6, 21CFR 514.8 revised as of April 1, 2012 the supplement application following documents should be submitted [85]:

1.	A completed form FDA 356V
2.	A detailed description of proposed change
3.	A description of drug(s) which are involved
4.	A description of manufacturing sit(s) or areas which are affected
5.	A description of the methods used and studies performed to access the effect of the change
6.	Product development reports see CTD module 3.2.P.2
7.	Appropriate documentation e. g. updated master batch records and specification sheets including previously approved documentation with the changes highlighted or references to previously approved documentation
8.	for the sterilization process and test methodologies related to sterilization process validation, relevant validation protocols and a list of relevant SOP’s are needed
9.	If the applicant wants a pre-review of the submitted documents then the supplement application form should be labeled as follows: “Prior Approval Supplement – Expedited Review Requested”
10.	Furthermore comparability protocols should be submitted. These protocols should be marked as follows: “Prior Approval Supplement – Comparability Protocol”

Table 23: Overview of required documents for a supplement application (PAS) in USA

The fees for a supplement application are 25.760 US dollar or ca. 20.000 Euros.

6.12.3 Regulatory requirements for Canada

For the regulatory assessment for the change of primary packaging at Health Canada the guidance document "Post Notice of Compliance (NOC) Changes: Quality Document", adopted 2009/09/02 is relevant [86]. The proposed change is described under section 3.2.P.7 Container Closure System. In the tabulated overview following classification to the change of primary container closure system is presented:

Description of change	33. Replacement or addition of a primary container closure system for a) sterile products
Conditions to be fulfilled	None
Supporting data	1 – 6
Reporting category	Supplement

Table 24: Overview of classification of a change from an ampoule to a pre-filled syringe in Canada

For this "supplement" the application should be submitted following information and documents:

CTD section	Relevant data or information
Module 1.3	Product Monograph, Part I
Module 3.2.P.2	Suitability of container closure system, information to extractable and leachable testing, permeation testing, light transmission
Module 3.2.P.3.5	For sterile products data of process validation, and/or evaluation studies are needed. The evidence of process validation for sterilization process for the proposed container and closure system should be presented.
Module 3.2.P.7	Information on proposed container closure system, which includes the description, the relevant materials, the specification and the results of transport studies, should be shown.
Module 3.2.P.8.1	Stability summary/conclusion to minimum 2 pilot scales of 3 months accelerated or 3 months long term testing and under stress conditions (e. g. photo stability) are needed.
Module 3.2.P.8.2	An updated post-approval stability protocol and stability commitment should be presented
Module 3.2.P.8.3	Stability studies of minimum 2 pilot scales of 3 months accelerated or 3 months long term testing and under stress conditions (e. g. photo stability) should be shown.

Table 25: Required documents for a supplement application for a change in the primary container closure system [86]

The fees for such supplement application are ca. 20.910 CAD (Canadian dollars). This value is equivalent to 16.300 Euros.

7. Which are the requirements for an auto-injector system?
7.1 Which auto-injectors are available on the market?

A third variant for the improvement of the primary packaging “ampoule” could be a change to an auto-injector system. At the moment two main systems are available on the market – the pen-injector and the auto-injector.

A pen-injector can be defined as follows: It is a cartridge-based device designed for a frequent manual injection and for those who require variable dose capabilities. Based on this they are not suitable for chronic users of fixed-dose medications. Furthermore the drugs which are filled in multidose cartridges needs preservatives. (87)

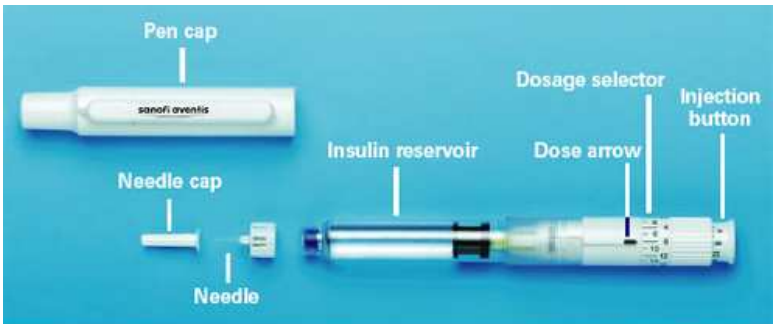


Figure 12: Components of a pen-injector system for the administration of insulin. (88)

An auto-injector can be characterized as follows: They automatically insert the needle and perform the injection. In general they are designed for the use of pre-filled syringes. The device system is a convenient method for drug delivery, especially for patients who may have dexterity issues (72).

The **essential components of an auto-injector** are the injection head, the delivery feeder, the view window for the drug check and a safety mechanism for deviation of needle stick injuries and to fast dose delivery.

Figure 13: Example of an auto-injector system which is filled with a pre-filled syringe. (89)

An influence for the development of reusable auto-injectors was the needle safety regulations driving the safety syringe systems and auto-injectors. Additionally the pressure on healthcare costs induced an increase of need for self-injections. (87)

One variant for an auto-injector system can be the fully disposable device. Here the pre-filled syringe is already packaged in the auto-injector. The patient need to remove only the rubber needle cap and press the device against the skin. After this the device made the injection and the needle is automatically covered. [87]

The advantage of auto-injector systems is to bring additional degree of ease-of use and safety. Furthermore for patients with needle phobia the use of an auto-injector, that can hide the needle and with an easier performance, can be a good option compared to a normal pre-filled syringe. [52]

The traditional auto-injector system use 1 ml long glass pre-filled syringes. The disadvantages of the glass-based system are as follows: [72]

- the glass breakage
- Another problem is the performance. Here the silicon oil can be distributed unevenly on the glass surface and this can induce an increase of sliding force that is required to operate the auto-injector. This could lead to delivery of partial dose to the patient.
- A third problem is the interaction between the drug substance and the syringe system. The silicone oil and tungsten residues can induce protein aggregation in the pre-filled syringe. This can be caused to particle generation.

An improvement of the glass-based auto-injector systems could be the use of silicone-oil-free plastic pre-filled syringe that can be loaded into the auto-injector. The advantages of this system are as follows:

- no use of silicone oil
- lower particle generation
- better performance

Disadvantages of the silicone-oil-free systems are the high costs and the limited experiences with such systems at the moment.

Additionally to the auto-injector system for pre-filled syringe there are also auto-injector systems for vials available on the market. An example of this system is the Flexi-Q-DV.

Figure 14: Flexi-Q-DV: auto-injector system for the safety application of vials. [90]

The advantage of this auto-injector system is that the manufacturing of vials is not so complex and expensive compared to the pre-filled syringe. The studies for the rubber closure system of the primary packaging "vial" regarding the extractables and leachables, a container closure integrity test and stability test are not so extensive and expensive compared to the tests for the pre-filled syringe. The test on glass quality is the same as for the glass ampoule.

7.2 Which are the regulatory requirements for auto-injector systems?

The auto-injector system consists of several parts: the pre-filled syringe or the vial and the auto-injector equipment without the filling. The medicinal product that is filled in the pre-filled syringe or the vial is classified as a drug and is regulated acc. to the drug law.
In general the auto-injector without the pre-filled syringe or the vial is classified as medical devices. In the next section a short overview about the regulatory requirements for medical devices especially for auto-injector systems in USA, Canada and Europe is presented.

7.2.1 Regulatory requirements for medical devices in the USA

In the Section 201(h) of the Federal Food, Drug and Cosmetic Act (FD&C) (21 USC 321(h)) the definition for medical device is described as follows [91]:

"… an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
(3) intended to affect the structure or any function of the body of man or other animals, and

which does not achieve its primary intended purposes through chemical action *within or on the body of man or other animals and* ***which is not dependent upon being metabolized for the achievement of its primary intended purposes****."*

The responsible department for medical devices at the FDA is the FDA´s Center for Device and Radiological Health (CDRH). It makes the review of the manufacture, the repackage, the re-labelling, and/or the import medical device sold in the USA.

The most medical devices are regulated in the 21 CFR Part 800 to 1299. [92] In this document following points are described;

- Design
- Clinical evaluation
- Manufacturing

- Packaging
- the labelling
- and post market surveillance

Based on the FD&C Act 513 [360]c [93] the medical devices can be classified into three classes: class I, class II and class III.

The auto-injector system is classified as a medical device of class II.

The regulatory requirements are different for each of the three classes. The general controls are for all three classes relevant. Whereas the medical devices of class II special controls and for medical devices of class III a premarket approval with a scientific review regarding to safety and effectiveness is required.

The general controls include following points [92]:

- The manufacturing of the medical devices acc. to GMP (see 21 CFR part 820)
- The labeling of the medical devices acc. to labeling regulation (see 21 CFR 801)
- The pre-market notification 510(k) (see 21 CFR Part 807 Subpart E)

The special controls for medical devices of class II are as follow [92]:

- Special labeling requirements
- Mandatory performance standard
- Post market surveillance acc. to 21 CFR 800 -898

The general notification of a medical device in the USA is a registration acc. to 510(k). Here the main rule for registration of medical devices in USA is the FDA´s guidance for Industry and FDA Staff “Implementation of Medical Device Etablishment Registration and Device Listing Requirements Established by the Food and Drug Adminstration Act of 2007 (Final), 08-Oct-2009. [94]

In the CFR 21 subchapter E following information to a 510(k) registration is described (95):
If an equivalent medical device is on the market a 510(k) summary is sufficient. With “equivalent” is meant that the proposed device type is listed in the database at the FDA. The 510(k) summary shall contain following information:

- The name, address, telephone number, contact person of the submitter and the date of the summary
- The name of the device and the trade name/proprietary name, common/usual name, classification name
- An identification of legally market device
- Description of the device should include:

(1) Labeling, promotional material
(2) Explanation of the device function

(3) The scientific concepts
(4) The significant physical and performance characteristics such as design, used material and physical properties
- A statement of the intended use

The labeling requirements for the auto-injector systems are as follows [92]:
21 CFR Part 801: General Device Labeling
21 CFR Part 820: Quality System Regulation

The standard fees for a 510(k) registration is 4.960 $ (3.711,77 Euros) and the annual establishment registration fee of 8.680 $ (6.495,60 Euros).

Additionally to the general guidance documents for medical devices the draft guidance "Technical Consideration for Pen, Jet and Releated Injectors Intended for Use with Drugs and Biological Products" (April 2009) [96] can be helpful for the regulatory assessment of an auto-injector system in the USA. In this guidance document following definition to injector systems are described:

"Pen, jet and releated injectors provide a method of accurately injecting a dose of drug/biological product from a cartridge, reservoir, or syringe through an automatically or manually inserted single lumen hyperdermic needle or through a high velocity jet."

In this draft guidance the applicant finds all relevant information to the registration documents, which are required for the complete 510(k) registration. A detailed description to the content of the registrations documents are not presented based on the limited scope of the master thesis.

7.2.2 Regulatory requirements for medical devices in Canada

In the Food and Drug Act the definition of a medical device is described as follows [4]:

"device" means any article, instrument, apparatus or contrivance, including any component, part or accessory thereof, manufactured, sold or represented for use in

> *(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,*
> *(b) restoring, correcting or modifying a body function or the body structure of human beings or animals,*
> *(c) the diagnosis of pregnancy in human beings or animals, or*
> *(d) the care of human beings or animals during pregnancy and at and after birth of the offspring, including care of the offspring,*

and includes a contraceptive device but does not include a drug…"

Furthermore in the Medical Device Regulation [97] the definition for a medical device is defined as *"a device within the meaning of the Act, but does not include any device that is intended for use in relation to animals"*.

Based on the Medical Device Regulation [97] the auto-injector belongs to the invasive medical devices, because the definition for invasive medical devices is described as follows: *"That is intended to come into contact with the surface of the eye or penetrate the body, either through a body orifice or through the body surface."*

Following guidance documents could be relevant for a registration of an auto-injector in Canada:

- Draft guidance for the risk-based classification system (GD 006), 04 May 1998 [98]
- Safe Medical Devices in Canada [99]
- Guidance Document: How to complete the application for New Medical Device Licence [100]
- Guidance Document: Information to be Provided by Manufacturers for the Reprocessing and Sterilization of Reusable Medical Devices [101]

An important aspect for the registration of the auto-injector is also the correct classification. In Canada the classification of medical devices is performed according to a risk-based approach. At the moment there are following classification groups: class I, II, III and IV. Only for the class I medical devices a medical device licences is not required. For all other classification groups a medical device licence is necessary. Additional to this classification the medical devices can be separate in in-vitro diagnostica (IVDDs) or in non-IVDDs.

The auto injector can be classified acc. to rule 2 of classification guideline as a medical device class 2, because to this category belongs all devices that are invasive via body orifice or which come in contact with the surface of the eye.

There are a lot of additional guidance documents as support for the correct filling of the medical device application available. Especially for the auto-injector following documents could be helpful:

- Guidance for the Interpretation of Section 28 to 31: License Application Type (GD002), 12-Jan 1999 [102]
- Recognition und Use if Standards under the Medical Device Regulations Sep. 11, 2006 [103]
- List of Recognized Standards [104]

Following documents are needed for a medical devices application:

- Application form for class II medical devices with the signature of manufacturer
- Licence fee
- Quality management system certificate e.g. acc. to ISO 13485

- Licence application disclosure request
- Attestation of labelling requirements acc. to section 21-23 of medical device regulation
- Purpose or indented use of the device
- A declaration of the content of DEHP and BPA (Bisphenol A) should be made.

In Canada there are three types of fees for medical devices existing. For the auto-injector registration following fees are relevant:

- The medical device licence application fee of class II medical devices: $ 375 (279 Euros)
- The establishment licence fee (annually fee): CAD 7.200 (5.353 Euros)
- The fees for the right to sell a licensed medical device (annually fee):
  Less than CAD 20.000 = CAD 50 (37 Euros)
  More than CAD 20.000 = CAD 330 (245 Euros)

7.2.3 Regulatory requirements for medical devices in Europe

In the EU directive 93/94/EEC [40] a medical device is defined as follows:

*"any **instrument, apparatus, appliance, software, material or any other article,** whether used alone or in combination, **including the software** intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application intended by the manufacturer, to be used on human beings for the purpose of:*

- *Diagnosis, prevention, monitoring, treatment or alleviation of disease*
- *Diagnosis, monitoring, treatment or alleviation of disease*
- *Investigation, replacement or modification of the anatomy or of a physiological process*
- *Control of conception*

*And **which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means**, but which may be assisted in its function by such means."*

The legal framework in Europe is very complex and high regulated. In the Medical Devices Directive 93/94/EEC [40] as amended by Directive 2007/47/EC the classification of medical devices is made acc. to following basic criteria in various combinations:

- Duration of body contact
- Degree of invasiveness
- The anatomy affected by the use of the device

The point "duration" can be categorised in transient (<60 minutes), short term (± 30 days) or long term (>30 days).

Based on these criteria the medical devices can be classified in four main types:

1.) active implantable medical devices (AIMDs)
2.) active medical devices
3.) non-active medical devices
4.) in-vitro diagnostic medical devices (IVDs)

These four main types can be classified acc. to a risk-based approach into 4 classification groups: medical device glass type I, IIa, IIb and III. For the correct classification the classification guideline MEDDEV 2.4/1 [105] can be used. Based on the classification guideline the auto-injector belongs to the invasive devices with a transient duration time.

According to MEDDEV 2.4/1 [105] the definition for an **invasive medical device** is as follows: *"A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body."*

Therefore the rules 5 to 8 and rule 11 of Annex I from the Medical Device Directive 93/94/EEC [40] are relevant for the classification of the auto-injector. Here the auto-injector is classified as medical device of class type IIa.

The registration of medical devices in Europe is made by the national "notified bodies". They perform the conformity assessment procedure (CE marking) that is described in the annexes of the Medical Device Directive 93/94/EEC [40]. Here also the **essential requirements** for a medical device registration included. In the following tabulated list a general overview about essential requirements for an auto-injector is presented:

No.	Essential Requirement
I.	General Requirements
	• Overall risk benefit • Reduction of risk, protective measures, residual risks • Intended performance • Stability and life time • Information to transport and storage • Acceptability of undesirable side effects • Clinical evaluation
II.	Requirements regarding to Design and Construction
7.	**Chemical, physical and biological properties** Information to toxicity, biocompatibility, flammability Information to contamination and residues Product and material compatibility Incorporation of medicinal products Leaking of toxic substances e. g. phthalates Ingress of substances
10.	**Measurement function** Accuracy Ergonomics Acceptable units of measure

13.	**Information supplied by the manufacturer** Use of symbols Label contents Intended purpose Identification of detachable components Instructions for use

Table 26: Overview about essential requirements for an auto-injector in the EU acc. to Medical Device Directive 93/94/EEC

The main role of the CE marking is the verification of the medical device regarding to safety and performance acc. to the relevant legislation.

In Annex II section 7 for devices of class type IIa is described that the notified body shall assess the technical documentation for at least on representative sample for each device subcategory [40].

If the auto-injector is used in Germany the national requirements for medical devices shall be observed. There are exists a large amount of different laws and regulations. Relevant laws and regulation are as follows:

- The Law on Medical Devices (Medizinproduktegesetz MPG) [106]
- The decree on Medical Devices = Medizinprodukte Verordnung (MPV) from the 10th of May 2010 [107]
- The decree on a Medical Device Vigilance System = Medizinprodukte-Sicherheitsplanverordnung (MPSV) from the 10th of May 2010 [108]
- The decree on Clinical Trials with Medical Devices (MPKPV) from the 10th May of 2010 [109]

According to the fees regulation (see Gebührenverordnung zum Medizinproduktegesetz from the 10th of May 2010) [110] following fees could be relevant for the registration procedure of an auto-injector in Germany:

- Consultancy fee for the correct classification acc. § 13 (2) and (3): 200 – 1.000 Euros
- Registration fee acc. to § 11 (1) 1: 2.500 - 10.300 Euros

7.3 Regulatory information for a registration of an auto-injector system within an existing marketing authorisation

Additionally to the registration as medical device, the MAH must give relevant information to the auto-injector in the CTD of the medicinal product. Concerned sections of the CTD are as follows:

Module No.	Titel
Module 1	Administrative Information
1.0 – 1.2	Cover letter, Comprehensive Table of Contents, Application Form
1.3 1.3.1	Product information SPC, Labelling and Package Leaflet
1.4	Information about the Experts
Module 2	
2.3	Quality Overall Summary (QOS)
2.5	Clinical Overview
2.7	Clinical Summary
Module 3	
3.2.P.2 3.2.P.2.4 3.2.P.2.5 3.2.P.2.6	Pharmaceutical Development Container closure System Microbiological Attributes Compatibility
3.2.P.3.5	Process validation
3.2.P.7	Container Closure System
3.2.P.8	Stability
A-part 3.2.A.2	 A ventitious Agents Safety Evaluation (TSE statement)
Module 3.2.R	Regional information (for EU) It includes all relevant information to the medical device.
Module 5	Clinical study reports

Table 27: Concerned sections of the CTD for a change from an ampoule to an auto-injector system

For the USA

The application type for this change is a Prior Approval Supplement (PAS) = Major change. The costs are: The fees for a supplement application are 25.760 US dollar or 20.000 Euros.

For Canada

A change from the glass ampoule to an auto-injector system which is filled with a pre-filled syringe or a vial is also classified as a supplemental application. Therefore the same documentation as described for the change from the glass ampoule to the pre-filled syringe is needed. The fees for such supplement application are ca. 20.910 CAD (Canadian dollars). This value is equivalent to 16.300 Euros.

For Europe (Germany)

In Europe and especially for Germany the change from the ampoule to an auto-injector system which is filled with a pre-filled syringe or a vial is classified as a line extension. The fees and the administrative documentation are the same as described for the change from the ampoule to a pre-filled syringe.

A cover letter
A completed EU application form
A full CTD module 1

An update of quality overall summary (QOS)
Relevant sections of the CTD module 3 (such as P.2, P.3, P.7 and P.8, A and R-Part)
Revised SmPC, PIL and labeling

8. Tabulated overview about regulatory evaluation of the primary packaging change

At the end of three months the regulatory affairs manager summarized the collected information in a tabulated overview (see ANNEX I). The advantage of this presentation was to receive a clear schedule about the relevant regulatory points of the concerned countries. Furthermore this overview was necessary for the performance of the decision analysis that should be made together with the other involved person of the project team.

9. Decision analysis for evaluation of the best regulatory strategy for a change in the primary container closure system

9.1 Overview about the advantages and disadvantages of the different variants of primary container closure system and related devices

Variant 1 **OPC ampoule**	**Variant 2** **OPC ampoule + ampoule opener**	**Variant 3** **Pre-filled syringe with glass barrel**	**Variant 4** **Pre-filled syringe with plastic barrel**	**Variant 5** **Auto-injector with pre-filled syringe**	**Variant 6** **Auto-injector with vial**
Advantage: • established primary packaging for sterile products • low costs	**Advantage:** • no cutting damage • temporary improvement of primary packaging • low costs compared to pre-filled syringe and the auto-injector	**Advantage:** • improvement of primary packaging regarding easier handling • time saving during product administration • established and accepted primary packaging (glass-based) in the oncological sector	**Advantage:** • improvement of primary packaging regarding easier handling • time saving during product administration • prevention of glass breaks and pH shift compared to the glass-based systems	**Advantage:** • highly innovative • improved safety aspect • prevention of needle phobia (improvement of patient compliance) • “competitive advantage”	**Advantage:** • highly innovative • improved safety aspect • prevention of needle phobia (improvement of patient compliance) • lower development costs for the change from the ampoule to a vial • “competitive advantage” • “unique selling proposition”

Variant 1 OPC ampoule	Variant 2 OPC ampoule + ampoule opener	Variant 3 Pre-filled syringe with glass barrel	Variant 4 Pre-filled syringe with plastic barrel	Variant 5 Auto-injector with pre-filled syringe	Variant 6 Auto-injector with vial
Disadvantage: • injuries at ampoule opening • less innovative primary packaging • pH shift and higher breakage based on the glass material • no improvement of patient compliant regarding “needle phobia” • many applications steps from ampoule opening up to drug application • no improvement of dose application regarding to dose accuracy	**Disadvantage:** • pH shift and higher breakage based on the glass material • no improvement of patient compliant regarding “needle phobia” • no reduction of opening time • no improvement of dose application regarding to dose accuracy • the ampoule opener is also usable for other ampoules of other drugs • only temporary innovation	**Disadvantage:** • injuries can be also occurred at pre-filled syringes that consist of a pre-stage needle. • higher development costs regarding the leachables and extractables tests and process validation • outsourcing of manufacturing process • higher costs of material • pH shift and higher breakage based on the glass material	**Disadvantage:** • injuries can be also occurred at pre-filled syringes that consist of a pre-stage needle. • higher development costs regarding the leachables and extractables tests and process validation • outsourcing of manufacturing process • higher costs of material • no established material for primary packaging • less information regarding to drug-material interaction are known	**Disadvantage:** • high development costs based on the requirement of performance studies with patients • higher costs for the patient for the auto-injector • there are also high development costs for the pre-filled syringe regarding the leachables and extractables tests and process validation • outsourcing of manufacturing process • higher costs of material	**Disadvantage:** • high development costs based on the requirement of performance studies with patients • higher costs for the patient for the auto-injector • there are also development costs for the vials regarding the leachables and extractables tests and process validation • outsourcing of manufacturing process

9.2 Definition of must criteria

1. Improvement of patient safety of 20 %
2. Implementation time: max. 3 years
3. Development cost: max. 1.5 million Euross
4. Increase of sale of 30 % within the next five years

9.3 Definition of wish criteria

a. Less regulatory “effort” (e. g. a new drug application)
b. Easier use for elderly people regarding to self-application
c. Positive cost-benefit ratio
d. High long-term effect for the pharmaceutical market
e. less change on the production place
f. limited use of external contractors
g. high innovation
h. acquisition of new customers on the oncological market
i. „Minimizing“ of stability studies
j. less increase of personal costs on current production place
k. “maintaining employment “ on the current production place

9.4 Determination of weighting of wish criteria with the support of preference matrix

		Wish criteria →													
		Less regulatory effort	Easier use for elderly people	Positive cost-benefit ratio	High long-term effect on the market	Less change on production place	Limited use of external contractors	High Innovation	Acquisition of new customers on the oncolog. market	Minimizing of stability studies	Less increase of personal costs	Maintaning employment on production place	**Sum of points for each criterion +1**	**Weighting factor in percent (%)**	**Place**
Wish criteria		**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**			
A	Less regulatory effort		B	C	D	E	A	G	H	A	J	K	4	3	**9**
B	Easier use for elderly people	B		C	B	B	B	B	B	B	B	K	16	13	**3**
C	Positive cost-benefit ratio	C	C		C	C	C	C	C	C	C	K	17	14	**2**
D	High long-term effect on the market	D	D	D		D	D	D	D	D	D	D	19	16	**1**
E	Less change on production place	E	B	E	D		E	G	H	E	E	K	10	8	**6**
F	Limited use of external contractors	A	B	C	D	E		G	H	I	J	K	1	1	**10**
G	High Innovation	G	B	C	D	G	G		H	G	G	K	11	9	**5**
H	Acquisition of new customers on the oncolog. market	H	B	C	D	H	H	H		H	H	H	14	12	**4**
I	Minimizing of stability studies	I	B	C	D	E	I	G	H		I	K	5	4	**8**
J	Les increase of personal costs	J	B	C	D	E	J	G	H	J		K	6	5	**7**
K	Maintaining employment on production place	K	K	K	D	K	K	K	H	K	K		17	14	**2**

For the weighting of the wish criteria all criteria are compared with each other. In total eleven wish criteria are selected for the decision analysis. On the first place the wish criterion ***"high long-term effect on the market"*** was selected. On last place the wish criterion ***"limited use of external contractors"*** was chose.

In the following comparison analysis the six different variants are compared each other acc. to the four must criteria and eleven wish criteria. The aim of this analysis is to find a preliminary strategy for the improvement of the current primary packaging material "glass ampoule".

Legend to the comparison analysis:
C = condition
W = weighting
PS = pre-filled syringe
V = variant
P = properties
V1 = glass ampoule
V2 = glass ampoule + ampoule opener
V3 = pre-filled syringe with glass barrel
V4 = pre-filled syringe with plastic barrel
V5 = auto injector for pre-filled syringes
V6 = auto injector for vials
 = conflict with the wish criterion
Implementation time = includes development time + time for authority assessment
Development costs = includes costs for the extractable and leachable studies, the stability studies and the submission

8.5 Comparison of the different variants acc. to the must and wish criteria

Must criteria	**C**	**V1**	**Y**	**N**	**V2**	**Y**	**N**	**V3**	**Y**	**N**	**V4**	**Y**	**N**	**V5**	**Y**	**N**	**V6**	**Y**	**N**
Improvement of patient safety	20 %	0		N	20 %	Y		30 %	Y		30 %	Y		50 %	Y		50 %	Y	
Implementation time	3 y	0	Y		1 y	Y		3 y	Y		3 y	Y		3 y	Y		3 y	Y	
Development costs Mill. in €	1.5	0	Y		0.1	Y		0.67	Y		0.8	Y		1.2	Y		1.0	Y	
Increase of sale within the next 5 years	20 %	0		N	20 %	Y		30 %	Y		40 %	Y		50 %	Y		50 %	Y	
Wish criteria	**W**	**P**	**C**	**WxC**	**P**	**C**	**WxC**	**P**	**C**	**WxC**	**P**	**C**	**WxC**	**P**	**C**	**WxC**	**P**	**C**	**WxC**
Less regulatory effort	3				yes	3	9	no	1	3	No	1	3	no	1	3	no	1	3
Easier use for elderly people	13				less	2	26	medium	3	39	medium	3	39	yes	4	52	yes	4	52
Positive cost-benefit ratio	14				medium	3	42	medium	3	42	medium	3	42	medium	3	42	yes	4	56
High long-term effect on the market	16				less	2	32	medium	3	48	medium	3	48	yes	4	64	yes	4	64
Less change on production place	8				yes	3	24	no	1	8	no	1	8	no	1	8	less	2	16
Limited use of external contractors	1				yes	3	3	less	2	2	less	2	2	Less	2	2	less	2	2
High Innovation	9				no	1	9	medium	3	27	yes	4	36	Yes	4	36	yes	4	36
Acquisition of new customers on the oncolog. Market	12				less	2	24	yes	4	48	yes	4	48	Yes	4	48	yes	4	48
Minimizing of stability studies	4				yes	4	16	no	1	4	no	1	4	No	1	4	no	1	4
Less increase of personal costs	5				yes	4	20	less	2	10	less	2	10	Less	2	10	less	2	10
Maintaining employment on production place	14				short-term	2	28	medium	3	42	medium	3	42	medium	3	42	medium	3	42
					place 5		**233**	**place 4**		**277**	**place 3**		**282**	**place 2**		**311**	**place 1**		**333**

9.6 Preliminary decision – interim status

At the comparison of the six different variants for the best strategy regarding the improvement of the current primary packaging it is shown that the variant 1 (OPC ampoule) does not fulfill the must criteria. The OPC ampoule provides no improvement of patient safety and does not promise an increase of the sale of 30 % within the next five years. Therefore the comparison analysis for the wish criteria is not continued with variant 1.

After this the performance of the comparison analysis was made with remained variants 2 – 6. The auto injector system, which is filled with vials, was award on the first place. On the second place the auto injector system for pre-filled syringes was placed and the pre-filled syringe with the plastic barrel came on the third place.

Based on the preliminary assessment the risk analysis (FMEA) was performed with the **variant 6 “auto injector system for vials”**. The risks are evaluated acc. to their probability (P) and their impact (I). For the assessment the numbers from 1 to 3 are assigned. 1 = less, 2 = medium and 3 = high.

9.7. Risk analysis (FMEA)

Risk anylsis				Improvement meassurements				
Process step	**Potential error**	**Possible conse-quence**	**Possible cause**	**Prophylactic measures**	**Mitigating action**	**Need for action** P | I	**Need for action** P x I	**Respon-sibility**
It relates to the complete develop-ment process.	The time line of 3 years cannot keep.	Time delay in the complete development process Increase of costs The competition brings a similar product faster on the market. The regulatory requirements will be worse for such change of marketing authorization.	The market analysis was not optimal based on time pressure or to fewer amounts of persons that are not involved in this project. Not all concerned departments of the company are asked regarding to possible risks. Performance of a scientific advice with the concerned authorities was not made. Time delay for the change assess-ment at the con-	Before the start of market analysis a house-internal questioning should be made with the concerned depart-ments to cover a broad perspective. A regular exchange with all concerned departments should be made in tight time schedules. (e g. at least once a month) Before of start with test batch a scientific advice should be made at the concerned authorities to avoid possible regulatory failures	Use of external support for a limited time frame	2 | 3	**6**	Marketing Regu-latory affairs Production Research & Deve-lopment

Risk anylsis				Improvement meassurements				
Process step	**Potential error**	**Possible conse-quence**	**Possible cause**	**Prophylactic measures**	**Mitigating action**	**Need for action** P I	**Need for action** P x I	**Respon-sibility**
		Acquisition of new custo-mers is delayed. fast deprivation of innovation no increase of sale loss of jobs	cerned authorities Time delay based on renovation or new building Process validation at the contractor needs more time.	Following aspect should be noted at a new building: • realistic time plan • place for new production or packaging line • use of external knowhow at the planning				
After market launch	to high production costs	the medicinal product is to expensive the patients have not the money to pay the costs themselves. the public health insurances do not cover	bad cost schedule for the manufac-turing process Many aspects such as new building or a new production line was not considered. increase of personal costs	At the planning additional costs based on time delay and unforeseen problems should calculated At the costs planning an upper limit of costs should be defined. An exceeding of the upper limit is a knock-out criterion of the project continuation.	Renegotiation with the con-tractor regar-ding the costs increase. Induction of a contract penalty if the costs are not conforming as contracted.	2 3	**6**	Production Health economy Legal depart-ment External contrac-tors

Risk anylsis				Improvement meassurements				
Process step	**Potential error**	**Possible conse-quence**	**Possible cause**	**Prophylactic measures**	**Mitigating action**	**Need for action** **P** **I**	**Need for action** **P x I**	**Respon-sibility**
		the costs for the medicinal product based on a bad cost-benefit ratio.	The process validation at the contractor needs more time and money based on unforeseen manufacturing problems.	A commitment of critical points with the external contractor should be discussed and fixed before project start.	Negotiation with the health insurances regarding special discount agreements for the medicinal product.			External consultant
Develop-ment phase	The stability program needs more time.	See point 1	Delay in manufacturing of validation batches The authority has some concerns regarding the planned stability study design. The extractable and leachable studies needs more time.	good communication with the external contractor A good preparation of a scientific advice is necessary to receive a suitable answer regarding the critical points of the project. The extractable and leachable test should be started early.	One part of the stability studies should out-sourced on external labs to receive all test parameters in the short time frame.	1 2	2	Marketing Regula-tory affairs Production Research &develop-ment

Risk anylsis				Improvement meassurements				
Process step	**Potential error**	**Possible conse-quence**	**Possible cause**	**Prophylactic measures**	**Mitigating action**	**Need for action** **P** **I**	**Need for action** **P x I**	**Respon-sibility**
Suitability test of the auto-injector on the patient	Problems with the use of the auto-injector system during the suitable test	The administra-tion of the proposed auto-injector system is not easy. Side effects such as an increase of local reactions and high temperature can be occurred.	Change in the doses application based on the different design of the auto-injector system. e. g. the system can be load only with 1 mL and not with 2 mL.	The study design should be planned with all concerned departments regar-ding the prevention of foreseen side effects. Maybe an external consultation is helpful. (e. g. with an external consultant or a scientific advice at the health authority)	Trial stop The study design should be reconsi-dered.	1 3	3	Research &develop ment Regula-tory affairs Medical affiars depart-ment Marketing Production External contractor

9.7. The final result of the decision analysis

Critical points of the risk analysis are the “adherence of the development time line of three years” and the “high production costs after market-launch”. Therefore a good market research and project planning are essential before project start.

The project team, which is involved in the project planning, should consist of representatives from all company departments. It should be noted that this project is not an individual project of the distributing/marketing division.

External consultations with the contract manufacturers before project launch should be made. Furthermore an exchange of experience between the project team and other manufacturer regarding the change from the glass ampoule to an auto-injector system can be support the project planning. Opportunities for the exchange of knowledge and experience could be national and international conferences, exhibitions and trade fairs (e. g. Pharmapack, TechnoPharm, Interpack etc.).

The increase of production costs should be kept in mind before market launch. That can be result to a bad cost-benefit ratio.

In Germany the possibility for a consultation meeting with the G-BA (Federal Joint Committee) and also with health insurances is available. Maybe a change from the sale in pharmacies to prescription drug could be an option, because in the oncology prescription drug are therapy standard. In Germany non-prescription drugs are excluded from the prescription and reimbursement. But in Annex I of the Pharmaceutical Directive (Arzneimittelrichtlinie – AM RL) [111] an overview about the non-prescription medicinal products is given which is necessary for the standard treatment of serious diseases. On this basis special discount agreements with the health insurances can be negotiated and so the prescription status of the drug could be maintained.

In USA the drug prices are regulated by a free market enterprise system. That means the prices are set by drug manufacturers, wholesalers, and dispensers. The reimbursement policies for drugs in USA are set by commercial health insurance companies and not from the FDA [112]. Therefore an increase of production costs could not have such an impact in USA compared to Germany, because most of the patients must buy the medicinal drugs privately.

In Canada, reimbursement of medicinal products is covered by provincial governments. The pricing of patented medicines is monitored by the Patented Medicines Pricing Review Board (PMPRB). The combination of PMPRB and provincial formularies tends to keep prices in Canada lower than in the United States. The reference price for patented medicines is orientated on the international prices of reference countries such as France, Germany, Italy, Sweden, Switzerland, UK and

USA. Therefore the price for the medicinal drug in Germany could have an indirect influence on the price for the medicinal product in Canada. [113]

The risks of the stability studies and the suitability study with patients can be minimized via external consulting. A possibility is the use of a scientific advice at the concerned health authorities such as BfArM, FDA and Health Canada. The scientific advice is a good option to receive a feedback regarding the study design and the possible problems. Furthermore consultation with the external contractor manufacturers regarding to the theme of extractable, leachable studies and stability concepts could be helpful, because they have made experiences with other companies, which have performed in the primary packaging material. In the literature is enough information regarding safety and user problems of the auto-injector system available that should be used for the project planning.

Based on these facts, the risk of the “time delay during the stability study” and “the occurrence of user problems during the suitability study with the auto-injector system” can be evaluated as low compared to the risk of costs increase after market-launch and the risk of time delay during the development phase.

10. Conclusion

In the decision analysis the auto-injector system for vials, was selected as the best strategy for the improvement of the current primary packaging material „glass ampoule“. But only if all aspects of the risk analysis are taken into consideration this global change strategy will be successful.

The project leader should keep in mind that the instrument of the decision analytic is only an additional tool in the whole planning concept, because this method cannot foreseen all potential problems and the assessment of the involved persons is subjective in many points. But all together this method is a necessary instrument for the assessment of single steps in the whole planning process.

The challenge for the regulatory affairs manager is to be a good support by developing and carefully implementing the regulatory strategy and by choosing qualified, effective partners inside and outside the company.

The next step from the project team is to summarize the collected information from the regulatory and production department regarding to the proposed change in the primary packaging material. In the proposed meeting with the upper management the results of the regulatory evaluation and the decision analysis should be presented via power point presentation. After this meeting the upper management must decide if this project is enforceable or not.

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ANNEX I

Variant 1 (change from the ampoule to ampoule + ampoule opener)

Regulatory aspect	**USA**	**Canada**	**EU (Germany)**
Variation type	CBE 30	Annual report	Type IA_{IN}
Regulatory costs	are included in the annual product costs	1.020 CAD = 766 €	ca. 310 – 410 Euros
Costs of the one ampoule opener + ampoule	10 – 30 cent for the glass ampoule + 15 € for ampoule opener	10 – 30 cent for the glass ampoule + 15 € for ampoule opener	10 – 30 cent for the glass ampoule + 15 € for ampoule opener
average time required processing the variation	implementation: 30 days after submission	not applicable	implementation: 30 days after submission
Time frame for stability study	not applicable	not applicable	not applicable
Change of secondary packaging Time line for validation of new secondary packaging	3 months	3 months	3 months
Costs of stability study	not applicable	not applicable	not applicable
Time frame for extractable/leachable study	not applicable	not applicable	not applicable
Costs for extractable/leachable study	not applicable	not applicable	not applicable
Time line for clinical trial (suitability study) and costs	not applicable	not applicable	not applicable
costs for clinical trial (suitability study)	not applicable	not applicable	not applicable
Concerned section of CTD	Module 1.3.1 (PIL, SmPC) Module 3.2.P.7	Module 1.3.1 (PIL, SmPC) Module 3.2.P.7	Module 1.3.1 (PIL, SmPC) Module 3.2.P.7 Module 3.2.R

Variant 2 (change from the ampoule to pre-filled syringe with glass barrel)

Regulatory aspect	**USA**	**Canada**	**EU (Germany)**
Variation type	Major change (prior approval supplement)	Supplemental change	Extension application
Regulatory costs	25.760 $ = ca. 20.000 €	20.910 CAD = ca. 16.300 €	ca. 19.200 €
Costs of the one ampoule opener + ampoule	1-2 € for the pre-filled syringe with glass barrel	1-2 € for the pre-filled syringe with glass barrel	1-2 € for the pre-filled syringe with glass barrel
average time required processing the variation	4-6 months	ca. 225 days	ca. 210 days
Time frame for stability study	accelerated and long term testing conditions of 6 months duration on 3 pilot batches of the finished product	minimum 2 pilot scales of 3 months accelerated or 3 months long term testing and under stress conditions (e.g. photostability)	accelerated and long term testing conditions of 6 months duration on 3 pilot batches of the finished product
Change of secondary packaging Time line for validation of new secondary packaging	3 months	3 months	3 months
Costs of stability study	ca. 242.000 € (for a batch size of 180.000 PFS)	ca. 242.000 € (for a batch size of 180.000 PFS)	ca. 242.000 € (for a batch size of 180.000 PFS)
Time frame for extractable/leachable study	ca. 6 months in accelerated and long-term stability study for the leachables time frame for extractable study: 1-2 months	ca. 6 months in accelerated and long-term stability study for the leachables time frame for extractable study: 1-2 months	ca. 6 months in accelerated and long-term stability study for the leachables time frame for extractable study: 1-2 months
Costs for extractable/leachable study	ca. 55.000 €	ca. 55.000 €	ca. 55.000 €
Time line for clinical trial (suitability study) and costs	not applicable	not applicable	not applicable
costs for clinical trial (suitability study)	not applicable	not applicable	not applicable
Concerned section of CTD	Module 1.3.1. (PIL, SmPC) Module 3.2.P.2 Module 3.2.P.3.5 Module 3.2.P.7 Module 3.2.P.8	Module 1.3.1. (PIL, SmPC) Module 3.2.P.2 Module 3.2.P.3.5 Module 3.2.P.7 Module 3.2.P.8	Module 1.3.1. (PIL, SmPC) Module 3.2.P.2 Module 3.2.P.3.5 Module 3.2.P.7 Module 3.2.P.8

Variant 3 (change from the ampoule to pre-filled syringe with plastic barrel)

Regulatory aspect	**USA**	**Canada**	**EU (Germany)**
Variation type	Major change (prior approval supplement)	Supplemental change	Extension application
Regulatory costs	25.760 $ = ca. 20.000 €	20.910 CAD = ca. 16.300 €	ca. 19.200 €
Costs of the one ampoule opener + ampoule	2-3 € for the pre-filled syringe with plastic barrel	2-3 € for the pre-filled syringe with plastic barrel	2-3 € for the pre-filled syringe with plastic barrel
average time required processing the variation	4-6 months	ca. 225 days	ca. 210 days
Time frame for stability study	accelerated and long term testing conditions of 6 months duration on 3 pilot batches of the finished product	minimum 2 pilot scales of 3 months accelerated or 3 months long term testing and under stress conditions (e.g. photostability)	accelerated and long term testing conditions of 6 months duration on 3 pilot batches of the finished product
Change of secondary packaging Time line for validation of new secondary packaging	3 months	3 months	3 months
Costs of stability study	ca. 242.000 € (for a batch size of 180.000 PFS)	ca. 242.000 € (for a batch size of 180.000 PFS)	ca. 242.000 € (for a batch size of 180.000 PFS)
Time frame for extractable/leachable study	ca. 6 months in accelerated and long-term stability study for the leachables time frame for extractable study: 1-2 months	ca. 6 months in accelerated and long-term stability study for the leachables time frame for extractable study: 1-2 months	ca. 6 months in accelerated and long-term stability study for the leachables time frame for extractable study: 1-2 months
Costs for extractable/leachable study	ca. 70.000 €	ca. 70.000 €	ca. 70.000 €
Time line for clinical trial (suitability study) and costs	not applicable	not applicable	not applicable
costs for clinical trial (suitability study)	not applicable	not applicable	not applicable
Concerned section of CTD	Module 1.3.1 (PIL, SmPC) Module 3.2.P.2 Module 3.2.P.3.5 Module 3.2.P.7 Module 3.2.P.8	Module 1.3.1 (PIL, SmPC) Module 3.2.P.2 Module 3.2.P.3.5 Module 3.2.P.7 Module 3.2.P.8	Module 1.3.1 (PIL, SmPC) Module 3.2.P.2 Module 3.2.P.3.5 Module 3.2.P.7 Module 3.2.P.8

Variant 4 (change from the ampoule to auto-injector system + pre-filled syringe)

Regulatory aspect	**USA**	**Canada**	**EU (Germany)**
Variation type	Major change (prior approval supplement)	Supplemental change	Extension application
Regulatory costs	25.760 $ = ca. 20.000 €	20.910 CAD = ca. 16.300 €	ca. 19.200 €
Costs of the one ampoule opener + ampoule	1-2 € for the pre-filled syringe with glass barrel costs auto-injector: up 60 € and higher	1-2 € for the pre-filled syringe with glass barrel costs auto-injector: up 60 € and higher	1-2 € for the pre-filled syringe with glass barrel costs auto-injector: up 60 € and higher
average time required processing the variation	4-6 months	ca. 225 days	ca. 210 days
Time frame for stability study	accelerated and long term testing conditions of 6 months duration on 3 pilot batches of the finished product	minimum 2 pilot scales of 3 months accelerated or 3 months long term testing and under stress conditions (e.g. photostability)	accelerated and long term testing conditions of 6 months duration on 3 pilot batches of the finished product
Change of secondary packaging Time line for validation of new secondary packaging	3 months	3 months	3 months
Costs of stability study	ca. 242.000 € (for a batch size of 180.000 PFS)	ca. 242.000 € (for a batch size of 180.000 PFS)	ca. 242.000 € (for a batch size of 180.000 PFS)
Time frame for extractable/leachable study	ca. 6 months in accelerated and long-term stability study for the leachables time frame for extractable study: 1-2 months	ca. 6 months in accelerated and long-term stability study for the leachables time frame for extractable study: 1-2 months	ca. 6 months in accelerated and long-term stability study for the leachables time frame for extractable study: 1-2 months
Costs for extractable/leachable study	ca. 70.000 €	ca. 70.000 €	ca. 70.000 €
Time line for clinical trial (application study)	ca. 1 year	ca. 1 year	ca. 1 year
costs for clinical trial (application study)	500.00 €	500.00 €	500.00 €
Concerned section of CTD	Module 1 Module 2.5, 2.3, 2.7 Module 3.2.P.2 Module 3.2.P.3.5 Module 3.2.P.7 Module 3.2.P.8 Module 3.2.A.2 Module 5	Module 1 Module 2.5, 2.3, 2.7 Module 3.2.P.2 Module 3.2.P.3.5 Module 3.2.P.7 Module 3.2.P.8 Module 3.2.A.2 Module 5	Module 1 Module 2.5, 2.3, 2.7 Module 3.2.P.2 Module 3.2.P.3.5 Module 3.2.P.7 Module 3.2.P.8 Module 3.2.A.2 Module 5 Module 3.2.R

Variant 5 (change from the ampoule to auto-injector system + glass vials)

Regulatory aspect	**USA**	**Canada**	**EU (Germany)**
Variation type	Major change (prior approval supplement)	Supplemental change	Extension application
Regulatory costs	25.760 $ = ca. 20.000 €	20.910 CAD = ca. 16.300 €	ca. 19.200 €
Costs of the one ampoule opener + ampoule	10-20 cent for one glass vial costs auto-injector: up 60 € and higher	10-20 cent for one glass vial costs auto-injector: up 60 € and higher	30 cent for one glass vial costs auto-injector: up 60 € and higher
average time required processing the variation	4 – 6 months	ca. 225 days	ca. 210 days
Time frame for stability study	accelerated and long term testing conditions of 6 months duration on 3 pilot batches of the finished product	minimum 2 pilot scales of 3 months accelerated or 3 months long term testing and under stress conditions (e.g. photostability)	accelerated and long term testing conditions of 6 months duration on 3 pilot batches of the finished product
Change of secondary packaging Time line for validation of new secondary packaging	3 months	3 months	3 months
Costs of stability study	ca. 242.000 € (for a batch size of 180.000 vials)	ca. 242.000 € (for a batch size of 180.000 vials)	ca. 242.000 € (for a batch size of 180.000 vials)
Time frame for extractable/leachable study	ca. 6 months in accelerated and long-term stability study for the leachables time frame for extractable study: 1 month	ca. 6 months in accelerated and long-term stability study for the leachables time frame for extractable study: 1 month	ca. 6 months in accelerated and long-term stability study for the leachables time frame for extractable study: 1 month
Costs for extractable/leachable study	ca. 30.000 €	ca. 30.000 €	ca. 30.000 €
Time line for clinical trial (application study)	ca. 1 year	ca. 1 year	ca. 1 year
costs for clinical trial (application study)	500.00 €	500.00 €	500.00 €
Concerned section of CTD	Module 1 Module 2.5, 2.3, 2.7 Module 3.2.P.2 Module 3.2.P.3.5 Module 3.2.P.7 Module 3.2.P.8 Module 3.2.A.2 Module 5	Module 1 Module 2.5, 2.3, 2.7 Module 3.2.P.2 Module 3.2.P.3.5 Module 3.2.P.7 Module 3.2.P.8 Module 3.2.A.2 Module 5	Module 1 Module 2.5, 2.3, 2.7 Module 3.2.P.2 Module 3.2.P.3.5 Module 3.2.P.7 Module 3.2.P.8 Module 3.2.A.2 Module 5 Module 3.2.R

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

Berlin, April 2013 Christin Selent-Stier