Assessment of the Quality Part of a Finished Product Dossier of old products
Typical gaps, possible root causes, consequences of gaps

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List of Abbreviations

Abbreviation	Explanation
AI	Acceptable Intakes
IPC	In Process Control
M	Month(s)
MA	Marketing Authorisation
nmt	not more than
PDE	Permissible Daily Exposure
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan: Development plan for a medicinal product which shall be applied on children
QA	Quality Assurance
RA	Regulatory Affairs
SmPC	Summary of product characteristics; contains important information on quality, safety and efficiency of the medicinal product intended for healthcare professionals
SPC	Supplementary Protection Certificate (for patented medicinal products)
TDI	Total Daily Intake
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of Toxicological Concern

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Introduction (Issues under examination)

Everyone in the industry knows that the cost of development of drugs are huge. Not every company has the financial, technical and human resources to do a full preclinical and clinical development of drug products. One option to circumvent the costs of preclinical/clinical studies is to bring generics to the market, so that only bioequivalence has to be shown and a pharmaceutical quality has to be proven. A second option is to in-licence a product developed by another company at a favourable price. Documentation from 3rd parties needs to be carefully checked and might require update, though. A third option is to undergo a general overhaul with a medicinal product developed in the past, possibly perform some changes to make it more attractive for the current market. This requires an update to the pharmaceutical documentation to today's regulatory requirements.

This thesis is intended to discuss CMC dossier updates for products which already have a marketing authorisation (or had a marketing authorisation in the past)

- For old dossiers that shall be reactivated but the product has not been on the market for some time
- For old dossiers that shall be reactivated but the marketing authorisation has been withdrawn due to economic reasons for some time.
- For old dossiers that have not been in the focus of maintenance
- For products from a 3rd party that shall be in-licenced

The focus is on the changes in the regulatory framework of the European Union within the last 20 years (2000- 2020). It will be explained, what the consequences for the pharmaceutical dossiers to be updated are:

- What are typical gaps in old product dossiers?
- Resulting consequences from the gaps

Changes in the regulatory framework have been investigated for each submodule of the quality part of the pharmaceutical documentation ("pharmaceutical dossier", "dossier") for human medicinal products. In favour of the volume of this thesis, advanced therapy medicinal products, biotechnical/biological products, herbals and radiopharmaceuticals are excluded from the scope. For the same reason the active substance part of module 3 (3.2.S) is not included.

Examples and Advice how to update the relevant dossier section of Module 3 (Drug Product) are mainly from own experience unless otherwise mentioned. Not much information on frequent gaps in module 3 from the health authorities of the European Union could be found. This was all the more reason for the choice of the topic of this thesis.

In fact, only a gap overview from the German BfArM from 2006[1] could be found by searching the BfArM website. Most of the gaps listed in this list were already mentioned by Hefendehl et al. in 1999[2]. It was used complementarily to hint on possible gaps in the dossier that cannot be concluded by reviewing the changes in the regulatory provisions only.
The target readers of this thesis are members of the pharmaceutical industry in charge of dossier compilation or providing the required source documents for the update of the documentation.

With Directive 2003/63/EC[3] the description of the CTD format and its contents was introduced. We know it today from the consolidated Directive 2001/83/EC[4], Annex 1 and the Notice to Applicants Volume 2B[5].

[1] BfArM, "Qualitätsdokumentation: häufig auftretende Mängel", D. Fertigprodukt (Drug Product)
[2] Professor Dr. F. W. Hefendehl, Dr. U. A. Muazzam, "Gute regulatorische Praxis, Arzneimittelzulassung Pharmazeutische Qualität", mbh Stuttgart, 1999
[3] Directive 2003/63/EC
[4] Directive 2001/83/EC, Consolidated
[5] European Commission, "European Commission, Notice to Applicants, Volume 2B: Presentation and Format of the Dossier, Common Technical Document (CTD)."

Directive 2003/63/EC entered into force on June 30th, 2003. One of the reasons was that the dossier content and structure should be according to the newly developed ICH (M4) structure. Moreover, the content should be adapted to recent regulatory requirements[6]. Since introduction of Directive 2003/63/EC, only a section for advanced therapy medicinal products has been included in Annex 1 of Directive 2001/83/EC. The Notice to Applicants, Volume 2B from 2008 provides more information on the content of the dossier modules than Annex 1 of Directive 2001/83/EC. However, the last update to the module 3 part of this document has been done by July 2004[7]. Since that, many provisions for specific types of substances/ products, manufacturing processes, product aspects have been developed. Those will be discussed in the following chapters.

It shall be noted, though, if it is known at which time the regulatory documentation was created, this does not necessarily mean that the documentation is up to date with the regulatory requirements of that time or with general regulatory/ scientific requirements. Possibly this has not been recognized by the health authority at that time due to various reasons. An example are Type IA variations, or notifications before the EU Regulation 1234/2008[8] was introduced. They are/ may have been checked only for completeness of the documentation, not for the content. In addition, authority assessors can be prone to human error and oversee a gap.
Thus, the reader of this thesis should have some basic regulatory and scientific knowledge in order to be able to update the product dossiers and recognize gaps that might exist and do not result from non-compliance with the regulatory changes of the last 20 years when he/she intends to update an old product dossier.

[6] European Commission, “Directive 2003/63/EC", reasons (2) and (3) (page 1)
[7] European Commission, “European Commission, Notice to Applicants, Volume 2B: Presentation and Format of the Dossier, Common Technical Document (CTD).”, first page
[8] European Commission, "Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products", Consolidated

Results

General

In order to explain how the investigation was done, the following chapters have been structured in this way: First, the basic (general) provisions, which have changed in the last 20 years have been briefly introduced. Basic provisions are interpreted as provisions that are either provided in the form of an instruction/ recommendations what to include in the relevant dossier parts by the authorities. Alternatively, basic provisions can be texts that apply to a large share of medicinal products. In the second case the definition as “basic provisions” has been justified.

“Basic provisions” in this context is meant irrespective of the legal status of the provision. They can include legally binding provisions, such as regulations, directives and the texts of the European Pharmacopoeia* (Ph.Eur.). Recommendatory provisions are also included in basic provisions, such as guidelines (e.g. guideline on the manufacture of finished dosage form).

Second, specific provisions for certain populations and subgroups of medicinal products and how they have developed, are given, if applicable.

Finally, the results are presented as described in the introduction. Details on the comparison of the basic provisions, which fall in the group “instruction/ recommendation what to include in the relevant dossier parts” as described above are included in the annex A to this thesis.

This thesis has been structured according to the CTD modules. Recommendations and other comments were also addressed with reference to the CTD structure. However, the CTD structure has been introduced in the European Union with the Directive 2003/63/EC[6]. It became mandatory for new marketing authorisations in July 2003 and was recommended to reformat the dossier when variations are submitted[9]. Parts of the dossier or even the whole old product dossier might be still in the previous NTA format. The EU Commission Notice to Applicants, Volume 2B provides a correlation table which helps to find information in the previous NTA format. It has been copied to this thesis for Module 3 in “Annex C Correlation Table for the EU CTD and NTA format (Module 3)” for facilitating dossier updates[10].

*the mandatory scope of Ph.Eur. includes the following chapters: chapter 1 General Notices, chapter 6 General Monographs and all chapters with a higher number than 6 plus the monographs A-Z. The chapters 2-5 are mandatory when they are referred to in a monograph[11].

[9] EU Notice to Applicants, Volume 2B, Introduction, subchapters "Presentation of European Marketing Authorisation Applications" and "Reformatting of dossiers of already authorised products"
[10] European Comission, Notice to Applicants, Volume 2B: Presentation and Format of the Dossier, Common Technical Document (CTD)", Corrleation table EU CTD vs NTA, page 28
[11] EDQM, Ph.Eur. Online, 10.2, 1. General Notices 07:2014/10000, 1.1 General Statement, Introduction Text and section "General monographs"

3.2.P.1 Description and Composition/ of the Drug Product

Types of regulatory provisions

Basic provisions on the content of module 3.2.P.1

The following provisions give some general instruction on the content of 3.2.P.1 today:

Table 1: basic regulatory framework for 3.2.P.1 Composition, sorted by publication date

Type and Title of regulatory framework	**Date**
EU Directive 2001/83/EC original version from 2001 without amendments[12], Annex 1, Part 2, Section A, Subsections 1-3	Published on 28.11.2001 Effective: 18.12.2001
2nd Amendment to EU Directive 2001/83/EC: 2003/63/EC[3] Annex I, Section 3.2.2.1	Published on: 27.06.2003 Effective: 01.07.2003
EU Commission Notice to Applicants (NTA), Volume 2B, 2008[5], Section 3.2.P.1	May 2008 Info on Module 3 is from July 2004

Furthermore, the "Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product" is also included in the basic provisions. Usually medicinal products contain excipients. This guidance, while mainly focussed on 3.2.P.4, gives some information on 3.2.P.1 as well.

Table 2: complementary regulatory framework for 3.2.P.1 Composition

Type and Title of regulatory framework	**Date**
EMEA Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product (Rev.2)[13] EMEA/CHMP/QWP/396951/2006	Published on: 19.06.2007 Effective on: 01.01.2008

No specific provisions in the frame of the scope of this thesis could be identified for 3.2.P.1.

Development of the regulatory provisions for module 3.2.P.1

To sum up, there were no changes to the regulatory framework that could be considered substantial. The following should be mentioned, though:

The requirement to include the function of the components into the composition has only been established in 2003 with the 2nd amendment of Directive 2001/83/EC (2003/63/EC). However, this is more of a formal issue in very old dossiers: The information on the function should be available in the development part of the pharmaceutical dossier. The CPMP Note for Guidance on development pharmaceutics from 1998[18] already requests this information in 3.2.P.2.1.2 (refer to Annex A, 3.2.P.2 Pharmaceutical Development).

[12] European Parliament and Council, "Directive 2001/83/EC Unconsolidated
[13] EMEA CHMP, "Guideline on excipient in the dossier for application for marketing authorisation of a medicinal product", EMA/CHMP/396951/2006

The same applies to overages. It is mentioned in Directive 2003/63/EC, whereas it had not been mentioned in Directive 2001/83/EC (first version, unconsolidated). But this information should be already included in the development section, too (3.2.P.2.2.2, refer to Annex A, 3.2.P.2 Pharmaceutical Development).

With the introduction of the NTA Volume 2B it was a new recommendation to provide the information on the quality standard. This information can be found in the active substance documentation (3.2.S.4.1, the specification provides usually information on the quality standard)[14] for the active substance. For excipients it can be found in the module 3.2.P.4.1[15] or for older dossiers in section Part II C.1.1 and C.1.2[16].

Before introduction of the "Guideline on excipients in the dossier […]" in 2007, the need for a description of the quantitative and qualitative composition has not been explicitly mentioned for mixtures of excipients (e.g. flavour mixtures, colorant mixtures, lubricants). Only for flavour mixtures it is sufficient to provide the qualitative composition only. Such mixtures are usually non-compendial. For some mixtures not commonly used in the pharmaceutical industry, receipt of that information might not be easy to get. This applies in particular if the excipient is purchased in small quantities only. Or it can be difficult when no unambiguous supplier agreement is in place. The manufacturers are possibly not willing to reveal the details because of the risk of imitator products. A strict supplier agreement can prevent this issue. But what happens if all measures taken to persuade the supplier show no success? It might be a possibility that the excipient manufacturer reveals the composition to the health authority only. However, this should be discussed with the authority beforehand. The manufacturer of the excipient still needs to assure the absence of any substance subject to inclusion in the labelling of the medicinal product. Further quality documentation (e.g. information on the use of residual solvents) should be provided, too. If a comparable excipient from another supplier can be found, it might also be an option to switch supplier. Yet the consequences would be to perform the relevant development studies again, e.g. compatibility, functionality of the excipient and stability studies for most excipients. Additionally, it can be necessary to show that the finished product analytical method is still specific for the relevant tests and the new excipient does not interfere[17]. Module 3.2.P.4 might need to be updated as well, e.g. the description of the excipients, identification test.

The names for compendial active substance(s) and excipients should be acc. to the pharmacopoeia. Further it should be checked if the quality of the excipient is specific enough, e.g. for Povidone there are several viscosity grades expressed by their K-value.

[14] European Commission, "Directive 2003/63/EC", Annex 1, Part I, 3.2.1.4
[15] European Commission, "Directive 2003/63/EC", Annex 1, Part I, 3.2.2.4 a)
[16] European Parliament and Council, "Directive 2001/83/EC Unconsolidated, Annex I, Part 2, C.1.1 & C.1.2
[17] EU Commission Variation Classification Guideline, Annex, B.II.a.3

3.2.P.2 Pharmaceutical Development

Types of regulatory provisions

Basic provisions on the content of the module for pharmaceutical development

The following provisions give some general instruction on the content of 3.2.P.2 today:

Table 3: basic regulatory framework for 3.2.P.2 Pharmaceutical Development, sorted by publication date

Type and Title of regulatory framework	**Date**
CPMP Guideline: Note for Guidance on development pharmaceutics CPMP/QWP/1551/96[18]	Published on: 28.01.1998 Effective: July 1998
EU Directive 2001/83/EC original version from 2001 without amendments[12]	Published on 28.11.2001 Effective: 18.12.2001
2nd Amendment to EU Directive 2001/83/EC: 2003/63/EC[3]	Published on: 27.06.2003 Effective: 01.07.2003
EU Commission Notice to Applicants (NTA), Volume 2B, 2008[5]	May 2008 *Info on Module 3 is from July 2004*
ICH Guideline Q8(R2*) "Pharmaceutical Development" EMA/CHMP/ICH/167068/2004 [19] **(First, unrevised version effective on 10.11.2005, Annex added in 2008 (R1), only minor corrections performed to R2)*	Published on: 01.06.2009 Effective on: 01.05.2006

In addition, the regulatory framework listed in Table 4 is considered to belong to the basics of the pharmaceutical development:

Table 4: complementary regulatory framework for 3.2.P.2 Pharmaceutical Development, sorted by publication date

Type and Title of regulatory framework	**Date**
EMEA CPMP Note for guidance on the investigation of bioavailability and bioequivalence (replaced) CPMP/EWP/QWP/1401/98[20]	Published: 26.07.2001 Effective: 01.01.2002
EMEA CHMP Reflection Paper: Formulation of choice for the paediatric population[21]	Published on: 28.07.2006 Effective on: 21.09.2006
EMEA Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product (Rev.2) EMEA/CHMP/QWP/396951/2006[13]	Published on: 19.06.2007 Effective on: 01.01.2008
CPMP Guideline on the Investigation Bioequivalence[22]	Published: 29.01.2010 Effective: 01.08.2010
EMA Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2[23]	Published on: 31.07.2013 Effective on: 15.02.2014

[18] EMEA-CPMP, "CPMP Note for Guidance on Development Pharmaceutics"
[19] ICH Expert Working Group, "ICH Q8(R2) Pharmaceutical Development"
[20] EMEA CPMP Note for guidance on the investigation of bioavailability and bioequivalence (replaced)
[21] EMEA-CHMP, "Reflection Paper: Formulations of Choice for the Paediatric Population "
[22] EMA, "Guideline on Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1."
[23] EMA, "EMA Guideline on Pharmaceutical Development of Medicines for Paediatric Use Rev. 2."

	(Draft of first version published in 2011)
EMA Reflection Paper on the pharmaceutical development of medicines for use in the older population (Draft) EMA/CHMP/QWP/292439/2017[26]	Published on: 01.08.2017
EMA Guideline on the manufacture of the finished dosage form EMA/CHMP/QWP/245074/2015, Revision 1, Chapter 4.3 General aspects [24]	Published: 14.08.2017 Effective: 14.02.2018

The reflection paper and guideline for medicinal products for paediatric use are relevant for most medicinal products. It is generally obligatory to authorize medicinal product for the paediatric population (with some exceptions)[25].

The age group of elderly patients has only recently been in the focus of pharmaceutical regulators. So far, a draft reflection paper was published. Medicines targeted to the elderly become more and more important, since a majority of patients belong to this age group. Therefore, the pharmaceutical development should include criteria derived from the special needs of this age group (see introduction to the reflection paper[26]).

Most medicinal products contain excipients. Thus it is obvious that the EMEA "guideline on excipients in the dossier for application for marketing authorisation of a medicinal product"[13] is a standard guideline for the description of the development of medicinal products in 3.2.P.2.

The so called "Bioequivalence Guideline" is relevant for systemic acting dosage forms and was mainly written for immediate release dosage forms[27]. That encompasses a large percentage of medicinal products.

Paediatric development:

All new marketing authorisations since July 26th, 2008 must include the outcome of studies performed based on an approved paediatric investigation plan (PIP). Alternatively, a waiver or deferral must be requested and approved by the authority. The same applies since January 26th, 2009 if the medicinal product is already authorised and protected by a supplementary protection certificate. Another applicability reason is a patent that is eligible to apply for a supplementary protection certificate. Eligibility is further given in case of new indications, pharmaceutical forms and administration routes. Exceptions to this rule are generic products, well-established use products, authorised homeopathic products and registered (traditional) herbal medicinal products[25].

The quality expert should therefore check if there is a need for development data on the paediatric formulation to be included in the dossier. When this can be answered with yes, it should be checked if the data are complete.

How can a check on the need for paediatric development data in module 3.2.P.2 be performed?

Step 1 involves checking of the plans that the applicant has with the medicinal product. In the following cases (see Figure 1: Business strategy- paediatric development[19]), information on the development of medicinal products for paediatric use usually has to be given:

- new applications for marketing authorisations are planned (Case 1, Case 3)
- and/or changes such as new indications/ new pharmaceutical forms/ new administration routes (Case 4) are planned

[24] EMA Guideline on the manufacture of the finished dosage form, Revision 1
[25] "Regulation EC/1901/2006 on Medicinal Products for Paediatric Use." Articles 7-9
[26] EMA, "EMA Draft Reflection Paper on the Pharmaceutical Development of Medicines for Use in the Older Population"
[27] EMA, "Guideline on Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1.", 2. Scope

- and no waiver or deferral has been granted (Article 7b, 7c, 7d, EC/1901/2006[25])

If the medicinal product of interest falls under one of the exceptions to this rule has to be investigated in a second step (refer to Figure 1: Business strategy- paediatric development[19] below). When the product is an exception according to Regulation 1901/2006, Article 9[25] no paediatric studies must be provided for the application to the authority.

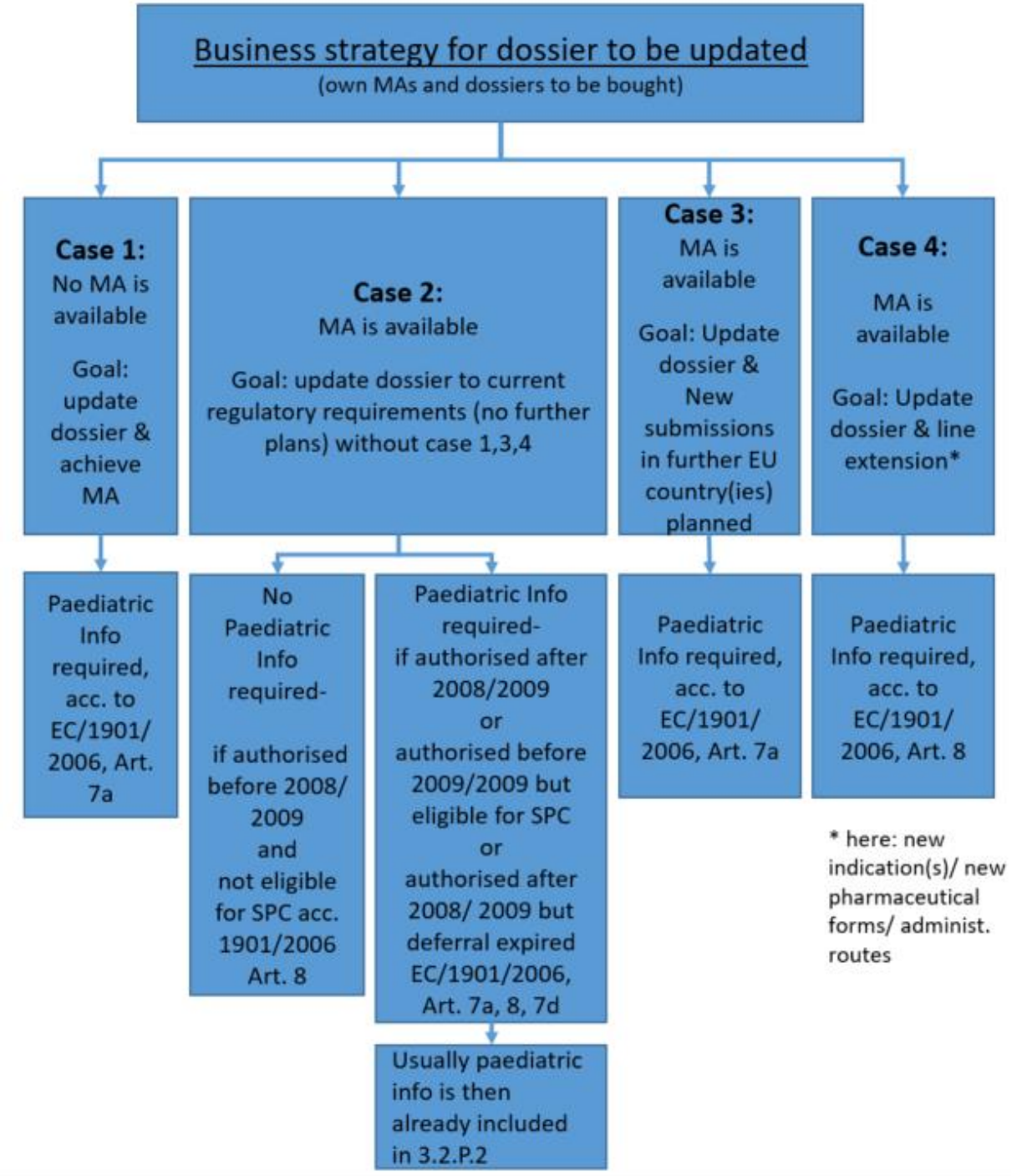

Figure 1: Business strategy- paediatric development[19]

MA= Marketing Authorisation, SPC= Supplementary Protection Certificate

On the other hand it should go without saying that medicinal products on the market authorised for the use on children should also be appropriately developed for this intended use- even if not in scope of directive EC/1901/2006[25]. This includes the development of the quality characteristics and is supported by directive 2001/83/EC, Article 23 (1), (2), (3)[4]. It says that the marketing authorisation holder has to reassess the medicinal product and introduce changes to comply with the technical and scientific status after receipt of the marketing authorisation. In addition, the CHMP "reflection paper: formulations of choice for the paediatric population" describes the importance of an appropriate development of a medicinal production targeted to its use in the respective age group as part of its introduction (section 1.1)[21].

Hence, for product dossiers of products authorised before 2008/2009 and having no marketing authorisation anymore it should be acted with caution. It shall be checked, if the development part of the dossier already includes information on the suitability of the formulation/ pharmaceutical form/ administration route for children. This should be checked for all age groups that are not excluded in the SmPC. The same applies for products with marketing authorisation eligible for application for a supplementary protection certification and in case a line extension is planned.

In addition, even if information on the paediatric development is already included, it should be checked if this data is still valid or could be amended. Such elaboration can be done based on the experience gathered with the product[28].

Development of medicines for the elder population

The draft reflection paper on the pharmaceutical development of medicines for use in the older population, published in 2017, is not final yet. Its principles given for the elderly population should be considered in any update of a marketing authorisation dossier (new applications and variations, all application types)[29], though. After all, the reflection paper could become final within the dossier preparation period or the review period of the health authority. The end of consultation was already in January 2018), so the reflection paper could be finalised any time.

Investigation of bioequivalence of immediate release formulations with systemic action

The guidance was primarily written for generic applications but can be also applied for all other types of applications (Herbal medicinal products excluded). It is not only relevant for marketing authorisation applications. Application is also possible for comparative studies of different formulations within development or for line extensions. Furthermore, the principles given can be applied for variations to marketing authorisations[30], e.g. in case of manufacturing process changes. The previous note for guidance on the investigation of bioavailability and bioequivalence was revised by the guideline on the investigation of bioequivalence in 2010. It not only describes the provisions on bioequivalence studies but also when waivers can be used. Additionally, the guideline gives advice on other medicinal products excluded in the scope in Appendix II (e.g. locally acting locally applied products, modified release forms). For this thesis in particular the provisions on in-vitro-dissolution studies are of interest.

Guideline on the manufacture of the finished dosage form

The Guideline on the manufacture of the finished dosage form contains in chapter 4.3, section General aspects some fundamental information on the development of manufacturing processes and controls. Those are applicable to section 3.2.P.2.3 for all medicinal products.

Specific provisions for 3.2.P.2

An overview over further regulatory framework to be taken into consideration is provided in Table 5. They are all specific for certain manufacturing processes/ substances/ pharmaceutical forms/ application

[28] EMA, "EMA Guideline on Pharmaceutical Development of Medicines for Paediatric Use EMA/CHMP/QWP/805880/2012 Rev. 2, Scope, paragraph 3."
[29]EMA, "EMA Draft Reflection Paper on the Pharmaceutical Development of Medicines for Use in the Older Population EMA/CHMP/QWP/292439/2017", Introduction
[30] European Medicines Agency, "Guideline on Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1.", sections 1.2, 1.3, 2

or delivery systems or medicinal product types. Some of them are common (e.g. topical application), others less common (e.g. intravenous medicinal products containing active substances solubilised in micellar systems). Due to the limited volume of this master thesis they will not be further explained, but are listed here in order to make the reader aware of further reading on the provisions in 3.2.P.2.

Table 5: Regulatory framework for specific manufacturing processes/ pharmaceutical forms/ delivery systems, sorted by publication date

Type and Title of regulatory framework	**Date**
EMA, The use of ionising radiation in the manufacture of medicinal products 3AQ4a[31]	Published: 01.12.1991 Effective: 01.07.1992
EMEA Note for guidance on inclusion of antioxidants and antimicrobial preservatives in medicinal products CPMP/CVMP/QWP/115/95[32]	Published: 08.07.1997 Effective: 01.01.1998
EMEA Concept Paper on the development of a committee for medicinal products for human use (CHMP) guideline on dosing delivery of injectable liquids EMEA/CHMP/QWP/1888/04[33]	Published: 02.06.2004
EMEA Guideline on suitability of the graduation of delivery devices for liquid dosage forms (Draft) CHMP/QWP/178621/2004[34]	Published: 18.02.2005
EMA Guideline on the pharmaceutical quality of inhalation and nasal products EMEA/CHMP/QWP/49313/2005[35]	Published: 21.06.2006 Effective: 01.10.2006
EMEA Guideline on medicinal gases: Pharmaceutical documentation (including recommendation on non-clinical safety requirements for well established medicinal gases) (Rev. 1) CPMP/QWP/1719/00 Rev 1[36]	Published: 09.07.2008 Effective: 01.11.2008
EMEA Guideline on radiopharmaceuticals EMEA/CHMP/QWP/306970/2007[37] *replaces 3AQ20a from 1991*	Published: 26.11.2008 Effective: 01.05.2009
EMA Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems[38]	Published: 20.03.2012
EMA Guideline on quality of oral modified-release products EMA/CHMP/QWP/428693/2013[39] *replace the previous guideline from 2000 ("Note for guidance on quality of modified release products: A: oral dosage forms B: transdermal dosage forms section I (quality)*	Published: 31.07.2014 Effective: 31.01.2015
EMA Guideline on quality of transdermal patches EMA/CHMP/QWP/608924/2014[40] *replaces the previous guideline from 2000 ("Note for guidance on quality of modified release products: A: oral dosage forms B: transdermal dosage forms section I (quality)*	Published: 16.12.2014 Effective: 17.06.2015
EMA Concept Paper Development of a guideline on quality requirements of medicinal products containing a device component for	Published: 16.02.2017

[31] EMA, The use of ionising radiation in the manufacture of medicinal products 3AQ4a
[32] EMEA Note for guidance on inclusion of antioxidants and antimicrobial preservatives in medicinal products
[33] EMEA Concept Paper on the development of a committee for medicinal products for human use (CHMP) guideline on dosing delivery of injectable liquid
[34] EMEA Guideline on suitability of the graduation of delivery devices for liquid dosage forms (Draft)
[35] EMA Guideline on the pharmaceutical quality of inhalation and nasal products
[36] EMEA Guideline on medicinal gases: Pharmaceutical documentation (including recommendation on non-clinical safety requirements for well established medicinal gases) (Rev. 1)
[37] EMEA Guideline on radiopharmaceuticals
[38] EMA Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems
[39] EMA Guideline on quality of oral modified-release products
[40] EMA Guideline on quality of transdermal patches

Type and Title of regulatory framework	Date
delivery or use of the medicinal product EMA/CHMP/QWP/BWP/661488/2016[41]	
EMA Concept Paper on the revision of the guideline on the pharmaceutical quality of inhalation and nasal products (Draft) EMA/CHMP/QWP/115777/2017[42]	Published: 22.03.2017
EMEA Guideline on quality and equivalence of topical products (Draft) CHMP/QWP/708282/2018[43]	Published: 14.12.2018
EMA Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container EMA/CHMP/CVMP/QWP/850374/2015[44] *replacing the CPMP Guideline: Note for Guidance on development pharmaceutics- Annex on decision trees for selection of sterilisation methods from 1999 CPMP/QWP/054/98 Corr*	Published: 08.03.2019 Effective: 01.10.2019
EMA Guideline on the quality requirements for drug-device combinations (Draft) EMA/CHMP/QWP/BWP/259165/2019[45]	Published on: 03.06.2019

Development of the regulatory provisions for module 3.2.P.2

The pharmaceutical product dossier to be updated should be checked for the following changes that were introduced to the regulatory law within the last 20 years: Refer also to Annex A Comparison tables on regulatory provisions, 3.2.P.2 Pharmaceutical Development for an overview table of the basic regulatory framework (see table Table 3: basic regulatory framework for 3.2.P.2 Pharmaceutical Development, sorted by publication date)

3.2.P.2.1.1 Components of the Drug Product- Drug Substance

No substantial changes have been made over the last 20 years for this section concerning the topics "physico-chemical characteristics" and "compatibility of the active substance with the excipients".

3.2.P.2.1.2 Components of the Drug Product- Excipients

Justification of quantities used

In 2003 with the 2nd amendment of the EU directive 2001/83/EC in 2003 (Annex 1, 2003/63/EC[3]), the justification of the quantity of each excipient in the formulation has been introduced as a requirement. This has not been included in the Note for Guidance on development pharmaceutics of 1998[18]. Within pharmaceutical development usually studies with different excipients and different quantities are performed. Information on the justification of the quantities therefore can be found in the development data, e.g. in the development report. If such data are not available anymore, it can be tried to reconstruct the choice of the quantities theoretically. Consulting an experienced development expert and scientific literature for formulations with excipients containing common substances and a common manufacturing process is recommended. However, this approach might not be accepted by the health authorities and it would be preferable to create data by performing development studies.

Proof of function

Acc. to the ICHQ8 Guideline from 2005/2006 the function of the excipients must be proven. This has not been mentioned as a must in the previous regulatory documents from the authorities. If currently no explanation is given in the old product dossier, check the controls done on the product. For example, when an antimicrobial preservative agent is added as excipient, then the antimicrobial preservative

[41] EMA Concept Paper Development of a guideline on quality requirements of medicinal products containing a device component for delivery or use of the medicinal product
[42] EMA Concept Paper on the revision of the guideline on the pharmaceutical quality of inhalation and nasal products (Draft)
[43] EMEA Guideline on quality and equivalence of topical products (Draft)
[44] EMA Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container
[45] EMA Guideline on the quality requirements for drug-device combinations (Draft)

effectiveness must be demonstrated. Acc. to ICHQ6A[46], which was already effective in 1999, this should be done for oral liquids throughout the shelf life. Unless replaced by dissolution, disintegration must be tested for solid dosage forms and can prove the effectiveness of a disintegrant[47]. For old dossiers, data are available, if those tests have already been included in the control strategy (in this case: final product specification).

For some excipients covered by a monograph of the Ph.Eur., tests were included in the chapter 5.17 functionality related characteristics of excipients, which have been published September 2006. One example is Lactose monohydrate, which is a commonly used filler. The tests particle size distribution and bulk and tapped density were added, if Lactose is used as a filler/ diluent in solid dosage forms[48]. The tests degree of polymerisation, crystallinity, particle size distribution and powder flow were added to the monograph of Cellulose, microcrystalline for usage as filler/ diluent/ disintegrant[49]. If the Ph.Eur. monograph contains such tests, it should be evaluated if they are relevant for the medicinal product dossier. The available development data (e.g. development report, information gathered from changes, technical transfers, etc) should be reviewed for information on these characteristics, experienced manufacturing and development experts for the relevant product could be asked as well, if available.

New introduction of guideline on excipients

In 2007 the EMEA Guideline on excipients in the dossier for Application for Marketing Authorisation of a medicinal product has been published and became effective in 2008. Whereas the guideline mainly describes the recommendations on chapter 3.2.P.4, it also gives guidance on the choice of excipients in the formulation: For example, for medicinal products applied on children special attention must be paid on the excipients, namely that they are not harmful, e.g. azo dyes and other synthetic colouring agents should not be added just for the appearance of medicinal products. It is also emphasized that a stringent control of permeation is required for transdermal medicinal products due to their influence on the in-vivo-performance.

Colorants and Flavours

Colorants and Flavouring agents included many years ago in the composition should be checked for their compliance with the current regulatory framework. This is of special importance, as the provisions has changed a couple of times during the last years.

a) Colorants

The CHMP “Guideline on Excipients in the Dossier for Application for Marketing Authorisations of a Medicinal Product”, coming into effect in January 2008[13], lists the following Directives for colorants: 78/25/EEC[50] and/or 94/36/EC[51] as well as 95/45/EC[52] for specifications in chapter 4.3. In the previous version from 1994 (3aQ9a), the respective regulatory framework had not been referenced yet, it was just mentioned that EU foodstuff legislation is applicable[53].

Directive 78/25/EEC on the approximation of the laws of the Member States relating to the colouring matters was replaced in 2009 by Directive 2009/35/EC[54] on the colouring matters which may be added to medicinal products (recast) and is still in force.

[46] ICH Q6A, chapter 3.3.2.2 d).
[47] ICH Q6A , chapter 3.3.2.1 b)
[48] Ph.Eur. 5.7, Monograph Lactose Monohydrate, 04/2007:0187
[49] Ph.Eur. 5.7, Monograph , Cellulose, microcrystalline 04/2007:0316
[50] Directive 78/25/EEC
[51] Directive 94/36/EC
[52] Directive 95/45/EC
[53] EU Guideline "Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product" 3AQ9A (based on Directive 75/318/EEC), Annex, Points 7 & 8
[54] EU Directive 2009/35/EC

Directive 94/36/EC on colours for use in foodstuffs was replaced in 2010 by EC/1333/2008[55] on food additives, which is still in force. Regulation EC/1333/2008 has been changed 87 times since it was published, therefore it is recommended to regularly check this directive.

Directive 95/45/EC for specific purity criteria concerning colours for use in foodstuffs was replaced in 2009 by Directive 2008/128/EC[56], which has been repealed, too in 2012. Regulation 231/2012 replaced the previous Directive 2008/128/EC[57] and is valid today. But has been changed over the years.

Whereas Directive 2009/35/EC provides an overview over the requirements on colorants, Regulation EC/1333/2008 includes a positive list of all colorants. Regulation 231/2012 adds specifications for each colorant, see graph on the next page (Figure 2: Development of the regulatory framework on colorants).

[55] EU Directive EC/1333/2008 (consolidated)
[56] EU Directive 2008/128/EC
[57] EU Regulation (EU) No 231/2012 (consolidated version)

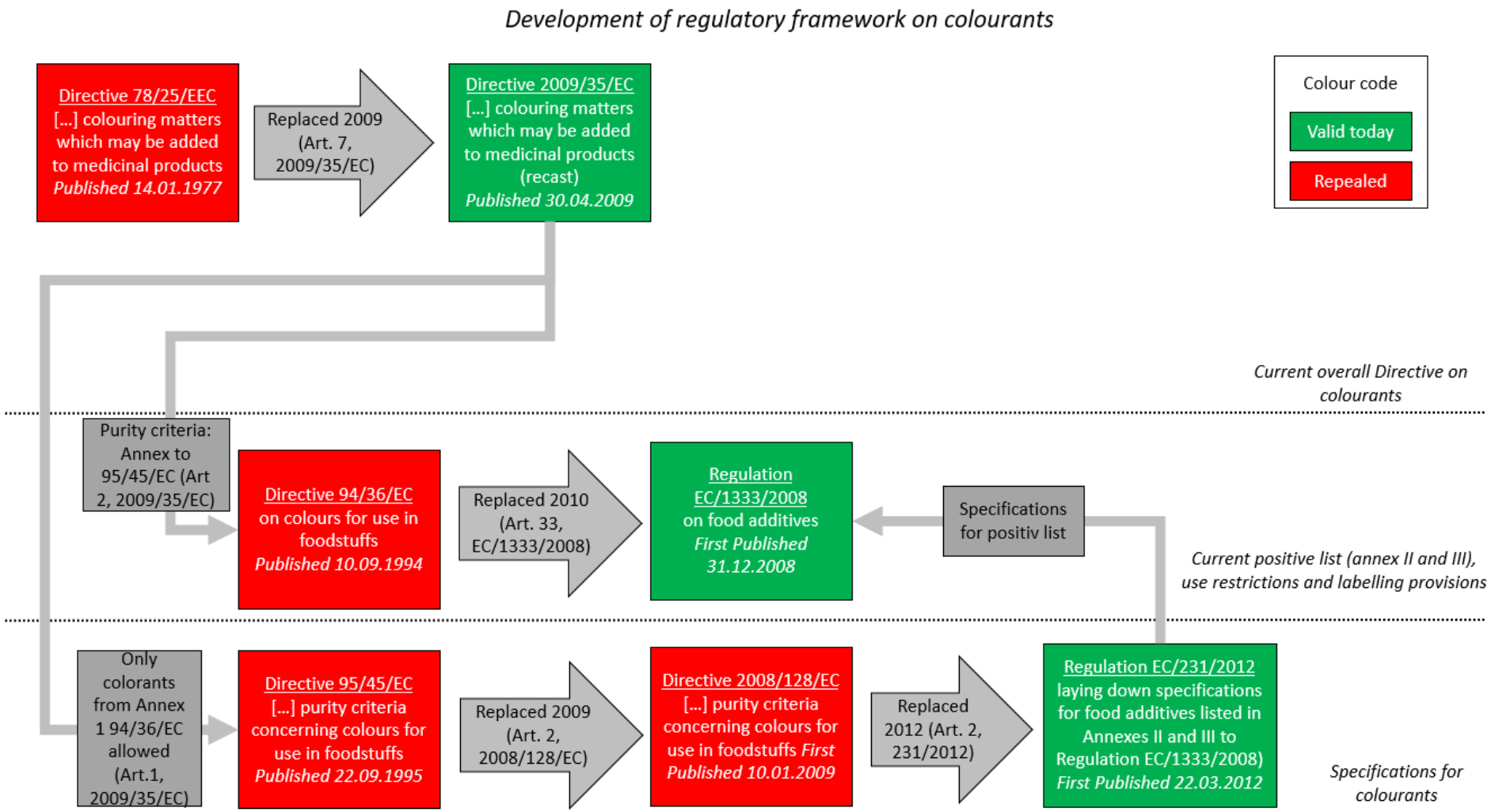

Figure 2: Development of the regulatory framework on colorants

b) Flavouring Agents

For flavours the CHMP "Guideline on Excipients in the Dossier […]" (January 2008[13]) merely refers to recommendations on purity, which have been internationally accepted by FAO or WHO for food. However, acc. to the "EU variation classification guideline"[58], new flavours must comply with Council Directive 88/388/EEC[59].

This Directive has been replaced in 2011 by Regulation EC/1334/2008[60] (still in force). The regulation includes in annex 1 a positive list of all flavours allowed in the EU in foods and the requirements on using flavours and provisions on labelling (see article 1). In consequence it is somewhat unclear if other flavours than listed in EC/1334/2008 would be accepted if compliant with FAO or WHO rules.

c) Consequences

Some colourants/ flavours used in the past, which were in compliance with the previous regulatory requirements may not be in compliance with current regulatory requirements anymore. In this case, they have to be replaced. One example is the flavour furan-2(5H)-one (FL No 10.066), which was found to be genotoxic and has been removed from the list with the 24th revision of EX/1334/2008[61]. This could have an influence on the patient compliance of the product and should be clarified with marketing. Additionally, appropriate studies e.g. on compatibility, influence on the specificity of analytical methods and stability have to be performed and might cause delays in the dossier update.

Completeness of excipients used

Furthermore, in the ICH Q8 Guideline it has been pointed out for the first time that all substances used in the manufacturing process have to be described in the development section of the dossier. Examples that may not have been mentioned before, are so called technical aids, e.g. magnesium stearate used as lubricant in the tabletting process, nitrogen gassing for preventing of contamination or oxidation of pharmaceutical products and medium chain triglycerides used as lubricants for gelatine bands used for soft gelatine encapsulation.
The master batch records can be checked as well as filled out batch records, if these substances are used in the pharmaceutical production. However, it is advisable to also review production SOPs and talk with experienced production staff in order to reveal the use of such substances. This is due to the fact that not always all process steps are described in the master batch record, but partially in SOPs. In addition, sometimes technical aids are not used for all batches, only if during production the staff finds there is a need for them (the circumstances must then be described in the dossier). Hence the information might not appear in the master batch record or the batch record of this particular batch(es) that were under review. Following EU GMP Part I Chapter 4 Documentation[62], section 4.17 and 4.18 the master document should actually contain all this information, yet it needs to be considered when those manufacturing instructions have been updated and checked for the last time.

Applicability for certain age groups

a) Suitability for paediatric use

The CHMP Reflection Paper: Formulation of choice for the paediatric population from 2006 discusses the suitability of different application routes, excipients (e.g. safety, taste), different illnesses, age groups. Some years later, in 2011, the draft EMA Guideline on pharmaceutical development of medicines for paediatric use was published and became effective in 2014. The guideline describes that

[58] EU "Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 […]" (so called variation classification guideline, see references), annex, B.II.a.3, condition 5
[59] Directive 88/388/EEC of 22 June 1988 (replaced 20.01.2011)
[60] Regulation (EC) No 1334/2008
[61] Regulation (EU) 2019/799, reason (7) of the introduction
[62] European Commission, Eudralex, Volume 4 Good Manufacturing Practice, EU GMP Part I, Module 4 Documentation, 4.17 and 4.18

all aspects of the formulation must be discussed for the application of children. For example, it must be explained why the excipients are required and if they are non-hazardous specifically for children[63].

b) Suitability for the elderly population

Since 2017 the draft Reflection paper on the pharmaceutical development of medicines for use in the older population has been published. It points out that excipients should be also appropriate for elderly people, e.g. sugars could increase the blood sugar level, or the use of colourants might be beneficial for differentiation of medicinal products in case of multiple-drug-use[64].

c) Consequences

Reviewing the application route and composition in favour of the age group might lead in the worst case e.g. to a change of the dosage form (line extension) or a change of the composition. This would require the generation of supportive data, potentially be costly and will take time before the data are available for a dossier update.

3.2.P.2.2.1 Drug Product- Formulation Development

All critical quality attributes of the medicinal product must be identified and described. This has been pointed out in the ICH Q8 Guideline from 2005/2006 but has not been mentioned in the previous guides. Critical quality attributes, their description and justification are an essential part of the drug product development.

Because of the Notice to Applicants from 2004/2008, it is recommended to describe the differences of the formulations used during clinical studies and the formulation used now. In addition, results from comparative in-vitro and in-vivo studies should be explained, if applicable.

With the introduction of ICH Q8 all special designs must be listed and justified, which was not the case before. An example would be scored tablets, the purpose of the break mark must be explained. When it shall be used to apply half or quarterly doses, e.g. for paediatric use, it must be shown that breaking of the tablet leads to equal halves/ quarters of equal masses. 30 Tablets must then be taken and tested according to the instructions in the Ph.Eur. dosage form monograph for tablets (No. 0478), test "Subdivision of tablets"[65].

According to the EMA Guideline on pharmaceutical development from 2014, the suitability of the formulation for the illness, intended dosage scheme and duration of the use of the medicinal product must be discussed specifically for children. For tablets a break could be applied if a smaller dose is needed for children, or it must be evaluated if the tablet could be chewed/ crushed in order to ease swallowing for small children. Another example is the prevention of adding too much volume of liquid parenterally to the smaller systems of babies[63].

Devices used for measuring and application must be also suitable for the doses for children or for application on the child[63] (e.g. nasal spray: the device should be suitable for the smaller nostrils of children).

Acc. to the draft reflection paper from 2017, the route of administration chosen, and the pharmaceutical form must be discussed in the context of the use for the elderly population. For example, they might have trouble swallowing uncoated tablets because they stick to the mucosa due to a lack of saliva compared to younger people. With liquid preparations intended for oral use it might be

[63] EMA, "EMA Guideline on Pharmaceutical Development of Medicines for Paediatric Use Rev. 2.", chapter introduction, 6.1, 6.2, 6.2.1
[64] EMA, "EMA Draft Reflection Paper on the Pharmaceutical Development of Medicines for Use in the Older Population.", chapter 2.5
[65] EDQM, Ph.Eur. 10.2, Dosage Forms, Tablets, 01/2018:0487 (online)

hard for older people with dexterity issues to measure the intended dose[66]. There are many more examples for each pharmaceutical form given in the reflection paper.

The general need for forced degradation studies of the drug product is not clearly mentioned, save in the ICH Q2(R1) Guideline for analytical procedure validation (refer to chapter 3.2.P.5)- although forced degradation studies may be performed in order to compare different formulations in drug development[67] (refer to 3.2.P.5.3). The exception is degradation through light, which has been addressed in ICH Q1B for Photostability testing (refer to 3.2.P.7).

3.2.P.2.2.2 Drug Product- Overages

No substantial changes have been made over the last 20 years for this section.

Note that in the past, authorities have been less strict when it comes to granting overages. If an overage is mentioned in the old product dossier, it should be checked, if the justification is sound- not only for the development in the past but also according to today's standard. Potentially there is a chance to optimise the formulation/ manufacturing process so that the overage is no longer needed, in particular if other updates have to be done to the medicinal product anyway. For example, in filling of liquid dosage forms, the accuracy of the filling pumps could be increased[68]. If an overage cannot be avoided, efficacy and safety have to be discussed in the preclinical/ clinical modules for the case of overdosage.

3.2.P.2.2.3 Drug Product- Physicochemical and Biological Properties

No substantial changes have been made over the last 20 years for this section in the basic regulatory framework. Yet, specifically for bioequivalence/ bioavailability the EMEA guidance has been revised and renamed in 2010. The previous "Note the Guidance on the Investigation of Bioavailability and Bioequivalence" (published 2001) was replaced by the Guideline on the Investigation of Bioequivalence. It describes recommendations on the comparability of the in-vitro-dissolution of different formulations in the formulation development or manufacturing process development. Furthermore, guidance is given on the justification of changes from the formulation used in the clinical studies to the commercial formulation. In particular criteria can be found in the sections 4.4 and Appendix (revision from 2010)[69] .

Some recommendations have been elaborated with the revision in 2010. For example, whereas the sampling time given in the Note for guidance from 2001 is not fixed precisely, the 2010 guideline says it should be done at least every 15 minutes. Concrete criteria have been determined for products to be dissolved 85% within 30 minutes, but not within 15 minutes: minimum 3 time points have to be tested, the first before 15 minutes, the second at 15 minutes and the third at approximately 85% release. The 2010 revision provides also additional recommendations on the similarity calculation of two dissolution profiles: The first time point may not deviate more 20% or more for all samples and in general, variability should not be more than 10%. See Annex A, Comparison of the recommendations on Bioequivalence for further information.

Unfortunately in old product dossiers there are sometimes in-vitro dissolution results that are not in compliance with the revised CPMP guideline on the Investigation Bioequivalence[22] . This applies in particular for the points mentioned above. In case a comparison of the current formulation/ manufacturing process to the initial one this might cause difficulties in proving the similarity. For

[66] EMA, "EMA Draft Reflection Paper on the Pharmaceutical Development of Medicines for Use in the Older Population.", chapter 2.3, 2.3.1

[67] Blessy M., Ruchi D. Patel, Prajesh N. Prajapati, Y. K. Agraval, "Development of forced degradation and stability indicating studies of drugs—A review", Journal of Pharmaceutical Analysis, Volume 4, Issue 3, June 2014, Pages 159-165, Chapter 2, Objective of forced degradation studies

[68] Kate McCormick, "Quality" (Pharmaceutical Engineering Series), Butterworth-Heinemann, chapter "World class manufacturing in the pharmaceutical industry", section "Process", page 255

[69] EMA, "Guideline on Investigation of Bioequivalence Rev. 1.", section 4.4., Appendix 1

composition changes not only a comparison with the previous (before the change) dissolution profiles should be done. It is also required with the reference product, i.e. the investigational product used in clinical studies or the originator product (generic applications)[70].

In general, the importance of demonstration of knowledge within in the pharmaceutical development section of the dossier has been emphasized in ICH Q8(R2)[71]. Therefore, information given on in-vitro dissolution should also be checked for traceability of the development of the analytical method for in-vitro- dissolution.

Example: Development of the dissolution method

In case of in-vitro dissolution proof of the discriminatory properties of the analytical procedure is crucial nowadays. Old product dossiers may not contain enough data on the development of the dissolution method, such as the comparison of "bad batches" vs "good batches". In those tests it is shown that the dissolution procedure would generate a result which is out of specification if there are deficits in the produced medicinal product. Data could be also generated years after the development by manufacturing those "bad batches", e.g. with a changed formulation due to varied amounts of disintegrants, binders, lubricants. It should be checked, if different stirring speeds have been studied and if the resulting stirring speed is justified. The bioequivalence guideline gives some recommendations here: paddle apparatus- normally 50 rpm, basket apparatus- normally 100 rpm[72]. Further examples of information on the development of the dissolution method to be included, should also address the selection of the medium (type, volume, pH value), solubility of the drug substance, sink conditions, the amount of surfactants used (if used) and the type of apparatus chosen. These tests should be performed on two batches, acc. to the BfArM gap analysis list from 2006[1], chapter 1.2.

3.2.P.2.3 Manufacturing Process Development

The "Note for Guidance on development pharmaceutics" from 1998 describes the rather traditional approach of manufacturing process development by developing the manufacturing process and then checking if appropriate specification parameters are possible. ICH Q8 from 2005/2006 describes a different strategy: It is pointed out that the critical properties of the formulation must be taken into account in the development of the manufacturing process. This approach is more prospective than the approach the Guide from 1998 proposes.

The prospective strategy fits into the ICH Q12 concept. ICH Q12 aims at improved planning of post-approval changes and optimisation of their performance. This can be achieved by gaining a better understanding of the product/ process: "*Increased knowledge and effective implementation of the tools and enablers described in this guideline should enhance industry's ability to manage many CMC changes effectively under the company's Pharmaceutical Quality System (PQS) with less need for extensive regulatory oversight prior to implementation. "*[73]

Moreover, in ICH Q8 from 2005/2006 it is emphasized that data collected on varying process conditions and the consequences on the drug product quality must be documented. They might be helpful for further development of the process.

Since the 2nd amendment of Directive 2001/83/EC in 2003 (Annex 1, 2003/63/EC[3]), it is obligatory to discuss the changes between the manufacturing process applied for the investigational medicinal product and the current manufacturing process as well as the impact they have. In case this has not been done, the changes must be investigated and should be tried to justify in collaboration with a development/ clinical expert.

[70] ICH Q8(R2), Part 1, 2.2.1 Formulation Development
[71] ICH Q8(R2), part II annex, chapter 1, "approaches to pharmaceutical development", paragraph 2
[72] European Medicines Agency, "Guideline on Investigation of Bioequivalence Rev. 1.", Appendix III, IV.1.1 (General aspects, Drug product)
[73] ICH Q12, 1.1 Objectives, Paragraph 1 and 3

The same applies for primary stability studies and the impact of the changes performed afterwards on the significance of the primary stability results. This has become mandatory since ICH Q8, 2005/2006.

With introduction of the 2017 Guideline on manufacture of the finished dosage form, it was also clarified that it shall be elaborated, how exactly the manufacturing process and the performed controls support in assuring the quality of the finished product. It must be shown, how the manufacturing process was developed and how the conditions for running the process and the parameters established have been chosen. For example, design spaces must be justified here. The wider the margins for running the process are (higher flexibility), the more data/ explanation needs to be given.

3.2.P.2.4 Container Closure System

General provisions and innocuousness

Mostly the basic criteria for this module have not changed. However, the innocuousness of the packaging materials is a new aspect, which has only been mentioned since the introduction of NTA Volume 2B, 2004/2008. In consequence, some of the older product dossiers might not contain this information. If they do, however, it is probable that the reference to the respective regulatory framework is outdated, since it has been changed frequently within the last 20 years. Particularly this is the case for plastic packaging materials.

With regards to the regulatory recommendations on the quality of packaging materials, the relevant monographs of the European Pharmacopoeia and/or the foodstuff legislation should be considered. In particular for the foodstuff legislation there were many changes to the regulatory framework in the last 20 years, which will be further explained in chapter 3.2.P.7.

Container Closure System for bulk/ intermediates

The guideline on manufacture of the finished dosage form (Rev.1) was published in 2017. It described for the first time the necessity to assess the suitability of packaging material used for the storage of intermediates or bulk. If bulk storage is done and the old product dossier does not contain these data, it must be checked if tests have been done and the information can be added. Stability studies can be helpful as well as leachable/ extractable studies for plastic packaging, if already available.

Plastic primary packaging materials

In 2005, the EMEA CMPH Guideline on Plastic Immediate Packaging Materials[74] for plastic materials in contact with the active substance or bulk/finished product was published, became effective and replaced the previous CPMP Guidance 3AQ10a[75]. The previous document 3AQ10a is not available on the EMA website anymore[76] and could not else be found. In addition, the Guideline from 2005 does not inform about the differences to the previous guide. It is to be assumed that the provisions on the extent of the tests to be done on plastic primary packaging materials were not that detailed in 3AQ10a. The reason is a general trend in the regulatory field that mostly new recommendations are added, and more details are included rather than the repeal of instructions/ advice.

For the development of plastic primary packaging materials, the 2005 guideline recommends to evaluated stability, integrity and compatibility for the intended administration type and if applicable, for sterilization procedures[77]. Compatibility testing can be done by testing on leachables/ extractables. Extractables studies have to be done for all non-solid dosage forms. The exception are non-solid dosage forms for oral/ topical application when they comply with a material chapter of the Ph.Eur. or with food packaging legislation. Leachable (Interaction) studies need to be performed for all liquid dosage forms and might be required for solid dosage forms for inhalation/ parenteral application, too.

[74] EMEA- CHMP, Guideline on plastic immediate packaging materials
[75] EMEA- CHMP, Guideline on plastic immediate packaging materials, 1.1 Objective of the guideline
[76] EMA Scientific Guidelines, Quality, Packaging, Plastic primary packaging materials, without date
[77] EMEA- CHMP, Guideline on plastic immediate packaging materials, chapter 2, "Development pharmaceutics"

Interaction studies shall prove that there are no interactions of the packaging material with the medicinal product[78]. Furthermore, photostability of the packaging must be discussed. Can light cause degradation products that leach into the product (see requirements for leachable studies above). The influence of certain manufacturing operations, such as sterilization, should be described (and tested if necessary)[77]. In case the studies listed above have not been performed yet but are required, they should be done retrospectively, provided the original packaging material is still available on the market (refer to chapter 3.2.P.7). Of course, such studies take time and cause costs, and they bear the risk that the results cannot confirm innocuousness and the packaging material must be changed. The latter would mean all the studies required for module 2.4 have to be started anew.

It needs to be said that the Ph.Eur. chapters 3.2.2 "Plastic containers and closures for pharmaceutical use" and 3.1.3 "Plastic additives" already recommended previous to publishing the EMEA-CHMP "Guideline on plastic immediate packaging materials" the performance of extractable/ leachable studies and the related toxicity studies. However, it did not guide in detail on the conditions under which such studies have to be performed (e.g. different dosage forms, administration routes).

Specifically, in Germany, the federal institute for risk assessments (Bundesinstitut für Risikobewertung, BfR), published recommendations on packaging materials. This applied when they found them to be compliant with the Regulation 1935/2004 "on materials and articles intended to come into contact with food […]" with a focus on plastic materials[79]. If the old dossier to be updated contains references on BfR recommendations (or the previous institutes BGVV and BGA[80]) it should be checked if they are still up to date. The BfR recommendations focus nowadays only on materials which are not included in the positive list of Regulation 10/2011 (e.g. aids to polymerisation, polymer production aids, silicone, paper, natural rubber)[79].

The food directives/ regulations on packaging material have been revised many times in the past 20 years or even replaced. See chapter 3.2.P.7 Container Closure System, Development of the regulatory provisions for module 3.2.P.7, subchapter Plastic Packaging Materials for further information. There are also non-plastic materials covered by the regulatory framework on food. Refer to 3.2.P.7 Container Closure System, Development of the regulatory provisions for module 3.2.P.7, Other Materials compliant with food law (e.g. Aluminium) for further information.

Child protection and Elderly-friendliness

Since 1984 there's an obligation in Germany for many medicinal products to make sure that the packaging of medicinal products is child resistant, which was established in §28, paragraph.2, No. 5 of the German Drug Law (AMG)[81]. Furthermore, there are technical norms that also require a child resistant packaging, like the DIN EN ISO 8317[82]. Consequentially this requirement is not new and this aspect should be described in all development parts already.

DIN EN ISO 8317 also describes how to check if the packaging is elderly-friendly. Furthermore, the draft reflection paper on the pharmaceutical development of medicines for use in the older population, published 3 years ago in 2017 requires to check the packaging for suitability for the elder population. It might be difficult for them to read and understand instructions how to open a container, for example. Elderly people might be tempted to remove the medicine from its original primary packaging in order

[78] EMEA- CHMP, Guideline on plastic immediate packaging materials, chapter 4 & 5
[79] Federal Institute for Risk Assessments (Bundesinstitut für Risikobewertung) Homepage, Databases, Recommendations on Food Contact Materials, Sections Legal relevance and legal basis, without date
[80] Federal Institute for Risk Assessments (Bundesinstitut für Risikobewertung) Homepage, Publikationen, Sonstige Publikationen, BgVV- Schriften, without date (available in German only)
[81] Gesetze-im-Internet, "Gesetz Über Den Verkehr Mit Arzneimitteln (Arzneimittelgesetz – AMG), §28 Auflagenbefugnis, Abs. 2, Nr. 5."
[82] Andreas Ziegler, Pharmazeutische Zeitung online, Ausgabe 21/2006, "Arzneimittelverpackung- Kindersicher und Seniorenfreundlich.

to put it in a multi-compartment compliance aid. This approach could influence the stability of the product negatively[83].

3.2.P.2.5 Microbiological Attributes

The principles have not changed in the last 20 years. With introduction of the NTA 2004/ 2008 the necessity to show that the container closure is sufficient to protect from microbial growth for sterile medicinal products has been documented. This could be shown by investigation of microbiological purity within stability studies.

3.2.P.2.6 Compatibility

No substantial changes have been made over the last 20 years for this section.

General: Approach to development/ Considerations for update of documentation

With introduction of ICH Q8 and its Annex in particular (first effective 2005, Annex added in 2008)[19], concepts how to approach pharmaceutical development have been introduced. It is now required to plan the quality attributes of a medicinal product beforehand in form of a quality target product profile, which includes the administration route, pharmaceutical form, strength, packaging and dose delivery system, drug substance release, and quality criteria. Furthermore, a specification must be established (finished product, active substance, excipients) with all tests which are critical for the product quality. Last but not least, all critical process parameters for the manufacturing process must be determined as well as in-process-controls[84].
ICH Q8 also proposed the "quality by design (QbD)" approach as an option for pharmaceutical development as described in the introduction. QbD is a structured way for a prospective design of all development steps.

For the optimisation of analytical procedure development, it is planned to publish ICH Q14, which is not referenced in Table 4: complementary regulatory framework for 3.2.P.2 Pharmaceutical Development because there is no draft available yet. According to the concept paper, the ICH Q14 will provide information on traditional and improved analytical procedure development strategies, including quality-by-design principles[85].

Introduction of a concept to development studies

A concept for development studies has never been introduced in the regulatory framework before ICH Q8. The lack of concepts such as the quality target product profile (introduced in 2008 with the annex to ICH Q8) in old product dossiers, can mean that it has not been established and the rationale behind the product development might be non-transparent. In fact, the traditional approach to pharmaceutical development was less target-oriented, many trails were performed in order to find a suitable quality. This meant often that if there was no obvious issue, the formulation/ manufacturing process was set up according to the best trial result. Specifications were then set up in accordance with the minimum requirements from Ph.Eur. / ICH Q-Guidelines and EU Guideline 3AQ11a[86]. However, not for many parameters concrete information on limits to be set is given here. Hence many specification parameters were set up according the results received from the development trials, in the past often with some tolerance to the limits. The same applied for process controls and technical parameters. Yet this approach bears a higher risk of testing into compliance compared to the systematic approach where quality targets must be defined at the beginning of development (QbD). The quality of the finished product can only be assured with an adequate control strategy. The higher the extent of the trails

[83] EMA, "EMA Draft Reflection Paper on the Pharmaceutical Development of Medicines for Use in the Older Population", Chapter 2.6
[84] ICH Q8(R2) Pharmaceutical Development, annex II, Chapter 1, 2.1, 2.5
[85] ICH Q14: Final Concept Paper Analytical Procedure Development and Revision of Q2(R1) Analytical Validation Dated, Issues to be resolved, 1st section
[86] EMA, Guideline "Specifications and Control Tests on the Finished Product", 3AQ11a

performed is, and the greater the knowledge gained thereof, the better are the chances for setting up an appropriate control strategy.

Depending on the extent of the tests performed in the pharmaceutical development and the knowledge gained thereof, is the level or risk for setting up an inadequate control strategy for ensuring product quality.

Demonstration of knowledge in pharmaceutical development

ICH Q8 emphasizes that the knowledge gained in the pharmaceutical development should be demonstrated in 3.2.P.2.[87]. Knowledge management is also further explained in the ICH Q10 Guideline from 2008[88]. One example is the request to investigation all conditions that influence the quality of the medicinal product (critical quality attributes)[89].

Whereas the note for guidance on development pharmaceutics is already rather detailed in its recommendations on 3.2.P.2, it merely mentions in chapter 2.1.1 that the physical parameters that are "variable and critical" for the quality of the product must be controlled. It does not mention that a systematic check of parameters has to be done in order to see if they are critical or not, though.

On first sight this fact might seem to be negligible. However, if not thoroughly checked and assessed initially, some quality attributes/parameters might turn out to be critical only when a change is introduced to the formulation/ manufacturing process, e.g. the particle size of the tablet filler lactose (see 3.2.P.4).

Information whether quality attributes or process parameters were investigated at all might be missing in old dossiers. Has knowledge or a risk assessment been available in order to assess their criticality to the product quality? Or were they found to be non-critical, but it is not mentioned in the documentation? Where information on additional control of parameters is included, which are not given by Ph.Eur. or the relevant regulatory framework- why were they established, and were they considered to be critical? Those are questions that may arise for old product dossier developments.

Note that this information is also needed in order to define the "established conditions" as described in the new ICH Q12 Guideline[90] which will, amongst others, define the reporting category to the health authority if changed in the future (prior approval/ notification). Controls which are not critical to product quality or to the performance in case of analytical procedures, will not have to be reported[91]. These rules have been already adopted in the current regulatory framework of the European Union, in the EU Variation Regulation 1234/2008 and the EU Variation Classification Guideline, acc. to the Note on EU Implementation of ICH Q12. All information that is considered an established condition has to be submitted to the authority in form of a variation acc. to current law already[92].

Source document for information on pharmaceutical development

In general, the document where all activities of the development of a medicinal product are summarized is the pharmaceutical development report. A lack of information in the dossier could be compensated by checking the development report and amending the information provided in 3.2.P.2, if available. If not, raw data from development tests must be checked and the information must be integrated in 3.2.P.2. In case neither development report nor raw data are available any more or not accessible (e.g. in case of in-licencing), development tests must be partially repeated, where possible.

[87] ICH Q8(R2) Pharmaceutical Development.", part II annex, chapter 1, "approaches to pharmaceutical development, paragraph 2
[88] ICH Q10 Pharmaceutical Quality System, chapter 1.6.1
[89] ICH Q8(R2) Pharmaceutical Development, part I, chapter 2 "pharmaceutical development", paragraph 4
[90] ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Life Cycle Management.
[91] ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Life Cycle Management, chapter 3.2.3.1 and 3.2.3.2
[92] EMA, Note on EU implementation of ICH Q12 (guideline on technical and regulatory considerations for pharmaceutical product lifecycle management)

In this case awareness must be raised within the company that those tests might be expensive and not necessarily result in a confirmation of the current formulation/ manufacturing process. If this is the case, major changes could be required. Where risk assessments need to be done, the recommendations from the ICH Q9 Guideline "Quality Risk Management"[93] from 2005 can be applied.

See also "Example: Development of the dissolution method" in chapter 3.2.P.2.2.3 Drug Product- Physicochemical and Biological Properties.

Application of life cycle management

Life Cycle Management for the product development section is yet another concept introduced by ICH Q8[94]. Prior to that the development part of a product dossier was often considered closed after the initial development- instead of being a living part of the dossier to be updated whenever new knowledge is gained.
If the old dossier has not been constantly maintained, then various sources for further information can be checked in order to update 3.2.P.2:

-Technical transfer documentation (e.g. technical transfer report),
- change control documentation,
- manufacturing process risk assessments,
- process validation reports,
- analytical validation and transfer reports,
- product quality review reports,
- deviations reports,
- customer complaint reports

All these documents could be sources for information how the medicinal product and its manufacturing/ control process have been changed in the past. They can also inform about the reason of changes or, quite generally, if there is a need for a change at all.
It shall be noted that with those old products some changes would be necessary in order to achieve a better product quality (e.g. repeated customer complaints about broken tablets in the blister). Consequently, those improvement activities must be completed before update of the 3.2.P.2 can take place.

[93] ICH Q9 "Quality Risk Management"
[94] ICH Expert Working Group, "ICH Q8(R2) Pharmaceutical Development.", part I, chapter 2 "pharmaceutical development", paragraph 2

3.2.P.3 Manufacture

Types of regulatory provisions

Basic provisions on the content of the module for manufacture

The following provisions give some general instruction on the content of 3.2.P.3 today:

Table 6: basic regulatory framework for 3.2.P.3 Manufacture, sorted by publication date

Type and Title of regulatory framework	**Date**
EU Commission Note for Guidance on Manufacture of the Finished dosage form CPMP/QWP/486/95[95] *(replaced by EMA Guideline on the manufacture of the finished dosage form)*	First published: 01.04.1996 Effective: 01.04.1996 *(replaced)*
EU Directive 2001/83/EC original version from 2001 without amendments[12], Annex 1, Part 2, Section B	Published: 28.11.2001 Effective: 18.12.2001
2nd Amendment to EU Directive 2001/83/EC: 2003/63/EC[3] Annex I, Section 3.2.1.2	Published: 27.06.2003 Effective: 01.07.2003
EU Commission Notice to Applicants (NTA), Volume 2B, 2008[5], Section 3.2.P.3	May 2008 Info on Module 3 is from July 2004
EMA Guideline on the manufacture of the finished dosage form EMA/CHMP/QWP/245074/2015 [96]	Published: 14.08.2017 Effective: 14.02.2018

Table 7: complementary regulatory framework for 3.2.P.3 Manufacture, sorted by publication date

Type and Title of regulatory framework	**Date**
EMEA CPMP Note for guidance on process validation CPMP/QWP/848/96[97] *(replaced by EMA Guideline on process validation for finished products- information and data to be provided in regulatory submissions)*	First Published: 01.03.2001 Effective on: 01.09.2001 *(replaced)*
EMEA CPMP Note for Guidance on Start of Shelf- Life of the Finished Dosage Form EMEA/CVMP/453/01 (Annex to Note for Guidance on the Finished Dosage Form)[98]	Published: 31.05.2001 Effective: 01.12.2001
EMEA CHMP/ CVMP Annex II to note for guidance on process validation CPMP/QWP/848/99 and EMEA/CVMP/598/99 non standard processes, CPMP/QWP/2054/03[99] *(replaced by EMA Guideline on process validation for finished products- information and data to be provided in regulatory submissions)*	First published: 10.08.2004 Effective: 01.01.2005 *(replaced)*
Guideline on process validation for finished products- information and data to be provided in regulatory submissions EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1 [100]	First Published: 28.02.2014 Effective on: 15.07.2014 *(Minor update to the glossary performed in 2016)*

[95] EMEA CPMP Note for Guidance on Manufacture of the Finished dosage form CPMP/QWP/486/95 (repealed)
[96] EMA Guideline on the manufacture of the finished dosage form, Revision 1
[97] EMEA CPMP Note for Guidance on Process Validation (repealed)
[98] EMEA CPMP Note for Guidance on Start of Shelf- Life of the Finished Dosage Form
[99] EMEA CHMP/ CVMP Annex II to note for guidance on process validation CPMP/QWP/848/99 and EMEA/CVMP/598/99 non standard processes, CPMP/QWP/2054/03 (repealed)
[100] EMA Guideline on process validation for finished products- information and data to be provided in regulatory submissions-Rev1,Corr.1

Both the previous EMEA CPMP Note for Guidance on Manufacture of the Finished Dosage Form as well as the current EMA guideline on the manufacture of the finished dosage forms provide the most detailed information on the content of 3.2.P.3. Yet, for module 3.2.P.3.5, there is a specific guideline on process validation which contains more information than the general regulatory framework on manufacture. The Note for guidance on shelf life calculation is not new, however it is new that this information has to be included in the dossier (see 3.2.P.3.4 Control of Critical Steps and Intermediates). Since process validation and the rules for shelf life calculation need to be addressed for all types of products, those guidelines are considered to be part of the basic regulatory provisions.

Specific provisions for 3.2.P.3

Due to the limited volume of this master thesis the specific provisions on sterilisation processes will not be further explained but are listed here in order to make the reader aware of further reading on the provisions in 3.2.P.3.

Table 8: specific regulatory framework for 3.2.P.3 Manufacture

Type and Title of regulatory framework	**Date**
EMA Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container EMA/CHMP/CVMP/QWP/850374/2015 *replacing the CPMP Guideline: Note for Guidance on development pharmaceutics- Annex on decision trees for selection of sterilisation methods from 1999* *CPMP/QWP/054/98 Corr*[101]	Published: 08.03.2019 Effective: 01.10.2019

Development of the regulatory provisions for module 3.2.P.3

The guideline on the manufacture of the finished dosage forms from 2017/2018 states in its executive summary that it does not set up new regulatory expectations. Herewith it refers to Article 23 of the Directive 2001/83/EC and the obligation of marketing authorisation holders to follow up on technical and scientific changes. It also points to the changes in the CTD format/content, industry changes towards more differentiated supply chains and globally distributed manufacturing sites as well as the introduction of ICH Q8. In fact, the provisions have changed and are much more precise, as described in the following subchapters. During the review of the EMA guideline on manufacture of the finished dosage forms the higher level of detail was commented by the industry. The EMA justified this approach by informing that marketing authorisation holders continued to provide less information leading to difficulties in assessing the manufacturing process[102].

3.2.P.3.1 Manufacturer(s)

Whereas the Note for Guidance from 1996 only mentions the inclusion of manufacturing sites for manufacturing operations and market release, Annex 1 to directive 2001/83/EC from 2001 already includes the requirement to clarify the responsibilities, which was not explicitly mentioned before. If the dossier to be updated is that old, it might only include the manufacturing/ release sites but not an information, e.g. which manufacturing steps are done by which manufacturer. This information can be received from the Quality Assurance (QA) normally. Moreover, Directive 2001/83/EC requests to list testing sites. Further the guideline on manufacture of the finished dosage form from 2017 addresses the need to list stability testing sites for ongoing studies. The testing sites used are often diverse from the manufacturing sites. Not every manufacturer has the laboratory equipment and capacity to e.g. perform microbiological purity testing, stability testing or if needed, special tests like a regular

[101] EMEA-CPMP, "Annex to Note for Guidance on Development Pharmaceutics: Decision Trees for the Selection of Sterilisation Method."
[102] EMA, Overview of comments received on 'Draft Guideline on manufacture of the finished dosage form, General comments- overview, Stakeholder no. 1

nitrosamine impurities test. Consequently, they are often contractors, too (to be included since effectiveness of Directive 2001/83/EC). With the guideline on manufacture of the finished dosage form it has also been clarified, that the EU retesting site for batch release needs to be mentioned, in case manufacture and a preliminary batch release are done in countries outside of the EU/EEA. All this information can be provided by QA because they have the obligation to audit and ensure GMP at those sites. Note that if audit activities have not been done yet, or GMP gaps are known of certain sites they should be immediately taken care of (further information on the relationship of GMP and dossier updates see section Excursion.

3.2.P.3.2 Batch Formula

The provisions on the manufacturing formula have not changed much in the last 20 year. Only the need to include the quality standard of all components has been introduced later on (Notice to Applicants, Volume 2B, Module 3 from 2004). As described in chapter Development of the regulatory provisions for module 3.2.P.1, this information can be retrieved from 3.2.S.4.1 and 3.2.P.4.1.

The information on the batch size definition has been changed massively with the introduction of the guideline on finished product manufacture in 2017, though.

Justification must be given on each batch size in the dossier now, not only for more than one batch size or ranges. For batch size ranges at least the batch formula for the smallest and biggest batch size must be given. For continuous manufacture, the definition of the batch size needs to be justified, too. However, continuous manufacture is a fairly new approach to manufacturing[103] and therefore most dossiers to update won't include this technology. Provisions have been given on the batch size for commercial manufacturing (in line with the capacities of the production equipment, large enough for commercial manufacture and for solid oral dosage forms it must be at least 100,000 units).

The justification of the batch size might be covered in the development part 3.2.P.2. If not, it is proposed to ask the manufacturing department and operational/ strategic planning/ supply chain expert* for the rationale. Besides regulatory recommendations, batch sizes are defined by the production equipment, the expected sales of the medicinal product and the requirements of the supply chain (e.g. due to limited storage time of the bulk product, batch sizes may not be too big in order to ensure timely packaging and release)[104].

*depending on the name of the function in the company that is involved with planning the product flow within the supply chain for the specific medicinal product.

The use of sub-batches must be described now by giving a justification, the batch formula, batch size and number of the sub-batches. Further division of the sub-batches must be described. too. The information about the sub-batches can be gained by reviewing the master batch record as it has to describe all manufacturing steps precisely acc. to GMP rules[105]. If it is known that the current master batch records have GMP gaps, the instruction should be verified with the manufacturing personnel or quality assurance should be asked to do so.

When bulks are divided in different presentation/ packs, it has been clarified in the 2017 guideline of manufacture of the finished dosage form, that the batch size is the size of the batch before division in different presentations/ packs. Additionally, the length of the following process should follow the worst-case scenario for description of the length of these steps in case of doubt. If the current batch size in the dossier to be reviewed and updated has been correctly defined, can be checked in the latest

[103] FDA, Drugs, News and Events for human drugs, "Modernizing the Way Drugs Are Made: A Transition to Continuous Manufacturing", Sau Larry Lee
[104] Pharmtech.com, Pharmaceutical Technology, Volume 2016 Supplement, Issue 3, pg s16–s19, Determining Minimum Batch Size, Naheed Sayeed-Desta, Ajay Pazhayattil, Srihari Chowdari
[105] EU Kommission, Eudralex, Volume 4, GMP Part I, Chapter 4 Documentation, 4.18 d)

version of the master batch record. The worst-case scenario should be part of the GMP process validation report.

For components that are intended to be removed from the product again, it has been added that the amount can be expressed in ranges. This means they should be given numerically, with an upper and lower limit. Amounts expressed as “q.s” or with a variable such as “xx mg” are not considered acceptable anymore. Since introduction of the NTA Volume 2B 2004/2008 the recommendation to not act exact amounts of components when the pharmaceutical form requires it, has been removed. Further, the BfArM gaps list from 2006[1] mentions in point 2.1 that these components must be listed with their amounts.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

Manufacturing Process Description

The expectations 20 years ago where much less precise acc. to the Note for Guidance on Manufacture of the Finished dosage form from 1996. Information on the manufacturing process, the equipment used, and the in-process controls was seen relative to the finished product release testing. In consequence, it was dependant on how thoroughly either the finished product testing or the manufacturing process and equipment or the in-process controls with their specifications could ensure the quality of the product.

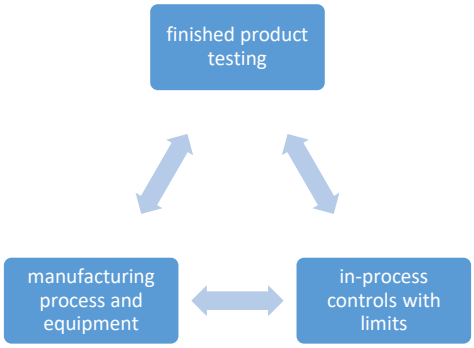

Figure 3: level of detail to be described acc. to Note for Guidance on manufacture of the finished dosage form

In consequence, manufacturing process, equipment and in-process controls did not have to be described in detail when the finished product testing would ensure the quality of the medicinal product. Exceptions presented were content uniformity or sterility.

Today, the approach is different. The focus is on highlighting the critical process parameters and material properties, but the overall control strategy needs to be described in detail as explained in chapters 2.5 and 3.3 of ICH Q8 (Part II). This may be due to the fact, that it has been recognized that finished product release testing only cannot ensure the quality of the finished product[106].

All details on the manufacturing process (incl. packaging process) and the operation principles per stage of the process must always be described in detail since introduction of the Guideline on manufacture of the finished dosage form (2017). The previous Notice to applicants (NTA) Volume 2B (2004) is not specific on the level of detail to be given but states that scientifically/ technical innovations have to be described more detailed. Acc. to both guidelines this description cannot be done generally but must be specific for the relevant batch size.
Furthermore, the equipment needs to be given by its type and its capacity. All process parameters need to be given (with numeric criteria). Since introduction of the Guideline on manufacture of the finished dosage form it has been specified that this description must include non-critical and supportive parameters. Both guidelines request a description of the environmental conditions if they are critical

[106] EMA Guideline on the manufacture of the finished dosage form, Revision 1, chapter 4.3, subheading "Expected level of detail in the manufacturing process description", first paragraph

now. In addition, if reprocessing is done, it must be mentioned and justified due to the NTA Volume 2B from 2004.

The BfArM Gap List from 2006[1] mentions the necessity to describe the filters used for gases, if applicable (material, pore size, filter surface area, compatibility with the used gases, active substance sorption by the filter) and present results of filter validation in chapter 2.2.

Usually the details on the manufacturing process that are missing in the dossier to be updated can be obtained from the master batch record. Therefore, the required data should be available and do not need to be generated first.

Flow Chart

More information has to be provided in the flow charts nowadays: Since 2004 (acc. NTA Volume 2B) the final product controls need to be included. The material flow and if applicable, the design spaces shall be part of the flow chart acc. to the guideline of finished product manufacture (2017). This should be easy to implement: the material flow should be already described in 3.2.P.3.3 narratively, the design spaces in 3.2.P.2 and 3.2.P.3.4. The final product controls can be found in 3.2.P.5.1.

Alternatives in manufacture

Whereas in the 1996 Note for Guideline on manufacture of the finished dosage form different steps/ methods in the manufacturing process were permissible, if appropriately justified with data, this is possible with limitation only today. Merely technical adaptions can be made since the guideline on manufacture of the finished dosage form from 2017 became effective. It still is a condition that the process follows the same manufacturing principle. Provided that the dossier to be updated contains alternative steps with different manufacturing principles this will be hard to justify. However, as the Guideline on manufacture of the finished dosage form is a guideline and therefore “soft law”, it could be tried to justify it in special cases when sufficient data have been generated to prove the equivalence. The topic should then also be reflected in 3.2.P.2.

Sterile products

For sterile products the new guideline on manufacture of the finished dosage form from 2017 does not give information as this topic is discussed in the separate Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container from 2019. This guideline replaces the annex to the note for guidance on development pharmaceutics (see Specific provisions for 3.2.P.3)

3.2.P.3.4 Control of Critical Steps and Intermediates

General

Massive changes have been introduced to 3.2.P.3.4. Since introduction of 2003/63/EC in 2003 not only the IPCs but also the tests performed on intermediates need to be included. Furthermore, the NTA Volume “B (2004) introduced the recommendation to describe the critical steps in the manufacturing process, why they are critical and how the specification limits have been set.

The biggest changes have been done with introduction of the guideline on manufacture of the finished dosage form (2017) as described in the following.

Critical steps

Not only the critical steps have to be identified, the control concept (monitoring) needs to be explained as well and specifications determined. For the critical steps a link to module 3.2.P.2 should be provided.
For in-process controls it has been specified that they need to be listed not only with the acceptance criteria but also with their test methods. Moreover, complex control models should be explained. For continuous manufacturing, the frequency of IPCs, the correlation to finished product release testing and release decisions should be explained in the frame of ensuring a consistent quality. As an example,

the handling of unexpected variations is given. For intermediates, information on the storage of intermediate, transportation and testing must be given, but stability data should be included in 3.2.P.8 and only a reference should be provided in 3.2.P.3.4. If information is missing in the current dossier, the data can usually be obtained from QA. In case of complex control methods, the correlation between the manufacturing controls and the finished product controls should be reviewed together with QA and a statistics expert.

Bulk/ Intermediate storage

The provision on bulk storage and its justification in 3.2.P.3 is completely new. So far a debate on bulk storage has only been addressed incidentally in ICH Q8, when it comes to the choice of the packaging material[107]. Now temperature, humidity and other environmental conditions of bulk storage, if applicable, need to be described in case bulk storage is performed. On top, the maximum hold time of the bulk needs to be given with a justification and data to support it. It is also emphasized that storage times should be reduced to a minimum and, again, justified if prolonged. A definition for prolonged storage has been included (more than 30 days for solid oral products and more than 24h for sterile products). In case of prolonged storage, bulk stability studies need to be performed at 2 batches at the intended storage conditions. It should be clarified with operational planning (or supply chain management) and with QA what the maximum hold time(s) are/ is and if a bulk stability study is required as well as the availability of bulk stability data if they haven't been included in the dossier yet. Bulk stability studies are required in many cases for solid oral dosage forms when the packaging site is not the same as the bulk manufacturing site (because of the time needed for transport). A second common cause for prolonged storage is a high degree of capacity utilisation of separate packaging equipment with other products as this makes it more difficult for the planning team to ensure timely packaging for each product. Another factor can be bottlenecks in the packaging material release by the laboratory or by the Artworks team which can prevent that packaging can be completed within the 30 given by the guideline.

Shelf Life Calculation

The Note for guidance on start of shelf-life of the finished dosage form is not new as it was introduced in 2001. However, so far this information was not requested in the dossier and needs to be included now.

Transportation of Bulk or Intermediates

It is also a new expectation to discuss if bulk transportation is done if there are cases where the temperature can reach values not within the intended storage conditions. If this is the case, data to proof that the quality of the product is not negatively impacted (stability data) must be provided.

It may have been new in 2017 that information on the transport validation need to be given in the dossier, but the recommendation to do a check of the transportation conditions (constant monitoring) and evaluate the risk had been already established in GMP Annex 15, Chapter 6, which became effective in 2015[108,109]. It is recommended to check with the quality department if the risk of the transport has been assessed and if data have been generated. If this is not the case, a time slot needs to be planned in order to conduct such studies. Note that normally studies are performed for a whole year, at least in summer and winter[110]. The consideration of seasonal conditions is also a recommendation from the GMP Annex 15, Chapter 6.2[108]. So, creating data on the transportation will

[107] ICH Q8(R2) Pharmaceutical Development, Chapter 2.4
[108] EU Commission, Eudralex, Volume 4, GMP Annex 15, Chapter 6
[109] Pharmout.net (GMP consulting service), without author, white paper "EU GMP Guide-Annex 15 Qualification & Validation draft released", February 2016, Chapter "What are the key changes in the new guidance?"
[110] WHO, Technical supplement to WHO Technical Report Series, No. 961, 2011, Annex 9: Model guidance for the storage and transport of time and
temperature–sensitive pharmaceutical products, "Transport route profiling qualification", Chapter 2.2 e)

take a while. In case the product has not been manufactured for some time a new company might perform the transport which might require a new investigation. This applies as well if the current manufacturing site shall be replaced. Consequently, the transport route and times will have to be changed leading to a new transport verification. Thus, existing data on the transport should be checked for their validity with the current supply chain and transportation conditions.

Packaging of Bulk or Intermediates

Reference to other parts of the dossier where the packaging material and specification is described shall be provided.

Elemental impurities and Residual Solvents

Solvents other than water might be used in the finished product manufacturing process[174]. If this is the case, it should be considered in the control strategy for Residual Solvents.

Further, elemental impurities might be created by the manufacturing process, in particular some operations such as hot melt extrusion[111] have an increased abrasion of the equipment.

Refer to chapter "Development of the regulatory provisions for 3.2.P.5", "3.2.P.5.6 Justification of Specifications" for more information.

3.2.P.3.5 Process Validation

Continuous process validation and hybrid approach

The concept of continuous process verification has been introduced with ICH Q8 (first published 2005). However, the concept is not explained in ICHQ8, only the definition is given[112]. An explanation of the concept has been introduced with the "Guideline on process validation for finished products- information and data to be provided in regulatory submissions" from 2014. This is one of the biggest changes in the regulation. As a consequence for introduction of the continuous process verification also the hybrid approach is explained in this Guideline[100]. If a continuous process verification or hybrid model has been developed and introduced before 2014 for the product to be reviewed, it should be checked if it fulfills all of the criteria given in the guideline.

Scale up

Another change is the obligation to point out the critical aspects for a scale up. This information needs is primarily part of 3.2.P.2 but has to be mentioned in 3.2.P.3.5 additionally- acc. to the Guideline on process validation for finished products from 2014. This is just a formal change, tough, if properly described in 3.2.P.2 the information can just be copied from there.

Additional criteria on the assessment of the extend of validation activities

The consistency of the process and the previous experience (amount and data available) from commercial manufacturing are two additional criteria, which have been addressed in the guideline on process validation from 2014. In case less than 3 consecutive batches shall be justified for a non-standard process or any other reduced approach (e.g. bracketing) is applied, it should be checked if the old dossier already takes these two criteria in account. Should they not be in favour of a reduced approach, revalidation should be considered (as well as the time and cost for such a new process validation and the delay of the CMC dossier update).

Design space

Design space- a concept introduced by ICH Q8[19] (e.g. Glossary), has also been included in the guideline on process validation from 2014: Design spaces are normally established as part of 3.2.P.2. A verification of the design space must be shown in 3.2.P.3.5 if it has not been shown in development,

[111] ICH Q3D (R1) on elemental impurities, chapter 5.3 "Potential elemental impurities derived from the manufacturing equipment"
[112] ICH Q8(R2) Pharmaceutical Development, part I, chapter 2.3 and Glossary

that the design space is independent of the batch size (scale-up). For continuous process verification, design space must be part of the verification concept. For already introduced design spaces it should therefore be checked if a validation/ verification has already been done for the relevant batch size or if this still needs to be done. This applies in particular if there are plans to change the batch size. Design spaces are part of a Quality by Design approach.

Standard/ Non-standard processes

Examples for non-standard processes have been given for the first time in the Note for Guidance on Process Validation from 2001 (Annex II). Only nanoparticulate preparations have been added and standard methods of sterilization with related application for parametric release have been deleted in the revision 1 from 2016. In case the dossier to be updated was created for a nanoparticulate product and it does not contain data from three commercial scale batches, it must be possible to justify this. It is proposed that the justifications include the same criteria as described for the selecting the number of validation batches[113]: The lower the variability of the process is, the better it is in terms of rating the risk (it means a lower risk). The more product and process knowledge is available from development, and the more experience the manufacturer has with this kind of product/ process, the lower is the risk. Alternatively a new process validation on commercial scale has to be performed. .

In February 2014 a revision of the GMP Annex 15 for Qualification and Validation was published, which became effective in 2015. It excluded the retrospective approach to process validation[114,115]. In consequence old product dossiers updated before 2014/2015 might still contain retrospective validation data. This is acceptable in case the dossier does not solely contain retrospective data but also sufficient information on prospective validation. A prospective process validation is much more suitable to assess the manufacturing process. If it has not been validated prospectively before it can occur during the prospective validation that the process needs to be changed because successfully validation is not possible. Such activities can be costly and timely.
Another issue might be that the recommendations for packaging validation have only been introduced with the update of the GMP Annex 15[109,116]. The current guideline for process validation from 2016 does not exclude packaging as a manufacturing step. In fact, the definition of process validation in the glossary “the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes” is independent from the step of the process. In many old dossiers, packaging validation has not been or not been sufficiently addressed consequently. In any case, the packaging validation experts of the relevant departments (e.g. QA and production) should check the current data, if available and a new validation should be performed when necessary.

[113] EMA Guideline on process validation for finished products- information and data to be provided in regulatory submissions, Rev1,Corr.1, chapter 5.1
[114] Website of GMP-Navigator, GMP News, New Details "Revision des EU GMP Annex 15 veröffentlicht - Gültig ab 1. Oktober 2015", 07.04.2015, without author
[115] EU Commission, Eudralex, Volume 4, GMP Annex 15, Chapter 5.3
[116] EU Commission, Eudralex, Volume 4, GMP Annex 15, Chapter 7

3.2.P.4 Control of Excipients

Types of regulatory provisions

Basic provisions on the content of 3.2.P.4

The following provisions give some general instruction on the content of 3.2.P.4 today:

Table 9: basic regulatory framework for 3.2.P.4 Control of Excipients, sorted by publication date

Type and Title of regulatory framework	**Date**
EU Commission Guideline on Excipients in the dossier for application for marketing authorisation of a medicinal product, 1st version [117] *(replaced by Revision 2)*	First adopted: February 1994 Effective: August 1994 *(replaced)*
EU Directive 2001/83/EC original version from 2001 without amendments[12], Annex 1, Part 2, Section C, Subsections 1.1-1.2 and D	Published: 28.11.2001 Effective: 18.12.2001
2nd Amendment to EU Directive 2001/83/EC: 2003/63/EC[3] Annex I, Section 3.2.2.4	Published: 27.06.2003 Effective: 01.07.2003
EU Commission Notice to Applicants (NTA), Volume 2B, 2008[5], Section 3.2.P.4	May 2008 *Info on Module 3 is from July 2004*
EMEA CHMP Guideline on Excipients in the dossier for application for marketing authorisation of a medicinal product, Revision 2, EMA/CHMP/396951/2006[13]	Published: 19.06.2007 Effective: 01.01.2008

As water is used for most dosage forms and the general Ph.Eur. monograph "Substances for pharmaceutical use" is applicable to all excipients, the following provisions are considered to be part of the basic provisions on the content of 3.2.P.4.

Table 10: complementary regulatory framework for 3.2.P.4 Control of Excipients, sorted by publication date

Type and Title of regulatory framework	**Date**
EMEA CPMP Note for Guidance on Quality of Water for Pharmaceutical Use CPMP/QP/158/01 Revision[118]	First Published: 01.05.2002 Effective: 01.06.2002
EMA Draft Guideline on the quality of water for pharmaceutical use EMA/CHMP/CVMP/QWP/496873/2018[119]	First Published: 15.11.2018 *Consultation closed, but not effective yet*
Ph.Eur. 10.2. General monograph "Substances for pharmaceutical use, Monograph 2034[120]	Last changed in supplement 9.3[121] (published 07/2017)[131]
ICH Guideline Q3C(R6) on impurities: guideline for residual solvents EMA/CHMP/ICH/82260/2006[122]	First Published: 26.10.2018 Effective: 08.10.2019

[117] EU Commission, Guideline on Excipients in the dossier for application for marketing authorisation of a medicinal product, Revision 2 (repealed)
[118] EMEA CPMP, Note for Guidance on Quality of Water for Pharmaceutical Use CPMP/QP/158/01 Revision
[119] EMA, Draft Guideline on the quality of water for pharmaceutical use EMA/CHMP/CVMP/QWP/496873/2018
[120] EDQM, Ph.Eur. 10.2, Substances for pharmaceutical use, 01/2018:2034
[121] EDQM, Ph.Eur. 10.2 online, History of the Ph.Eur. Monograph 2034 Substances for pharmaceutical use
[122] ICH Guideline Q3C(R6) on impurities: guideline for residual solvents

Type and Title of regulatory framework	Date
	The initial version became effective in 1997 acc. to the document history
ICH Q3D (R1) on elemental impurities EMA/CHMP/ICH/353369/2013[123]	First published: 29.03.2019 Effective: 29.03.2019 *The initial version became effective in 2014 acc. to the document history*
EDQM, Pharmeuropa Journal, edition 32.1, Reference: PA/PH/SG (19) 57 ANP, "Substances for pharmaceutical use"[124]	Published: January 2020

Furthermore, the ICH guidelines ICH Q3C and ICH Q3D are applicable to excipients in general, as well and can be applied depending on the Option chosen according the ICHQ3C (R6)/ ICH Q3D (R1).

The Journal Pharmeuropa publishes draft of new/ revised Ph.Eur. monographs for commenting. It is included here because a revision of the Ph.Eur. monograph "Substances for pharmaceutical use" is planned.

Specific provisions

An overview over further regulatory framework to be taken into consideration is provided in Table 11.

Due to the limited volume of this master thesis they will not be further explained but are listed here in order to make the reader aware of further reading on the provisions in 3.2.P.4

Table 11: Specific regulatory framework on 3.2.P.4 Control of Excipients

Type and Title of regulatory framework	Date
EMEA Note for guidance on inclusion of antioxidants and antimicrobial preservatives in medicinal products CPMP/CVMP/QWP/115/95[32]	Published: 08.07.1997 Effective: 01.01.1998
EMEA CPMP position statement on the quality of water used in the production of vaccines for parenteral use[125] *(intended to be replaced by new guideline on the quality of water for pharmaceutical use – currently draft)*	First published: 20.10.2003
ICH Guideline Q3C(R8) on impurities: guideline for residual solvents (Draft) *specific for the solvents: methyltetrahydrofuran, tert-butanol and cyclopentylmethylether[126]*	Endorsed: 25.03.2020
ICH Q3D (R2) Final Concept Paper *to be updated with regards to PDEs for cutaneous and transdermal application[127]. The current work plan foresees public consultation in Q2/Q3 of this year (2020)[128]*	Dated 01/2020

[123] ICH Q3D (R1) on elemental impurities
[124] EDQM, Pharmeuropa 32.1, Substances for pharmaceutical use
[125] EMEA CPMP, position statement on the quality of water used in the production of vaccines for parenteral use
[126] ICH Guideline Q3C(R8) on impurities: guideline for residual solvents (Draft) specific for the solvents: methyltetrahydrofuran, tert-butanol and cyclopentylmethylether
[127] ICH Q3D (R2) Final Concept Paper, Statement of the perceived problem
[128] ICH Q3D (R2) Maintenance EWG Work Plan, 1.b. Future anticipated key milestones

Development of the regulatory provisions for 3.2.P.4

3.2.P.4.1 Specifications and 3.2.P.4.4 Justification of Specifications

General- compendial and non-compendial excipients

Not much has been changed in the basic guidelines instructing on the dossier content (refer to Annex A - 3.2.P.4 Control of Excipients). But bigger changes have been done to specific aspects of the excipient control.

Within the basic guidelines on the dossier content, for excipients that are not described within a pharmacopoeia of the EU member states but a 3rd country pharmacopoeia, the following has been added: A justification is required and the 3rd country pharmacopoeia has to comply with the Ph.Eur. monograph "Substances for pharmaceutical use" acc. to the EMEA CHMP Guideline on Excipients in the dossier […], Revision 2, from 2007/2008.
Until 2008 the monograph 2034 Substances of pharmaceutical use has become mandatory for substances monographed in the European Pharmacopoeia only[129], nowadays this monograph applies to all excipients- compendial or not.

Furthermore, the recommendation for flavours/ colorants to comply with the relevant foodstuff provisions as explained in section Development of the regulatory provisions for module 3.2.P.2, 3.2.P.2.1.2 Components of the Drug Product- Excipients, Colorants and Flavours has been included in the 2007/2008 EMEA CHMP Guideline on Excipients. It additionally expresses the need for microbiological purity and endotoxin testing on sterile products (except when tested on the bulks before sterilisation) and the necessity to provide information and data on residual solvents.

In comparison to the 2007/2008 EMEA CHMP Guideline on Excipients […], the Ph.Eur. monograph 2034 "Substances for pharmaceutical use" describes more extensively the tests to be performed on excipients. It has been changed within the last 20 years. An overview has been provided in Table 12: Changes monograph 2034 Substances for Pharmaceutical Use[129,130].

Particularly important is the change of the scope of the monograph "Substances for Pharmaceutical Use" to all substances and therefore all excipients (Supplement 6.3, published 2008). This means that all the tests listed in the monograph should be taken into consideration for an excipient specification. Some additional tests must be considered even if it is a compendial excipient. Residual solvents, elemental impurities, microbiological purity, sterility, bacterial endotoxins, pyrogens and additional characteristics may need control depending on the manufacturing process of excipient/ finished product, the nature of the substance or its planned use. This also means that a justification of specification has to be provided for compendial excipients.

[129] EDQM, Ph.Eur. 10.2 online, Monograph 01/2018:2034 "Substances for pharmaceutical use", Knowledge Database, History (record) of the monograph
[130] EDQM, Ph.Eur. Online, Archive Search on publication/ implementation dates and the monograph Substances for pharmaceutical use in Ph.Eur. 5.5, 5.7, 6.0, 6.3, 6.5, 7.7, 8.8, 9.1, 9.3, monograph 5.1.4 microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use in Ph.Eur. 5.0, monograph 5.1.10 in Ph.Eur. 8.8, monograph 5.17 in Ph.Eur. 5.8

Table 12: Changes monograph 2034 Substances for Pharmaceutical Use

Ph.Eur. Edition	Date published	Date implemented	Changes	Comments on consequences
5.5	12/2005	07/2006	Related substances: exemptions from the related substances test in the monograph now allowed if the monograph for the excipient does not sufficiently control the purity. Residual solvents: now the content of residual solvents must be considered for calculation of the specific optical rotation and specific absorbance	From an analytical point of view the tests optical rotation and specific absorbance should already include this criteria in the calculation formula but if not, the formula must be changed accordingly.
5.7	09/2006	04/2007	Exclusion of herbal drugs, herbal drug preparations/ extracts for applicability of the monograph	n.a. for this theses (→ see introduction)
5.8	12/2006	07/2007	Reference to 5.1.7 Viral safety added	In Ph.Eur. 5.8 the monograph 5.1.7 Viral Safety was introduced (and hasn't been changed since[131]).
6.0	07/2007	01/2008	Related substances: The option to deviate from the provisions given on the limits of related substances has been given, if it can be sufficiently explained (for active substances). Microbiological quality: Inclusion of the requirement to test pharmaceutical substances on microbiological purity acc. Ph.Eur. 5.1.4, depending on their nature and the planned use if such a test is not already included in the respective Ph.Eur. monograph for the substance.	All excipients need to be checked on the necessity to be tested on microbiological purity, if not already reflected in the dossier.
6.3	06/2008	01/2009	**The monograph substances for pharmaceutical use is now mandatory for all substances, not only for those which are already Ph.Eur. monographed**. It has been formally added that finished product manufacture has to be done within GMP rules.	The new scope includes non-compendial excipients now. The obligation to fulfil GMP is not a new requirement but has been added in the supplement 6.3.
6.5	01/2009	07/2009	Identification: it has been clarified that if more than one test is given for first identification, those are equivalent. Reporting, identification and qualification threshold have been added for peptides (when they are the active substance). For veterinary drug substances, limits on impurities have been added.	No consequences on old dossiers within the scope of this thesis.
7.7	10/2012	04/2013	Introduction of the requirement for active substances to comply with the guidelines on genotoxic impurities and relevant Q&As	Not relevant for the scope of this thesis

[131] EDQM, Ph.Eur. 10.2 online, Monograph 01/2008:50107 "5.1.7 Viral safety", Knowledge Database, History (record) of the monograph

8.8	01/2016	07/2016	Chemical precursors for radiopharmaceutical preparations are removed of the scope of the monograph substances for pharmaceutical use as those requirements have been published in a separate monograph	No consequences on old dossiers within the scope of this thesis.
9.1	07/2016	01/2017	The reference to the guideline on genotoxic impurities and Q&As introduced in Ph.Eur. 7.7 is replaced by the reference to the new ICH Guideline M7 (for active substances) Due to the substantial revision of the chapter 5.1.10 Guidelines on using the test for bacterial endotoxins as published in Ph.Eur. 8.8, it has been added that substances to be used in parenteral medicinal products or irrigation products have to comply with 5.1.10 if the endotoxin limit is not already given by the respective excipient monograph. Although if there is a procedure in place to remove endotoxins in the manufacturing process then it is not needed acc. to 5.1.10.	Genotoxic impurities in active substances: not relevant for the scope of this thesis Parenteral/irrigation products: Has endotoxin testing been established for the excipients and are the limits compliant with 5.1.10? Alternatively: is a procedure in place to remove endotoxins from the medicinal product acc. to the current monograph substances for pharmaceutical use (e.g. Ultrafiltration)?
9.3	07/2017	01/2018	A section on elemental impurities has been added, referring to the ICH Q3D guideline and the Ph.Eur. general chapter 5.20. For production of substances the manufacturer must also ensure compliance with Ph. Eur. 5.10.	A control strategy for elemental impurities must be in place now, which includes (depending on the option chosen and results), that the excipients have to include tests on the purity with regards to elemental impurities.
Draft revision published in Pharmeuropa edition 32.1 from January 2020 but not yet in the Ph.Eur.			A section on the requirement to… -perform a risk assessment -if necessary, to modify the manufacturing process of the substance. - and implement a control strategy for recognition and control …on N-Nitrosamine impurities was added.	Within the overall control strategy of Nitrosamine impurities, it should be checked if excipients are a potential source of contamination. For further information refer to the results of development of the module 3.2.P.5.6

In general, it should be considered that there are many general chapters in the European Pharmacopoeia that describe requirements for specific types of tests, e.g. Ph.Eur. chapter 2.2.32 Loss on drying. Explaining their change history would go beyond the allowed volume for this thesis and can be looked up in the Ph.Eur. online change history in the knowledge database.

For non-compendial excipients it should be checked if they have been introduced in either the European Pharmacopoeia or another official pharmacopoeia of one of the EU member states. If this is the case the specification must be updated to comply with the relevant monograph or equivalency has to be proven[132]. In case of an update to the pharmacopoeia monograph, it is then questionable if the previous supplier/ manufacturer can provide the pharmacopoeia quality or if a new supplier/ manufacturer has to be qualified. If a certain edition/ supplement of a compendial excipient is mentioned or the whole Ph.Eur. specification of a previous version is included, this has to be updated to the current Ph.Eur. monograph.

It should be taken into account, that the excipient specification should reflect the functional properties of the excipients as identified in the pharmaceutical development (refer to Development of the regulatory provisions for module 3.2.P.2, 3.2.P.2.1.2 Components of the Drug Product- Excipients, Proof of function). If not done already, these tests must be established, a suitable test procedure must be developed and validated which will take some time, depending on the laboratory capacities.

Microbiological purity

The microbiological purity testing was introduced into the general monograph "Substances for pharmaceutical use" in 2008/2009 (Ph.Eur. 6.0). Now it is the requirement to control the microbiological purity if needed for all excipients, where the test is not already included in the monograph. The criteria for the obligation to control microbiological purity are the nature of the excipient and its planned use. For the use in sterile products the above mentioned 2007/2008 EMEA CHMP Guideline on Excipients […] requires the microbiological purity test unless tested on the bulk before sterilisation (see above). Information on the necessity to test excipients on microbiological purity might be missing in old product dossiers in section 3.2.P.4.4. In this case, the need to perform this test must be evaluated and justified in 3.2.P.4.4. Where needed, the test should be included in the relevant excipient specification. As the analytical methods are described in Ph.Eur. 2.6.12./ 2.6.13 verification is required and should be done before the dossier is finalised.

Endotoxins

For parenteral/irrigation products it should be checked if endotoxin testing has been established for the excipients and if the limits are compliant with the current 5.1.10. The general text Ph.Eur. 5.1.10 was largely revised in Ph.Eur. 8.8 (2016). It should be taken under consideration if a procedure is in place to remove endotoxins from the medicinal product acc. to the current monograph substances for pharmaceutical use (e.g. Ultrafiltration). Provided that no procedure for removing endotoxins is in place, it must be checked if an endotoxin test is in place and if it is compliant with the current Ph.Eur. 5.1.10. Else the test must be included in the excipient specification and a verification must be done. This is a mandatory requirement in the monograph "Substances for pharmaceutical use" since its revision in Ph.Eur. Supplement 9.1.

Viral safety

see subchapter 3.2.P.4.5 for further information.

Residual Solvents

It is not a new expectation to establish a control strategy for residual solvents as the first version of the ICH Q3C guideline was published in 1997. However, there were several changes to the guideline within the last years and revision 6 is currently valid, while revision 8 has already been drafted. The

[132] EMEA CHMP, "Guideline on excipient in the dossier for application for marketing authorisation of a medicinal product", Revision 2, , Chapter 4.3 Specifications (3.2.P.4.1 a)

new draft intends to include information specifically for the residual solvents methyltetrahydrofuran, tert-butanol and cyclopentylmethylether. According to the document history published in ICH Q3C (R6), PDEs have been revised due to new data and a PDE for Triethylamine has been introduced. Thus, it should be checked if the information given on residual solvents in excipients is still up to date (to be clarified with the excipient manufacturer/ supplier), depending on the control strategy on the medicinal product (refer to 3.2.P.5, Development of the regulatory provisions for 3.2.P.5, 3.2.P.5.6 Justification of Specifications).

Elemental impurities

With Ph.Eur. Supplement 9.3 the heavy metals test was deleted from all monographs of the European Pharmacopoeia. Instead, a new section was introduced in the general monograph "Substances for pharmaceutical use" referring to the ICH Q3D (R1) Guideline from 2019 and its Ph.Eur. implementation in the general chapter 5.20. Depending on the control strategy of the medicinal product (refer to 3.2.P.5, Development of the regulatory provisions for 3.2.P.5, 3.2.P.5.6 Justification of Specifications) experimental data, elemental impurities need to be considered in the excipient specifications. The respective test procedure needs to be verified or validated. The ICH Q3D (R1) Guideline is currently under revision in order to include impurity limits for cutaneous and transdermal applications.

Water

The current effective guideline EMEA CPMP Note for Guidance on Quality of Water for Pharmaceutical from 2002 use will be updated in order to reflect several changes done in the European Pharmacopoeia. Among others, it is allowed to produce Water for injections now by other procedures than distillation[133,134]. As a consequence, compliance of water used should be checked with the current Ph.Eur. monographs and also with both EMA/EMEA Guidelines, current and new.

3.2.P.4.2 Analytical procedures

No relevant change has been done for 3.2.P.4.2 (see Annex), but the specification changes that might be required as described in chapter Development of the regulatory provisions for 3.2.P.4, 3.2.P.4.1 Specifications and 3.2.P.4.4 Justification of Specifications, should be considered. If new tests need to be set up, an appropriate analytical procedure must be established or a suitable procedure from the Ph.Eur. must be applied, if possible.

3.2.P.4.3 Validation of Analytical Procedures

The fact that validation should be done for analytical procedures has been mentioned first in Directive 2003/63/EC [3] (see Annex), but not much information is given in the basic regulatory provisions on the contents of 3.2.P.4.3. On the other hand, ICH Q2 (R1) has been introduced in the 90s and describes the recommendations on validation. Excipients are not specifically mentioned, though. ICH Q2 (R1) will be amended by ICH Q2(R2)/ Q14, but a draft of the new guideline has not been published on the ICH homepage yet. The ICH concept paper explains the need to describe more recent analytical procedures and their recommendations on validation as well as giving some instruction how to provide and use data created in the procedure development[135]. According to the timetable, the draft should be already in preparation[136]. Once it is published, it should be considered for upcoming submissions.

On the lines of the previous section 3.2.P.4.2 Analytical procedures, the effort, time and cost of validation of the analytical procedures for new tests (if required), or changes in the analytical procedure, should be considered for the dossier update.

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[133] EMA, Draft Guideline on the quality of water for pharmaceutical use, 1. Introduction (background)
[134] GMP-Compliance.org, without author, "Revision of EMA's Guideline on the Use of Pharmaceutical Water"
[135] ICH, Final concept paper, "ICH Q14: Analytical Procedure Development and Revision of Q2(R1) Analytical Validation,dated 14 November 2018", Section "Statement of the perceived problem"
[136] EDQM, Ph.Eur. 10.2 online, Monograph 01/2008:50107 "5.1.7 Viral safety"

3.2.P.4.5 Excipients of Human or Animal Origin

With introduction of the monograph 5.1.7 Viral safety in Ph.Eur. 5.8 (2008) it became mandatory to perform a risk assessment on the viral safety for excipients of human or animal origin[137]. For materials of human or animal origin a summary of the risk assessment mentioned above, and the conclusions/ controls performed should be included in the dossier.

Excipients not derived from human or animal origin: A statement should be included confirming the absence (e.g. excipient manufacturer/ supplier statement and/or results of literature search on the origin of well-known excipients). Suppliers for the pharmaceutical and food industry usually have such a statement readily available.

For consideration of the TSE risk for materials of human or animal origin, it should be checked if certificates of suitability for compliance with the Ph.Eur. monograph 5.2.8 "Minimising the risk for transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" for absence of TSE provided are still up to date. The excipient suppliers may have changed their sourcing/ manufacturing process in the meantime therefore should provide the updated information. This should be checked with the suppliers/ manufacturers of the excipients or for certificates of suitability the EDQM database can be checked. The currently valid "note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev. 3) was introduced in 2011. Previous versions were in place from 2004-2011(Rev. 2) and 2001-2004 (rev.1) and information included in the dossier according to revision 1 or 2 may not reflect the current scientific knowledge[138],[139].

In general, the information provided in chapter 3.2.R "Certificates of Suitability" and "Medicinal products containing or using in the manufacturing process materials of animal and/or human origin" should be considered for the update of this chapter as well, if relevant.

3.2.P.4.6 Novel Excipients

Both, the superseded EU Commission Guideline on Excipients in the dossier for application for marketing authorisation of a medicinal product, 1st version and the EMEA CHMP Guideline which replaced it (Revision 2) provide the most detailed information on the recommendations for this dossier module. Most recommendations have not changed, however with the Revision 2 introduced in 2007/2008 it has been specified that for novel excipients the same criteria are expected as for active substances- they have to comply with the provisions given in the guideline on the chemistry of the active substance. Since the guideline on chemistry of the active substance has changed within the last 20 years, those changes need to be considered for the description of novel excipients, too[140]. Furthermore, the same provisions on stability data apply as for active substances and stability has to comply with ICH Q1A (R2).

It may have happened, that an excipient, which was considered novel in the past, is not novel anymore, e.g. it has been included in the European Pharmacopoeia or a pharmacopoeia of one of the EU member states. See description on the development of 3.2.P.4.1 Specifications and 3.2.P.4.4 Justification of Specifications.

However, if the formerly novel excipient is still considered to be novel, it will be very time consuming to update it to the current recommendations.

[137] EDQM, Ph.Eur. 10.2 online, Monograph 01/2008:50107 "5.1.7 Viral safety"
[138] European Commission, Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev. 3), introduction
[139] EMEA CPMP/CVMP note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 rev. 2), introduction
[140] EMA Homepage, Chemistry of active substances, Document history

3.2.P.5 Control of Drug Product

Types of regulatory provisions

Basic provisions on the content of 3.2.P.5

The following provision gives some general instruction on the content of 3.2.P.5 today:

Table 13:basic regulatory framework for 3.2.P.5 Control of Drug Product

Type and Title of regulatory framework	**Date**
EU Commission Guideline "Specifications and Control Tests on the Finished Product", 3AQ11a[141]	Published: 01.12.1991 Effective: 01.06.1992
2nd Amendment to EU Directive 2001/83/EC: 2003/63/EC[3] Annex I, Section 3.2.2.5	Published: 27.06.2003 Effective: 01.07.2003
EU Commission Notice to Applicants (NTA), Volume 2B, 2008[5], Section 3.2.P.5	May 2008 *Info on Module 3 is from July 2004*

In addition to the Guideline 3AQ11a, there are further guidelines considered to be basic, but for specific topics:

Table 14 complementary regulatory framework for 3.2.P.5 Control of Drug Product, sorted by publication date

Type and Title of regulatory framework	**Date**
ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology CPMP/ICH/381/95[142] *Revision 1 was created in 2005, when part Q2A and Q2B of the guideline were fused together.*	Published: 01.06.1995 Effective: 01.06.1995
ICH Q3B "Impurities in New Medicinal Products", first version CPMP/ICH/282/95 *(replaced)*[143]	Published: 11/1996
EMEA CPMP "Note for guidance on stability testing of existing active substances and related finished products"[234] CPMP/QWP/556/96 *(replaced by the EMA Guideline on stability testing CPMP/QWP/122/02)*	Published: 03/1997 Effective: 10/1998
ICH Q6A "Specifications: test procedures and acceptance criteria for new drug substances and new products: chemical substances CPMP/ICH/367/96[144]	Published: 01.05.2000 Effective: 01.05.2000
ICH Q3B (R2) Impurities in new drug products CPMP/ICH/2738/99[145] *The attachment was introduced in 2006 but the main document in 2003. Revision R1 was implemented in 2003, first version from 1996*	Published: 01.06.2006 Effective: 01.08.2003

[141] EU Commission Guideline "Specifications and Control Tests on the Finished Product", 3AQ11a
[142] EMA Homepage, ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology CPMP/ICH/381/95
[143] ICH Q3B "Impurities in New Medicinal Products", first version
[144] ICH Q6A, Note for Guidance Specifications: Test Procedures and Acceptance Criteria for new Drug Substances and New Drug Products: Chemical Substances
[145] ICH Q3B(R2), Note for Guidance on Impurities in New Drug Products

Type and Title of regulatory framework	Date
EMEA CPMP "Guideline on stability testing: Stability testing of existing active substances and related finished products", CPMP/QWP/122/02 Rev. 1 corr.[240] *The initial guideline from 1996 was revised in 2002 and received an new number.* The first version of CPMP/ICH/421/02 has been revised again in 2003.	Published: 17.12.2003 Effective: 01.03.2004 *Initial version from 2002*
EMEA Guideline on the limits of genotoxic impurities EMEA/CHMP/QWP/251344/2006[146]	Published: 28.06.2006 Effective: 01.01.2007
EMA Questions and answers on the 'Guideline on the limits of genotoxic impurities' EMA/CHMP/SWP/431994/2007 Rev.3[147]	Published: 14.01.2010
ICH M7 (R1) guideline on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk[148] *First published (unrevised) in 2014, for version R1 the Addendum was added*	Published: 21.07.2017 Effective: 21.07.2017
ICH Guideline Q3C(R6) on impurities: guideline for residual solvents EMA/CHMP/ICH/82260/2006[122]	First Published: 26.10.2018 Effective: 08.10.2019 *The initial version became effective in 1997 acc. to the document history*
ICH Q3D (R1) on elemental impurities EMA/CHMP/ICH/353369/2013[123]	First published: 29.03.2019 Effective: 29.03.2019 *The initial version became effective in 2014 acc. to the document history*
EMA Information on nitrosamines for marketing authorisation holders EMA/189634/2019[149]	Dated: 19.09.2019
CMDh Information to marketing authorisation holders CMDh/404/2019[150]	Dated: 26.09.2019
CMDh and EMA Questions and answers on "Information on nitrosamines for marketing authorisation holders" EMA/CHMP/428592/2019 Rev. 3[151]	Dated: 27.03.2020
CMDh practical guidance for Marketing Authorisation Holders of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5(3) Referral on Nitrosamines CMDh/412/2019, Rev. 4[152]	Dated: March 2020

The guidelines mentioned can be applied to all medicinal products in scope of this thesis and are therefore considered basic.

Specific provisions on 3.2.P.5

An overview over further regulatory framework to be taken into consideration is provided in Table 15.

Due to the limited volume of this master thesis they will not be further explained but are listed here in order to make the reader aware of further reading on the provisions in 3.2.P.5. Antibiotics are a small

[146] EMEA Guideline on the limits of genotoxic impurities
[147] EMA Questions and answers on the 'Guideline on the limits of genotoxic impurities' EMA/CHMP/SWP/431994/2007 Rev.3
[148] ICH M7 (R1) guideline on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk
[149] EMA Information on nitrosamines for marketing authorisation holders EMA/189634/2019
[150] CMDh Information to marketing authorisation holders CMDh/404/2019
[151] CMDh and EMA Questions and answers on "Information on nitrosamines for marketing authorisation holders"
[152] CMDh practical guidance for Marketing Authorisation Holders of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5(3) Referral on Nitrosamines CMDh/412/2019, Rev. 4

group of medicinal products among all of them, and generic solid oral dosage forms may not be rare. But the "EMA Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action" is specific on the dissolution test only, therefore it will not be further discussed in this thesis. The new ICH Q3C(R8) currently available as draft, is specific for merely three solvents. The ICH Q3D(R2) has not been published as draft yet and will contain changes specific for transdermal and cutaneous applications. The Guidelines on inhalation and nasal products, transdermal patches and oral modified-release products are specific for certain application routes. The Guidelines on Parametric Release have been written for a certain type of batch release system (control strategy) only and will not be further explained in favour of the volume of this thesis.

Table 15: Specific regulatory framework on 3.2.P.5 Control of Drug Product

Type and Title of regulatory framework	**Date**
EMEA Note for Guidance on Parametric Release CPMP/QW/3015/99 *(replaced)*[153]	Published: 01.03.2001 Effective: 01.09.2001
EMA Guideline on the pharmaceutical quality of inhalation and nasal products EMEA/CHMP/QWP/49313/2005[35]	Published: 21.06.2006 Effective: 01.10.2006
EMA Guideline on Real Time Release Testing (formerly Guideline on Parametric Release) EMA/CHMP/QWP/811210/2009-Rev1[154]	Published: 13.04.2012 Effective: 01.20.2012
EMA Adopted guideline on setting specifications for related impurities in antibiotics EMA/CHMP/CVMP/QWP/199250/2009 corr[155]	Published: 13.07.2012
EMA Guideline on quality of transdermal patches EMA/CHMP/QWP/608924/2014[40] *replaces the previous guideline from 2000 ("Note for guidance on quality of modified release products: A: oral dosage forms B: transdermal dosage forms section I (quality)*	Published: 16.12.2014 Effective: 17.06.2015
EMA Guideline on quality of oral modified-release products EMA/CHMP/QWP/428693/2013[40] *replace the previous guideline from 2000 ("Note for guidance on quality of modified release products: A: oral dosage forms B: transdermal dosage forms section I (quality)*	Published: 31.07.2014 Effective: 31.01.2015
EMA Concept Paper on the revision of the guideline on the pharmaceutical quality of inhalation and nasal products (Draft) EMA/CHMP/QWP/115777/2017[42]	Published: 22.03.2017
EMA Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action EMA/CHMP/CVMP/336031/2017[156]	Published: 15.08.2017
ICH Guideline Q3C(R8) on impurities: guideline for residual solvents (Draft) *specific for the solvents: methyltetrahydrofuran, tert-butanol and cyclopentylmethylether[126]*	Endorsed: 25.03.2020
ICH Q3D (R2) Final Concept Paper *to be updated with regards to PDEs for cutaneous and transdermal application[127]. The current work plan foresees public consultation in Q2/Q3 of this year (2020)[128]*	Dated 01/2020
EDQM, Ph.Eur. 10.2 online, Chapter 07 Dosage forms *with its subchapters for the different dosage forms*	*Various*
EDQM, Ph.Eur. 10.2 online, Chapter 02 Methods of analysis and 05 General Texts	*Various*

[153] EMEA Note for Guidance on Parametric Release *(replaced)*
[154] EMA Guideline on Real Time Release Testing (formerly Guideline on Parametric Release) -Rev1
[155] EMA Adopted guideline on setting specifications for related impurities in antibiotics, corr
[156] EMA Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action

Development of the regulatory provisions for 3.2.P.5

In contrast to previous chapters, no overview table will be presented in Annex A for module 3.2.P.5.1, 3.2.P.5.2 and 3.2.P.5.3. There have been no changes in the more detailed, general guidelines specific for these modules: 3AQ11a, ICH Q6A, ICH Q2(R1). However, the ICHQ3B (R2) for impurities has changed and its changes are listed in Annex A. The basic dossier content provisions published within the last 20 years (Directive 2001/83/EC initial version, Directive 2003/63/EC, NTA Volume 2B) did not provide new requirements/ recommendations, respectively the description it too unprecise to allow a comparison and to conclude on the development of the regulatory expectations.

Ph.Eur. general chapters & monographs for the dosage forms

There are many general chapters in the European Pharmacopoeia that describe requirements for specific types of tests, e.g. Ph.Eur. chapter 2.2.46 Chromatographic separation techniques. Explaining their change history would go beyond the allowed volume for this thesis and can be looked up in the Ph.Eur. online change history in the knowledge database. The Ph.Eur. texts on dosage forms should be considered for the dosage form described in the old product dossier, the required tests described in those texts should be performed and up to date with the current monograph. Non-compliance with this aspect has also been mentioned as frequent issue in the BfArM gap analysis from 2006[1], point 4.1. For example, in the dosage form text for "tablets" the requirement on the number and samples for the test the subdivision of tablets have been clarified. This is also described in an EMA Q&A. Usually the subdivision of tablets is only tested during pharmaceutical development[157].

3.2.P.5.1 Specifications

There was no change in the general guidelines on the specification for medicinal products, 3AQ11a and ICH Q6A. Both guidelines were already published 20 years ago. Little changes have been done to the guideline for shelf life specification, though. For guidelines addressing impurities, there have been some changes, too.

Shelf life specification (Guideline on stability testing: Stability testing of existing active substances and related finished products)

The initial EMEA "note for guidance on stability testing of existing active substances and related finished products" from 1997 was revised in 2002 and 2003. Unfortunately, the revision from 2002 could not be found in the internet anymore in order to do a detailed comparison of the provisions on the specification for shelf life. Therefore, the initial version and the revision from 2003 were compared (see Annex A, 3.2.P.5, Comparison of recommendations on the shelf life specification)

The version from 2003 does not contain significant changes for the shelf life specification in 3.2.P.5.1.

The 2003 revision includes a more precise description of the tests to be done in order to show the preservative content effectiveness within product development. This includes the need to test one primary stability batch at the recommended shelf life for preservative content and preservative effectiveness. This specific recommendation has not been included in any guidance before, including the "Note for Guidance on inclusion of antioxidants and antimicrobial preservatives in medicinal products"[32]. Results from a primary stability batch may not be available in 3.2.P.2. for old product dossiers. But there should be post-approval stability tests which prove the absence at the proposed shelf life. A reference to the relevant data in 3.2.P.8.3 can be done then.

[157] EMA, Q&As on Quality, Part I, "European Pharmacopoeia- Monograph on tablets", question 1 "European Pharmacopoeia (Ph.Eur.)- Harmonised chapter uniformity of dosage units", "How should industry demonstrate compliance wiht the European Pharmacopoeia with regard to uniformity of dosage units"

Impurities general & ICH Q3B (R2)

Active substance changes

In case there have been changes in the active substance part (e.g. new manufacturer, changed synthesis) and new degradation products are found, they should be included in the finished product specification[158]. This means setting up an appropriate analytical procedure (or taking over the active substance analytical procedure, if possible) and performing analytical procedure validation for the drug product.

ICH Q3B (R2) Impurities in new drug products

The current version ICH Q3B (R2) became effective in 2006, the previous version R1 was published in 1999 (step 2) and became effective (Step 4) in 2003, and the initial version is from 1996 (Step 4) [159]. Unfortunately ICH Q3B (R1) is not available anymore, neither on the ICH nor on the EMA website and the history of changes in the version R2 (ICH document only*) does not give any information on the changes done[159]. Therefore, a comparison was done between the current Revision 2 and the initial version of ICH Q3B from 1996 (refer to Annex A, Comparison of ICH Q3B first version and Revision 2):

In contrast to the initial version from 1996, the current revision 2 contains an explanation, when degradation products have to be reported and how they should be included in the specification formally (e.g. determination of decimal places, numerical reporting) as well as scientifically (when to report as identified, specified/ unspecified). The reporting/ identification/ qualification thresholds given have not been changed, except for the identification and qualification threshold for a maximum daily dose of more than 2 grams. For this dosage the identification threshold has been tightened marginally by adding a 2nd decimal place. For the qualification threshold the limit has been widened a little bit, though. Furthermore, the TDI from the Qualification threshold has been widened from 2 to 3 mg.

In course of a dossier update current data on degradation products should be reviewed by quality assurance. Are new data available that require a change of the specification tests or limits? Such data can be follow-up- stability data or data from stress studies (see 3.2.P.5.3, development of regulatory provisions) Is the specification set up in a way that correlates with the formal and scientific recommendations elaborated in revision 2? Has a rationale been given for the specification set-up? See also section 3.2.P.5.6 (development of regulatory provisions). Is the maximum daily dose higher than 2g and the changes in the identification threshold has a negative impact on the results? For example, previous stability results have been in the range of 0.11 to 0.14 and are now out of specification. If changes are required, the consequences could be that…

a) …specification limits have to be changed and it needs to be checked if the analytical procedure validation is suitably validated to cover the new limit (e.g. linearity, range, limit of quantification). If this is not the case, a new validation must be done.

b) …new degradation product(s) need to be specified (identified or unidentified) when it is/ they are higher than the reporting thresholds. When it is/ they are higher than the identification threshold, trials for identification must be done and e.g. a reference substance must be qualified. In addition, specificity of the analytical procedure for the new specified degradation product needs to be proven, i.e. revalidation activities need to be started.

c) …the quantitation limit is exceeded, and changes need to be performed in order to reduce the amount of impurities (e.g. manufacturing process changes, more protective primary bulk or finished product packaging material) or the higher limit needs to be qualified by a toxicological risk assessment.

[158] ICH Q6A, 3.2.2 d
[159] ICH Q3B(R2), Note for Guidance on Impurities in New Drug Products, Document History

The technical progress in the last 20 years might also lead to higher degradation results. Analytical equipment nowadays detects impurities much better than 20 years ago.

The mass balance of assay and impurities should be reviewed and discussed (e.g. do the impurities have the same detectability by the analytical procedure than the active substance?) when changes are done.

All the changes above require appropriate human resources, time and are costly. They need to be done before the dossier can be updated and should be planned appropriately.

*The document history is only included in the ICH Q3B (R2) on the ICH homepage but not in the adopted version of the EMA. The initial version and revision one not reached step 5 [159] and have not been implemented in the European Union.

Mutagenic impurities acc. to ICH M7 (R1) and Nitrosamines

The first version of ICH M7 on the assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potentially carcinogenic risks was published in 2014. Since then it is mandatory to check on the occurrence of mutagenic impurities in medicinal products (for further information refer to 3.2.P.5.6).

There are three triggers for changes of tests or acceptance criteria of potentially mutagenic impurities in the finished drug product specification: First, mutagenic impurities are already included in the specification due to the control strategy already set up, but the limits need to be narrowed due to the introduction of acceptance criteria in ICH M7(R1). Second, changes, that result in changed amounts of mutagenic impurities or in new mutagenic impurities (e.g. an active substance synthesis change leads to new mutagenic degradation products). Third, new mutagenic impurities were present in the past but are detected just now and a risk assessment needs to be done. This assessment might lead to new tests in the finished product specification for those impurities as part of the control strategy.

A popular example for the third case is Nitrosamine impurities. The awareness for those impurities was raised in 2018/2019 and an Article 5(3) referral was started with the result that all marketing authorisation holders need to assess the risk of Nitrosamine impurities (see also: 3.2.P.5.6 Justification of Specifications).

Residual solvents in the finished product ICH Q3C(R6)

The concept of residual solvent control has not changed within the last 20 years. Consequently, it merely needs to be checked, if changes concerning the excipients, active substance and drug product manufacturing process lead to new residual solvents or altered limits in the finished product specification. Alternatively, the limits implemented or changed in the past revisions of this guideline may lead to new tests or changed specification limits. For further information refer to the development of the regulatory provisions for module 3.2.P.5.6.

Elemental impurities in the finished product ICH Q3D (R1)

In 2014, the ICHQ3D guideline was introduced in its first version and revised in 2019. Resulting from that, it can be necessary to either implement additional tests for elemental impurities in the drug product specification or change the acceptance criteria of existing impurities. This would be the case if no control strategy has been established yet or if changes are planned requiring an updated risk assessment. For further information see development of the regulatory provisions for module 3.2.P.5.6.

3.2.P.5.2 Analytical Procedures

There has been no relevant change in the guidelines that apply for this module: 3AQ11a, ICHQ6A and ICH Q3B(R2). Changes in the specification as mentioned above (e.g. new degradation products) can have an impact on the analytical procedure description, though (refer to Development of the regulatory provisions for 3.2.P.5, 3.2.P.5.1 Specifications .

3.2.P.5.3 Validation of Analytical Procedures

ICH Q2(R1) was created in 1995 and the content has not changed since then. Thus, the basic provisions on analytical procedure validation have not changed within the last 20 years. But it should be checked, if changes in the tests were performed and the acceptance criteria as described in the chapters 3.2.P.5.1 lead to new verification or validation activities. The same applies to changes in the in-process-controls if they are changed due to updates of the control strategy (see development of regulatory provisions for 3.2.P.5.6). A new degradation product that is included in the finished product specification with an HPLC procedure requires a validation of the analytical procedure and the results should be included in 3.2.P.5.3, for example.

Specifically, for the detection of possible impurities, stress testing should be performed with light, heat, humidity, acid/base hydrolysis and oxidation. This recommendation is in included in ICH Q3B(R2), chapter 2, but has not been included in the initial version from 1996 (refer to Annex A, 3.2.P.5). Therefore, it may be that the old product dossier does not contain such data. Stress studies need to be performed then and the results should be discussed. The worst case for timelines and effort is, when a new degradation product is found, and it cannot be excluded that it might be generated under normal conditions at a limit over the reporting threshold. That might be the case, if there are not much stability data from the finished product are available yet. It may also happen when analytical equipment has become more better within the last years and detects more impurities than it has before. The specification must be updated thereupon (for consequences see above, 3.2.P.5.1).

Other changes in the specification might also demand a revalidation or new validation of additional analytical procedures. The second would derive from additional tests for impurities (refer to Development of the regulatory provisions for 3.2.P.5, 3.2.P.5.1 Specifications).

The BfArM gap list from 2006[1] mentions as frequent gap that in case alternative test procedures are applied, their comparability is often not shown, e.g. by F-test or t-test. If this is the case comparability must be investigated or one of the procedures should be deleted. Further chromatograms for the proof of the detection limit and individual values for test results (not just mean/ standard deviation) should be presented (point 4.2).

3.2.P.5.4 Batch Analyses

For Batch Analysis the EU Commission “Specifications and Control Tests on the Finished Product” 3AQ11 still provides the most detailed recommendations. They have not been changed since 1991/1992. As mentioned above, the basic dossier content provisions published within the last 20 years (Directive 2001/83/EC initial version, Directive 2003/63/EC, NTA Volume 2B) did not provided new requirements/ recommendations (for further information refer to Annex A, 3.2.P.5).

Nevertheless, it shall be noted, that changes in the specification have to result in updated batch analysis data. Even if this is not the case, old batch analysis data (e.g. older than 3 years) shall be replaced with current data in order to reflect the current compliance of the finished product with the specification (not just the past compliance). The BfArM gap analysis list from 2006[1] additionally mentions the need to include the batch size and date of the certificate of analysis (point 4.5).

3.2.P.5.5 Characterisation of Impurities

The Notice to Applicants Volume 2B from 2004/2008 includes the recommendation to describe the characterisation in this module if it has not been already done in 3.2.S.3.2. of the active substance dossier part. If no new degradation products appear in the drug product (new compared to degradation products in the drug substance), only a reference to 3.2.S.3.2 needs to be provided (refer to Annex A, 3.2.P.5). This is hardly a new expectation, though, because the CTD section for characterisation of impurities has been there before indicating that information needs to be given on this topic (the CTD was introduced in 2003, see chapter Results, subchapter General).

ICH Q3B(R2) from 2006 describes the need for to justify why an impurity was identified or when identification was not successful (chapter 5), whereas this had not been described yet in the initial version of 1996. Thus, efforts for identification should be described in this chapter, if not already included.

If information has not been provided on this topic yet, it'll be good to check the analytical development documentation for availability. For new impurities found (see 3.2.P.5.1), which solely originate from the drug product, this information should be reported when the impurity is investigated. The information should be summarized in 3.2.P.5.5 then.

3.2.P.5.6 Justification of Specifications

General: Need for a control concept

With the introduction of ICH Q8 (R1) and Part II to ICHQ8 in 2008 it was explained that the authorities expect a description of the control concept for the whole medicinal product, which should be described in 3.2.P.5.6 (refer to Part II, Chapter 3.3 and 2.4) The details should be given in the following chapters[160]:

- Control of excipients (3.2.P.4)
- Control of the manufacturing process (3.2.P.3.3)
- Control of critical steps and intermediates (3.2.P.3.4)

The overall strategy for the control concept should be described in this chapter, if the dossier was written after 2008. If not, the information may be found in the development report, if available, or in parts in other documents (e.g. manufacturing process risk assessment). In case the control concept has not been explained, the available data and all controls must be re-discussed among the experts of product development, quality assurance and quality control, manufacturing/ operations and regulatory affairs. When the control concept has not been fully described in any document before, the risk is increased that it is not well-thought-out, and gaps will be found. Those gaps will have to be closed first, i.e. the relevant changes done, before the old product dossier can be updated with this information in order to meet current regulatory provisions.

ICH Q9

The principles applied to set up the control strategy should be based on quality risk management, for example according to ICH Q9[93]. The ICH Q9 guideline was published in 2006 and has been unrevised since that. Many guidelines refer to ICH Q9, for example ICH Q8 (R2) refers in its chapter 2.5 control strategy to ICH Q9[84].

Degradation products ICH Q3B (R2)

With revision of the ICH Q3B guideline (refer to development of the regulatory provisions for 3.2.P.5.1) more advice has been given, how alternative impurity thresholds than those given in the guideline could be justified.

Further guidance on…

- when to specify degradation products,
- how unidentified degradation products can be explained and
- what must be considered if higher degradation product limits than applied in the clinical safety studies shall be applied…

has been provided (see also Annex A, Comparison of ICH Q3B first version and Revision 2).

[160] ICH Q8(R2) Pharmaceutical Development., part II annex, Chapter 2.5, 3.3

This additional guidance might be helpful for defending the choice of degradation products as well as the limits in the specification in course of the dossier update. The justification should be included if it has not been given so far.

Mutagenic impurities ICH M7 (R1)

ICH M7, first version, was published in 2014. Currently the first revision is effective, which was published in 2017. With the first revision an appendix 3 (attachment) was introduced, containing acceptable intakes (AIs) and Permissible Daily Exposures (PDEs) for many mutagenic substances[161].

Revision 2 is already planned (draft not published yet) and it shall contain further instructions on the implementation of the control concepts and recommendations for AIs/ PDEs for additional mutagenic substances[162].

Previous to ICH M7, the meanwhile superseded "Guideline on the limits of genotoxic impurities" (2006/2007) and the superseded "Questions and answers on the guideline on the limit of genotoxic impurities" (2010) were valid. With introduction of ICH M7, a harmonisation between the provisions of the EMA and FDA were done[163].

For example, the previous Guideline on the limits of genotoxic impurities targeted active substances only. Thereof solely those known substances were addressed, where investigation showed no safety with regards to new/ bigger amounts of genotoxic impurities for new. Additionally, the guideline was effective for variations to active substance synthesis routes[164]. In contrast, ICH M7 applies also for variations, renewals, new applications of drug products with known active substances. But this is the case only when formulation/composition/ description of the manufacturing process are changed and cause new degradation products or a widening of previous degradation product specification. Moreover, changes in the indication and posology are also in the scope, when they lead to alteration of the acceptable cancer risk level[165]. ICH M7 also elaborated some concepts such as the application of TTCs and answered open questions[163].

In consequence, for old product dossiers the PDEs determined in ICH M7(R1) may not have been considered yet and in the worst case, adaptions e.g. for the active substance part (e.g. change of purification steps) will have to be done or adaptions in the finished product manufacturing process, choice of excipients, packaging etc. It depends on the source of the mutagenic impurity where the adaption will have to be done in order to meet the given PDEs. Alternatively, a justification can be found to justify the current limits as described in ICH M7 (R1), chapter 7.5. But beforehand it must be clear, which genotoxic impurities can be present, how much of them and where the source is.

There's not only the risk of not meeting PDEs established in 2017. It needs to be considered that changes done (e.g. to the active substance synthesis) lead to new potential mutagenic impurities and if they are degradation products, they must be controlled in the finished product specification[158] (and a toxicological assessment needs to be done). Second, for potential mutagenic impurities already identified, the amount of scientific data (carcinogenicity data) available for the toxicological assessment may have changed and confirmation may now be available for the carcinogenicity of the impurity. In consequence, it will then be a class 1 impurity[166] and the general Threshold of

[161] ICH M7 (R1) guideline on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk, Document history
[162] ICH M7 (R2) Maintenance Concept Paper, "ICH M7(R2) : Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk", Statement of the Perceived Problem
[163] ICH Homepage, ICH M7 (R1) Concept Paper, M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, Statement of the perceived problem
[164] EMEA Guideline on the limits of genotoxic impurities, 2. Scope
[165] ICH M7 (R1) guideline on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk, 2. Scope of the guideline
[166] ICH M7 (R1), 6. Hazard assessment elements (Table) and 7.2.1 1st paragraph

Toxicological Concern (TTC) can no longer be applied but a substance- specific risk assessment and determination of the limit for the specification must be done. Therefore, review of the situation with regards to potential mutagenic impurities and subsequent update of the respective risk assessment together with the toxicological expert of the company is recommended.

A dossier written and authorised before 2006 or before 2014, with none of the changes within the scope of ICH M7 as mentioned above, may not contain information on genotoxic impurities at all. So first of all a risk assessment has to be done in order to find out if there's a risk for such impurities to be present. Subsequently further measures can be established, if the risk was confirmed, as described above.

Overall the strategy to control potentially mutagenic impurities needs to be described in this module: Are potentially mutagenic impurities present? If yes, are they controlled directly or indirectly* in the drug substance part (3.2.S), drug product specification, in one of the material specifications (solvents, excipient, packaging material) or by controls in the manufacturing process (e.g. in-process-controls, process parameters)?

*indirectly: prevent formation of the potentially mutagenic impurity

Nitrosamines

Nitrosamine impurities belong to those mutagenic impurities, that are considered "high potency" acc. to ICH M7(R1), and therefore the general TTC of 1.5 µg/day does not apply to them[167]. Due to Nitrosamines found in medicinal products with Sartanes (e.g. Valsartan, Losartan) as active substances and further products it is obligatory for all medicinal products with marketing authorisation to perform a risk assessment on the presence of Nitrosamines until 30.09.2020. This obligation is independent from the marketing status[168,169] If the risk is confirmed, further steps/ measures have to be taken[170,171]. On the lines of this strategy, old dossiers without marketing authorisation but with plans to achieve that must be evaluated for the risk of nitrosamines as well, and the risk evaluation must be submitted with the marketing authorisation application[172].

Since the topic Nitrosamines only came into focus of the authorities just recently, it is probable that an assessment with regards to this group of impurities has not been done yet. On the other hand, if a marketing authorisation is in place for the medicinal product, then risk assessment may have been done already- as the original deadline for submitting the outcome for all marketing authorisations was end of March 2020 [170]. The risk assessment will require data on the active substance, finished product manufacture (including manufacturing process and impurities in excipients) and packaging material, so it will need some time for creation. This applies in particular, if 3rd parties are involved, because they may have many requests received on that topic currently. If a risk cannot be included, step 2 and potentially step 3 will have to follow, which will require further time and resources. This should be taken into consideration, when the dossier update is planned.

[167] ICH M7 (R1), 3. General principles, paragraph 2
[168] CMDh practical guidance for Marketing Authorisation Holders of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5(3) Referral on Nitrosamines CMDh/412/2019, Rev. 4, Introduction and 1. Step 1- Risk Evaluation
[169] EMA Homepage, Post- authorisation, Referral procedures, Nitrosamine Impurities, Subsection "Guidance to avoid nitrosamines in human medicines"
[170] EMA Information on nitrosamines for marketing authorisation holders EMA/189634/2019, Subsection "Call for review"
[171] CMDh Information to marketing authorisation holders CMDh/404/2019, Subsection "Call for review"
[172] CMDh and EMA Questions and answers on "Information on nitrosamines for marketing authorisation holders", Question No. 13

The risk of presence of Nitrosamines and their control strategy should be described in this module. For step 2 (confirmatory testing) an analytical method shall be included into Ph.Eur for certain Nitrosamine impurities, refer to chapter 2.4.36 in edition 32.2 of Pharmeuropa[173].

Residual Solvents

The ICH Q3C guideline has been in place 20 years ago already, but it has been revised several times since then. Thus, a risk assessment and control strategy should be established and described in 3.2.P.5.6 but it may have to be revised due to changed PDEs that were implemented during the revisions of the guideline. Furthermore, a PDE for Triethylamine was introduced in revision 6 according to the document history.

For changes that have been done or are planned to the excipients, active substance or drug product, the risk assessment may have to be updated (depending on the impact of the change). The presences of residual solvent impurities can originate from the active substance, excipients or the drug product. They can be formed or intentionally added in their production[174]. Depending on their source, residual solvents can be controlled within the active substance specification, the excipient specification, in-process-controls in the drug product manufacturing process and/or finished product controls.

In relation to what has been changed, the tests performed/ limits must be corrected in the respective specification and/or in- process controls. For example, a change in the manufacturing process of an excipient, which leads to higher amounts of residual solvents present, can be controlled in the excipient specification. In case the amount of the residual solvent is higher than the PDE for the excipient, testing on the drug product must be performed (and the required test introduced) in order to show compliance of the drug product with the PDE.

The most time and effort causing scenario would be, that the PDE for the drug product is exceeded due to the change performed in either the product itself, or the revision of the ICH Q3C guideline and measures need to be taken to reduce the residual solvents (e.g. purging steps, change of the manufacturing process, qualification of a different supplier for the respective component). Such measures must be discussed, planned, implemented, controlled- all of which takes time and will cause costs for the trials and changes performed.

Note that the ICH Q3C(R6) guideline may not include existing marketed drug products in its scope[174], but the Ph.Eur. general text 5.4 makes it obligatory for existing active substances, excipients and medicinal products[175].

Elemental impurities

Since introduction of ICH Q3D(R1) Guideline in 2019 and its predecessor guideline ICH Q3D in 2014 it is mandatory to perform a risk assessment on elemental impurities. The outcome of this risk assessment may be, that elemental impurities can be present and have to be controlled. That applies basically, if the amount of the relevant elemental impurity in the drug product is more than 30% of the Permitted Daily Exposure limit (PDE) given in the ICH Q3D(R1) guideline[176]. For those impurities a control strategy has to be set up: The elemental impurities can be controlled in the active substance specification and/ or in the excipient (or other material) specification and/ or within in-process controls and/ or in the drug product[177], depending on the source of the impurity. The source of the impurity should be identified[178].

[173] EDQM, Pharmeuropa 32.2, 2.4.36. *N*-Nitrosamines in active substances
[174] ICH Q3C(R6), 2. Scope of the guideline
[175] Ph.Eur. 10.2, General texts, 5.4 Residual Solvents, 1st paragraph
[176] ICH Q3D(R1), 5.6 Summary of Risk Assessment Report
[177] ICH Q3D (R1), 6. Control of elemental impurities
[178] ICH Q3D (R1), 5.5. Evaluation 2)

If the amount of elemental impurities exceeds the PDEs, measures should be taken to reduce the amount of these impurities, such as establishment of purification steps in the manufacturing process. The packaging material could be changed, when it is the source [177].

Between the first version and the first revision only the PDE of Calcium in inhalation products had been changed acc. to the document history of ICH Q3D(R1). The ICH Q3D (R1) Guideline is currently under revision in order to include impurity limits for cutaneous and transdermal applications[127].

Product dossiers written before 2014 probably still contain the general Ph.Eur. heavy metals test, which has been removed from all monographs, but no information on occurrence of elemental impurities. If a risk assessment is not included in the dossier yet, it may have been done by the quality department already. However, if this is not the case (e.g. because the product was not on the market), a risk assessment will have to be done. Several possibilities are given by the ICH Q3D guideline for the evaluation of the risk[179]. How much effort it will take to create this risk assessment depends a little bit on the approach that is chosen. Drug product testing is usually done rather quickly for example (provided that it can be done in-house), however it does not give any information on the source of the elemental impurities. Following a positive test result with more than 30% of the PDE, it will have to be investigated, where the source of the impurities is.

Another approach is to request information of all active substance manufacturers, excipient suppliers/ manufacturers, the drug product manufacturing process and the packaging material supplier/ manufacturer and sum it up, but it will take some time to get all this information. On the other hand, in case of change it makes it easier to recalculate the total amount of elemental impurities in the drug product and no money has to be spent on the drug product analysis. Additionally, in case of a test result that exceeds 30% of the PDE, it will be obvious where the source(s) is/are.

When measures are required in order to reduce the elemental impurities in the drug product, it will need a project to determine those and control if the measures were effective, which will also have an effect on the resources time and cost.

But even if the result of the risk assessment is that no risk for the presence of elemental impurities is identified, it should be explained how this conclusion was drawn[180].

The ICH Q3D(R1) recommendations are reflected in the general chapter 5.20 of the European Pharmacopoeia.

[179] ICH Q3D (R1), 5.5. Evaluation 2nd paragraph
[180] ICH Q3D (R1), 5.5. Evaluation 1)

3.2.P.6 Reference Standards or Materials

Basic provisions on the content of module 3.2.P.6

The following provisions give some general instruction on the content of 3.2.P.6 today:

Table 16: basic regulatory framework for 3.2.P.6 Reference Standards or Materials, sorted by publication date

Type and Title of regulatory framework	**Date**
EU Commission Guideline "Specifications and Control Tests on the Finished Product", 3AQ11a[141]	Published: 01.12.1991 Effective: 01.06.1992
2nd Amendment to EU Directive 2001/83/EC: 2003/63/EC[3] Annex I, Section 3.2.2.6	Published on: 27.06.2003 Effective: 01.07.2003
EU Commission Notice to Applicants (NTA), Volume 2B, 2008[5], Section 3.2.P.6	May 2008 Info on Module 3 is from July 2004

Furthermore, the Ph.Eur. General Text 5.12 contains general recommendations on Reference Standards. In addition, the ICH Q6A provides some guidance, as well as ICH Q2(R1).

Table 17: complementary regulatory framework for 3.2.P.6 Reference Standards or Materials

Type and Title of regulatory framework	**Date**
ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology CPMP/ICH/381/95[142] *Revision 1 was created in 2005, when part Q2A and Q2B of the guideline were fused together.*	Published: 01.06.1995 Effective: 01.06.1995
ICH Q6A "Specifications: test procedures and acceptance criteria for new drug substances and new products: chemical substances CPMP/ICH/367/96	Published: 01.05.2000 Effective: 01.05.2000
Ph.Eur. 10.2. General text 5.12 Reference Substances[181]	Last changed in supplement 9.5 (published 01/2018)

[181] Ph.Eur. 10.2 online, 5.12 Reference Substances 07/2018:51200

Development of the regulatory provisions for module 3.2.P.6

The following provisions have been compared on reference standards/materials in Annex A, chapter 3.2.P.6 :

- All the provisions mentioned above, which give some general instruction on the content of 3.2.P.6
- ICH Q6A
- ICH Q2(R1)

It was found that they do not contradict each other, they rather have to be seen as complementary to each other. This makes sense, considering that all of them are effective today. There have been no relevant changes within the last 20 years. Of the above, Guideline 3AQ11a and the ICH Q6A provide the most detailed recommendations on reference substances but have been effective already 20 years ago. ICH Q2/ ICH Q2(R1) only informs that reference materials (of active substance and impurities) used for validation should be well-characterised (non-compendial) and of defined purity and have not changed. Since then, it has only been added that information must not be provided in 3.2.P.6, if it is for all reference standards/ materials already included in the active substance part of the dossier. However, there might be tests in the drug product that require reference substances not covered in the active substance dossier. One example is a reference standard for an impurity, which is a leachable from a component of the primary packaging.

Ph. Eur. Reference Standards

The Ph.Eur. General text 5.12 Reference Substances is more extensive than the regulatory framework mentioned above, though. On the other hand, it describes only European Pharmacopoeia reference standards and not reference materials generally. It has originally been introduced with Ph.Eur. 6.0 (published in 07/2007 and implemented in 01/2008). Changes of the Ph.Eur. General text 5.12 "Reference Substances" are described in Table 18[182, 183].

For the use of reference standards from the European Pharmacopoeia, dossiers normally provide the information that a Ph.Eur. reference standard is used. The intended use should be given. As Ph.Eur. reference standards have usually been established for active substance testing, a justification for use in the drug product testing should be provided. For the use as assay standard, chapter 3 of Ph.Eur. 5.12 includes some guidance how this can be done:

- It must be the same chromatographic assay procedure as given in the active substance monograph
- It must be shown by verification that excipients in the composition do not interfere with the method
- Pre-treatments required on the sample must be validated for the drug product

Such a justification usually does not change unless e.g. there was a change in the composition of the drug product and a new verification needs to be done.

Ideally, no further information obtained from Ph.Eur. 5.12 is given in the dossier (e.g. how they have been qualified, monitored, manufactured etc. by the EDQM). However, if this is the case, this information must be updated to the current version of Ph.Eur. 5.12.

This applies in the same way if it is referred to a certain version of Ph.Eur. 5.12 within chapter 3.2.P.6, e.g. Ph.Eur. edition 7.4. (This may be the case when the dossier document had been used for

[182] Ph.Eur. 10.2 online, History of the Ph.Eur. General Text 5.12 Reference Standards
[183] Ph.Eur. Online, Archive Search

submissions in non-EU countries, who do not acknowledge the provisions of the European Pharmacopoeia).

To sum up, none of the changes performed to the general text 5.12 should have an influence on the qualification of Ph.Eur. reference standards done in the past. The prerequisite is that no contents of Ph.Eur. 5.12 have been described in 3.2.P.6 or the precise Ph.Eur. edition has been given for chapter 5.12.

Table 18: Changes to Ph. Eur. general text 5.12

Ph.Eur. Edition	Date published	Date implemented	Changes	Comments on consequences (of the content of 3.2.P.6)
8.4	10/2014	04/2017	The chapter has been completely revised. 1. Introduction Clarification provided: Definition for reference materials and chemical reference materials included in this text, but no further guidance is given in this Ph.Eur. chapter. The section on applicability of the text on biological reference preparations has been deleted. 2. Terminology The definition of the primary, secondary, international standard and reference material has been elaborated and stated more precisely. The terminology has been harmonised with the ISO Guides/ WHO Technical report series 932 3. Use of Reference Standards For the case that a reference standard is used for a different purpose than for which it has been established, the need for qualification of this different use should be described in the dossier "if applicable". The section for use of the secondary standard has been rephrased and a comment on the use of international standards for characterisation/ calibration of secondary standards has been added. 4. Establishment of Reference standards Some parts of this chapter have been rephrased/ corrected (minor changes). Guidance on herbal reference standards has been included. Recommendations on biological reference preparations have been included, as well as guidance on chemical reference substances for biologicals. Description of tests to be done for a secondary standard deleted.	Usually not relevant (biological and herbal medicinal products are not in scope of this thesis (see introduction). Usually not relevant, minor changes only- the explanation is a bit different, but the overall meaning isn't. In case a European Pharmacopoeia standard is used for a different purpose than stated in the monograph, it should be checked if it has been qualified for the intended use and the qualification has been described in the dossier. However, this is not really a new requirement. ICH Q6A, Chapter 2.11 from 2000 states already that a reference standard should be qualified for its intended use. And Guideline 3AQ11a recommends to add a description and specification of the substance in the dossier, therefore it is only a logical consequence to add information about qualification for purpose other than given in the monograph to 3.2.P.6.

Ph.Eur. Edition	Date published	Date implemented	Changes	Comments on consequences (of the content of 3.2.P.6)
			5. Manufacturing, Labelling, Storage and Distribution of European Pharmacopoeia Reference Standards The information for labelling of non-pharmacopoeia reference materials was deleted. Elaboration on the description of storage and packaging of the reference standards has been done. 6. Re-test programme of European Pharmacopoeia Standards Deletion of the description of the monitoring program of the EDQM General: some editorial changes were done, e.g the addition of the EDQM Internet address for checking the stability of the reference standards. Information on the type of standard (e.g. powder/ solution), type of packaging and related retesting frequency as well as tests done deleted.	Not relevant for the scope of this thesis (biological and herbal medicinal products excluded) Usually not relevant for 3.2.P.6 Usually not relevant for 3.2.P.6 Usually not relevant for 3.2.P.6
9.5	01/2018	07/2018	*Acc. to the history in Ph.Eur. 10.2 online for the General text 5.12, the Terminology has changed, namely the definition of CRSs by deleting the paragraph referring to ISO Guide 34.* The deleted section contained some explanation on the difference of pharmacopoeial reference standards versus reference materials and certified reference materials. In addition, it provided information on the definition of the specifity of pharmacopoeial reference standards in ISO Guide 34.	No consequences on the dossier update, the section deleted was an explanation on the differentiation between reference standards and materials.

In house Reference Materials

For non-compendial in-house standards an extensive description must be done (specification, characterisation, CoAs, further data such as impurity profiles). It should be verified with QA/QC if the reference materials is still qualified with the same specification and analytical methods. If the reference material is sourced from a third party, these questions should be raised to the third party. Certificates of Analysis should be updated. It shall also be checked, if the source of the reference material has changed and the information in the dossier should be updated when this is the case.

3.2.P.7 Container Closure System

Basic provisions on the content of the module 3.2.P.7

The following provisions give some general instruction on the content of 3.2.P.7 today:

Table 19: basic regulatory framework for 3.2.P.7 Container Closure System, sorted by publication date

Type and Title of regulatory framework	**Date**
EU Directive 2001/83/EC original version from 2001 without amendments[12], Annex 1, Part 2, Section A 1.1, C 1.1. and C 1.2	Published on 28.11.2001 Effective: 18.12.2001
2nd Amendment to EU Directive 2001/83/EC: 2003/63/EC[3**Fehler! T extmarke nicht definiert.**] Annex I, Section 3.2.2.7	Published on: 27.06.2003 Effective: 01.07.2003
EU Commission Notice to Applicants (NTA), Volume 2B, 2008[5], Section 3.2.P.7	May 2008 *Info on Module 3 is from July 2004*
EMA Guideline on the manufacture of the finished dosage form EMA/CHMP/QWP/245074/2015[96]94	Published: 14.08.2017 Effective: 14.02.2018

Furthermore, for non-compendial packaging materials there are some Directives/ Provisions relating to food packaging in general or plastic packaging materials. Plastic packaging materials are widely used, thus provisions on them are considered part of the basic provisions on the content of 3.2.P.7, too. The ICH Q3D Guideline gives some general recommendations on elemental impurities in packaging materials and the Ph. Eur. chapters on glass containers, plastic packaging and plastic additives (incl. additives and extractables) are also applicable to many medicinal products and therefore discussed in this thesis.

Table 20: complementary regulatory framework for 3.2.P.7 Container Closure System, sorted by publication date

Type and Title of regulatory framework	**Date**
Directive 89/109/EEC on the approximation of the laws of the member states relating to material and articles to come into contact with foodstuffs *(revised in 1989, replaced by Regulation EC/1935/2004)*[184,185]	Published: 21.12.1988 Effective: 10.01.1989 Replaced: 03.12.2004
Directive 90/128/EEC relating to plastic materials and articles intended to come into contact with foodstuffs[186],[187] *(revised in 1992, 1993, 1995, 1996, 1999, 2001, replaced by Directive 2002/72/EC)*	Published: 21.03.1990 Effective: 31.12.1990* Replaced: 04.09.2002
Ph.Eur. General Chapter 3.2 Containers[188] *(Chapter 3.2 was established before 2000)*	No content changes since 2000
Directive 2002/72/EC relating to plastic materials and articles intended to come into contact with foodstuffs[189, 190] *(revised in 2004, 2005, 2007, 2008, 2009, replaced by Regulation EU/10/2011)*	Published: 15.08.2002 Effective: 04.09.2002 Replaced: 01.05.2011

[184] Directive 89/109/EEC, unconsolidated
[185] Directive 89/109/EEC, consolidated
[186] Directive 90/128/EEC, unconsolidated
[187] Directive 90/128/EEC, consolidated
[188] Ph.Eur. 10.2, General chapter 3.2
[189] Directive 2002/72/EC, unconsolidated
[190] Directive 2002/72/EC, consolidated

Type and Title of regulatory framework	Date
Regulation EC/1935/2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC[191,192], *revised in 2010*	Published: 13.11.2004 Effective: 03.12.2004
EMEA CHMP/CVMP Guideline on plastic immediate packaging materials CPMP/QWP/4359/03	Published: 19.05.2005 Effective: 01.12.2005
Regulation (EU) No. 10/2011 on plastic materials and articles intended to come into contact with food[193, 194] *(revised in 2001, 2011, 2012, 2014, 2015, 2016, 2017, 2018, 2019)*	Published: 15.01.2011
Ph.Eur. General Chapter 3.1 Materials used for the manufacture of containers[195] *(Chapter 3.1 was established before 2000)*	Last changed in supplement 7.6 (published 07/2012)
Ph.Eur. General Chapter 3.2.2 Plastic containers and closures for pharmaceutical use[196] *(Chapter 3.2.2 was established before 2000)*	Last changed in supplement 8.4 (published 10/2014)
Ph.Eur. General Chapter 3.2.1. Glass containers for pharmaceutical use[197] *(Chapter 3.2.1 was established before 2000)*	Last changed in supplement 9.6 (published 07/2018)
ICH Q3D (R1) on elemental impurities EMA/CHMP/ICH/353369/2013[123]	First published: 29.03.2019 Effective: 29.03.2019 *The initial version became effective in 2014 acc. to the document history*
Ph.Eur. General Chapter 3.1.13. Plastic additives[198] (*Chapter 3.1.13 was established in 2000)*	Last changed in edition 10.0 (published 07/2019)
Ph.Eur. 2.4.35 Extractable elements in plastic materials for pharmaceutical use, so far only published as draft in Pharmeuropa[199]	Pharmeuropa 32.2 (April 2020

*only partially

Specific provisions on 3.2.P.7

An overview over further regulatory framework to be taken into consideration is provided in Table 21.

Due to the limited volume of this master thesis they will not be further explained but are listed here in order to make the reader aware of further reading on the provisions in 3.2.P.7. They are either specific to a specific type material/ component/ medicinal product (e.g. blood products) or administration type.

Table 21: specific regulatory framework for 3.2.P.7 Container Closure System, sorted by Ph.Eur. chapter No.

Type and Title of regulatory framework	Date
ICH Q3D (R2) Final Concept Paper *to be updated with regards to PDEs for cutaneous and transdermal application[127]. The current work plan foresees public consultation in Q2/Q3 of this year (2020)[126128]*	Dated 01/2020

[191] Regulation 1935/2004, unconsolidated
[192] Regulation 1935/2004, consolidated
[193] Regulation (EU) 10/2011, unconsolidated
[194] Regulation (EU) 10/2011, consolidated
[195] Ph.Eur. 10.2, General chapter 3.1
[196] Ph.Eur. 10.2, General chapter 3.2.2
[197] Ph.Eur. 10.2, General chapter 3.2.1
[198] Ph.Eur. 10.2, General chapter 3.1.13
[199] GMP Navigator"Update zu COC / COP und Extractable Elements in Kunststoffmaterialien"

Type and Title of regulatory framework	Date
Ph.Eur. General Chapter 3.1.3. Polyolefins[200] *(Chapter 3.1.3 was established before 2000)*	Last changed in supplement 9.4 (published 10/2017)
Ph.Eur. General Chapter 3.1.4. Polyethylene without additives for containers for parenteral preparations and for ophthalmic preparations[201] *(Chapter 3.1.4 was established before 2000)*	Last changed in supplement 9.2 (published 01/2017)
Ph.Eur. General Chapter 3.1.5. Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations[202] *(Chapter 3.1.5 was established before 2000)*	Last changed in supplement 9.4 (published 10/2017)
Ph.Eur. General Chapter 3.1.6. Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations[203] *(Chapter 3.1.6 was established before 2000)*	Last changed in supplement 9.4 (published 10/2017)
Ph.Eur. General Chapter 3.1.7. Poly(ethylene- vinyl acetate) for containers and tubing for total parenteral nutrition preparations[204] *(Chapter 3.1.6 was established before 2000)*	Last changed in supplement 9.2 (published 01/2017)
Ph.Eur. General Chapter 3.1.8. Silicone oil used as lubricant[205] *(Chapter 3.1.8 was established before 2000)*	Last changed before 2008
Ph.Eur. General Chapter 3.1.10. Materials based on non-plasticized poly(vinyl chloride) for containers for non-injectable, aqueous solutions[206] (*Chapter 3.1.10 was established before 2000)*	Last changed in supplement 8.4 (published 10/2014)
Ph.Eur. General Chapter 3.1.11. Materials based on non-plasticized poly(vinyl chloride) for containers for solid dosage forms for oral administration[207] (*Chapter 3.1.11 was established before 2000)*	Last changed in supplement 9.6 (published 07/2018)
Ph.Eur. General Chapter 3.1.14. Materials based on plasticized poly(vinyl chloride) for containers for solid dosage forms for oral administration[208] (*Chapter 3.1.14 was established in 2000)*	Last changed in edition 10.0 (published 07/2019)
Ph.Eur. General Chapter 3.1.15. Polyethylene terephthalate for containers for preparations not for parenteral use[209] (*Chapter 3.1.15 was established in 2002 with Ph.Eur. 4.0)*	Last changed in supplement 7.5 (published 01/2012)
Ph.Eur. 3.1.16 Cyclo-olefin polymers, so far only published as draft in Pharmeuropa[199]	Pharmeuropa 32.2 (Aril 2020
Ph.Eur. 3.1.17 Cyclo- olefin copolymers, so far only published as draft in Pharmeuropa[199]	Pharmeuropa 32.2 (Aril 2020
Ph.Eur. General Chapter 3.2.2.1. Plastic containers for aqueous solutions for infusion[210] (*Chapter 3.2.2.1 was established in 2001 with Ph.Eur. 3.3)*	Last changed in edition 6.0 (published 07/2007)
Ph.Eur. General Chapter 3.2.9. Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze- dried powders[211] (*Chapter 3.2.9 was established before 2000)*	Last changed in supplement 9.5 (published 01/2018)

[200] Ph.Eur. 10.2, General chapter 3.1.3
[201] Ph.Eur. 10.2, General chapter 3.1.4
[202] Ph.Eur. 10.2, General chapter 3.1.5
[203] Ph.Eur. 10.2, General chapter 3.1.6
[204] Ph.Eur. 10.2, General chapter 3.1.7
[205] Ph.Eur. 10.2, General chapter 3.1.8
[206] Ph.Eur. 10.2, General chapter 3.1.10
[207] Ph.Eur. 10.2, General chapter 3.1.11
[208] Ph.Eur. 10.2, General chapter 3.1.14
[209] Ph.Eur. 10.2, General chapter 3.1.15
[210] Ph.Eur. 10.2, General chapter 3.2.2.1
[211] Ph.Eur. 10.2, General chapter 3.2.9

Type and Title of regulatory framework	Date
Ph.Eur. General Chapter 3.3.1. Materials for containers for human blood and blood components[212] *(previously chapter 3.1.1, chapter 3.1.1 was established before 2000)*	Last changed before 2008*
Ph.Eur. General Chapter 3.3.2. Materials based on plasticised poly(vinyl chloride) for containers for human blood and blood components[213] *(previously chapter 3.1.1.1, chapter 3.1.1.1 was established in 2000 with Ph.Eur. 3.3)*	Last changed in supplement 9.6* (published 07/2018)
Ph.Eur. General Chapter 3.3.3. Materials based on plasticised poly(vinyl chloride) for tubing used in sets for the transfusion of blood and blood components[214] *(previously chapter 3.1.1.2,, chapter 3.1.1.2 was established before 2000)*	Last changed in supplement 9.6* (published 07/2018)
Ph.Eur. General Chapter 3.3.4. Sterile plastic containers for human blood and blood components[215] *(previously chapter 3.2.3, chapter 3.2.3 was established before 2000)*	Last changed in supplement 9.6* (published 07/2018)
Ph.Eur. General Chapter 3.3.5. Empty sterile containers of plasticised poly(vinyl chloride) for human blood and blood components[216] *(previously chapter 3.2.4, chapter 3.2.4 was established before 2000)*	Last changed in supplement 9.6* (published 07/2018)
Ph.Eur. General Chapter 3.3.6. Sterile containers of plasticised poly(vinyl chloride) for human blood containing anticoagulant solution[217] *(previously chapter 3.2.5, chapter 3.2.5 was established before 2000)*	Last changed in supplement 9.6* (published 07/2018)
Ph.Eur. General Chapter 3.3.7. Sets for the transfusion of blood and blood components[218] *(previously chapter 3.2.6, chapter 3.2.6 was established before 2000)*	Last changed in edition 10.0 (published 07/2019)
Ph.Eur. General Chapter 3.3.8. Sterile single-use plastic syringes[219] *(previously chapter 3.2.8, chapter 3.2.8 was established before 2000)*	Last changed in edition 10.0 (published 07/2019)

* no editorial changes considered

Development of the regulatory provisions for module 3.2.P.7

General

The provisions on the content of module 3.2.P.7 have not changed much, except for two aspects. The guideline on manufacture of the finished dosage form in its first revision from 2017/2018 includes in its chapter 4.4. the recommendation to describe the container closure systems of bulk and intermediates. This requirement has only been addressed in the EMA Q&As before[220].

Intermediate/ Bulk product container closure system

It shall be noted, that it has not been fully clarified, if data on bulk containers and closures should be provided in module 3.2.P.7 or 3.2.P.3.4. On one hand, the EMA Q&A, Part 2 Question "What information should be provided on the bulk container" states that the information should be included

[212] Ph.Eur. 10.2, General chapter 3.3.1
[213] Ph.Eur. 10.2, General chapter 3.3.2
[214] Ph.Eur. 10.2, General chapter 3.3.3
[215] Ph.Eur. 10.2, General chapter 3.3.4
[216] Ph.Eur. 10.2, General chapter 3.3.5
[217] Ph.Eur. 10.2, General chapter 3.3.6
[218] Ph.Eur. 10.2, General chapter 3.3.7
[219] Ph.Eur. 10.2, General chapter 3.3.8
[220] EMA, Overview of comments received on 'Draft Guideline on manufacture of the finished dosage form' EMA/CHMP/QWP/104223/2016, 2. Specific comments on text, Stakeholder no. 4, page 71, line 2 on the draft guidelines's lines 251-252

in 3.2.P.3.4[221]. However, acc. to experience of the author not all EU member states agree. The guideline on manufacture […], Rev. 1 2017/2018 does not specify the module[222]. Irrespective in which module the information is provided, addition of a reference to the other module is recommended.

For intermediate and bulk containers, a description of the materials used and a specification (for the primary packaging) shall be included.

This information can be available from development studies included in the product dossier already (module 2.4). Nonetheless it should be checked if the information is still up to date. Usually compliance certificates and/or CoAs must be updated to comply with current Ph.Eur. monographs or the current food packaging Regulations.
However, it is more probable that neither suitability of the bulk materials (module 3.2.P.2.4) nor specifications/ materials have been described in the old product dossier. Please be aware that information on containers and closures can also be part of module 3.2.P.3.

When information is not available in the dossier, QA and the department for manufacture and development have to be asked for this information. In case it turns out, packaging suitability of the intermediate/ bulk material has never been evaluated, this must be done, and information must be included in module 3.2.P.2.4. The material used and the specification will then depend on the results of the respective development studies.

Finished product container closure systems

For the finished product, similar checks should be done. Specifications must be examined for changes. CoAs should be updated and for Certificates of Compliance the validity of references to current Ph.Eur./ other provisions shall be checked.

Sometimes old product dossiers do not contain a specification in a tabular format used for release of the packaging material at the manufacturer but a technical data sheet from a packaging material supplier. Usually those technical data sheets contain tests that are either not relevant for the finished product manufacturer (e.g. width of the plastic foil when it is furled, which is not relevant because for blistering or packaging in sachets it will be cut in smaller pieces). Or the tests are performed by complex test methods which cannot be performed within a finished product manufacturer laboratory normally). In absence of other information these technical data sheets are the approved specification. They should be replaced by an adequate specification for testing at the finished product manufacturers incoming good control. A specification for the packaging material should be available from the finished product manufacturer. However, there are sometimes gaps when release is only done based on a visual check and “Fehlerbewertungslisten” (Failure Assessment List are an industry standard but do not replace a certificate of analysis). When marketing authorisations still exist, many variations might be required for all test parameters in order to replace the technical data sheet.

In general specifications shall be checked if they contain a test on critical dimensions. It was first recommended to do so explicitly in the Notice to Applicants Volume 2B (refer to Annex A, 3.2.P.7). The unrevised Directive 2001/83/EC and its revision 2003/63/EC already contained the requirement to describe the packaging, though, and dimensions testing could be seen as part of that.

Provisions of Ph.Eur. and compendial materials

Chapter 3.1 Materials used for the manufacture of containers

Chapter 3.1 is a general introduction in the texts on materials describing the content of this. It points to the fact, that the use of any other material than described in this chapter must be approved by the health authority. In 2012 (Ph.Eur. Supplement 7.6) it has been revised in order to include the requirement to assess the risk of presence of TSE in the packaging materials and if required, establish

[221] EMA, Q&As on Quality, Part II, "Stability- Stability issues of pharmaceutical bulk products use in manufacture of the finished product", question 2
[222] EMA Guideline on the manufacture of the finished dosage form, Revision 1, Chapter 4.4

follow up measures. The reason was, this it is still an industry practice to use them for the manufacture of plastic materials occasionally [223].

Note that there will be two new chapters for specific materials in Ph.Eur. , which have currently only been published in Pharmeuropa: Ph.Eur. 3.1.16 Cyclo-olefin polymers and 3.1.17 Cyclo- olefin copolymers.

Chapter 3.2 Containers

Chapter 3.2 containers has been unchanged in its content for the last 20 years[224]. It defines the terminology of different types/ attributes of containers and a container itself ("an article that contains or is intended to contain a product and is, or may be, in direct contact with it. The closure is a part of the container"[188]). If further describes the following requirements:

- It must be possible to remove the content for the applicant (patient, caregiver, nurse, physician)
- Protection against environment and degradation
- no interaction (physical/ chemical) with components of the content which changes the quality beyond the regulatory requirements

Chapter 3.1.13 Plastic Additives

The chapter for plastic additives defines them as impurities in container closure systems, intended to have an influence on the chemical/ physical properties of the material within the production process or within the final container. A list of plastic additives is included in Ph.Eur. 3.1.13 which can be used. Other additives may be used if approved by the authority. The requirement to identify all additives used, their impurities, reaction and degradation products and qualify them toxicologically is described. Within the packaging material specification, identity, physico-chemical properties, purity and assay must be investigated for all components with appropriate specification limits (e.g. additive content should be as low as possible)[225]. Only minor adjustments have been done to the monograph in the last 20 years. The structure of plastic additive 24 ($C_{26}H_{48}O_4$) has been corrected with Ph.Eur. 10.0 (published 07/2019), and 4 additional additives have been included with supplement 9.6 (07/2018). Within the same supplement 9.6 the general information on plastic additives (as summarized above in this section) has been provided. However, all these changes listed above will not have an influence on compliance with a material and its additives with Ph.Eur. 3.1.13. If a packaging material had been compliant with this chapter in the past, it will also be compliant today.

3.2.1. Glass containers for pharmaceutical use

Many changes have been done to chapter 3.2.1. They are explained and evaluated for their relevance in Table 22: Changes done to Ph.Eur. 3.2.1 within the last 20 years. Chapter 3.2.1 provides an overview over different type of glass materials and for which medicinal products they can be used. In the subchapter "Production" different glass corrosion effects and risk factors for their occurrence are described as well as the recommendation to assess those risks specifically for the medicinal product[197]. (The suitability should be justified in module 3.2.P.2.4).

Dossiers depicting contents of Ph.Eur. 3.2.1, referring to a previous version of the text (supplement 9.6 and below) or containing test results referring to a such a previous version should be updated. Tests may have to be repeated and the relevant descriptions adapted to the current Ph.Eur. 3.2.1.

[223] EDQM, Ph.Eur. 10.2 online, History of the chapter 3.1
[224] EDQM, Ph.Eur. 10.2 online, History of the chapter 3.2
[225] Ph.Eur.10.2, chapter 3.1.13 "Plastic Additives", subchapter Definition and General Requirements

Table 22: Changes done to Ph.Eur. 3.2.1 within the last 20 years

Ph.Eur. Edition	Date published	Date implemented	Changes	Comments on consequences (of the content of 3.2.P.7)
5.0	06/2004	01/2005	Complete revision of the chapter: Addition of hydrolytic surface test (Test A) by titration. Addition of the 2nd test method flame spectrometry as annex. (Alignment with ISO 720 and 4820) Test B (Glass Grains) has also been completely revised, e.g. the whole method description has changed. Test C (for identification if type I or II glass): For the Arsenic test the analytical method was changed to atomic absorption spectrometry. For the light transmission test for coloured glass containers the analytical method was changed to perform the measurement with a UV-VIS spectrophotometer.	The changes are relevant for module 3.2.P.7, as they affect all tests for all glass methods.
6.8	01/2010	07/2010	For Test B (Glass grains) limits have been adapted to comply with ISO 720 (1985)	Relevant if glass type I is used. Test B (Glass grains) has been changed. It is necessary to prove the glass type I.
8.3	07/2014	01/2015	The whole section production has been included, explaining the glass corrosion effects and possible causes. Some editorial changes for alignment with ISO 4802-1 and 4802-2 have been done. A section on syringes and cartridges has been introduced. Test A (Inner surface test) for Type I and II glass containers for distinguishing to glass type II: The cleaning, filling and heating procedure has been revised, e.g. requirements on time and temperature have been changed. Acceptance criteria for volumes of 2-3 ml have been added. Test B (Glass grains): Option for using a ball mill included (for alternative grinding). Test C (for identification if type I or II glass): Cartridges and Syringes added. Annex: Editorial changed, addition of acceptance criteria for 2.3 ml volume	Relevant as Test A (Surface test) has been changed, which is necessary to prove that the glass is type I or II and not type III.

Ph.Eur. Edition	Date published	Date implemented	Changes	Comments on consequences (of the content of 3.2.P.7)
8.4	10/2014	04/2015	It has been added, that the container must not release substances, which could be toxic. In some cases, therefore information on the risk for chronic use for vulnerable patient groups has to be provided.	Relevant change: Assessment on toxicity to be done.
9.6	07/2018	01/2019	The Test for hydrolytic resistance has been revised. General: The section for the equipment has been revised (additional details provided) Test A for Type I and II glass containers for distinguishing to glass type II: The cleaning procedure was revised for better reproducibility. Information on autoclaving of small containers added. The specifics of test B for determination of glass type I remain unchanged. In the annex for determination of hydrolytic resistance by flame spectroscopy limits for small filling volumes have been added.	The changes are applicable to all types of glass products. Tests performed before this revision may not be compliant with the current requirements of Ph.Eur. 3.2.1 anymore. This applies with the exception that the hydrolytic resistance has been measured with flame spectroscopy, this is justified and approved by the authority and the volume of the container is more than 2 ml

Chapter 3.2.2 Plastic containers and closures for pharmaceutical use

This chapter was established more than 20 years ago. It describes that additives may be present. However, when they leach into the container content, they can only be accepted in amounts that do not influence the efficacy/ stability or are a risk in terms of toxicity. The preparation within the container shall not be adsorbed heavily by the material or migrate into/ through the packaging material. Further information is given on the nature and purpose of additives.

Ph.Eur. 3.2.2 also emphasizes the importance of knowing the composition and manufacturing formula. For the choice of packaging materials, they should be tested under the conditions that are used in practice (e.g. sterilisation). The compatibility with the preparation packaged should be tested. The following criteria apply:

- no changes in physical properties
- no loss or gain because of permeating
- no pH changes
- no changes induced by light
- chemical and biological test should be done

Compatibility must be reassessed when changes to the composition, the manufacturing process (e.g. temperature changes) of the container closure system are done. Recycling must be validated. All materials described in Ph.Eur. are compliant with the requirements in chapter 3.2.2 if used as described in the pharmacopoeia.

Chapter 3.2.2 has only been changed in supplement 8.4 (published 10/2014)[226]. It has been added, that the container must not release substances, which could be toxic. In some cases, therefore information on the risk for chronic use for vulnerable patient groups has to be provided. This information is relevant for a dossier update of 3.2.P.7 as it means that a toxicity assessment needs to be done.

There are many texts in the European Pharmacopoeia on different kinds of materials and containers, but not all materials on the market are covered by the Ph.Eur., e.g. PVDC (Polyvinylidenchlorid), which is commonly used in blisters. It is not mandatory to use only materials and containers which fulfil the specification requirements of one of the Ph.Eur. chapters. This has been described in general chapter 1.3. Materials complying with the food legislation can also be used for solid dosage forms, if approved by the authority but a specification must be included in the dossier[227,228].

Plastic Packaging Materials

It has been explained in chapter 3.2.P.2.4 Container Closure System that the "Guideline on Plastic Immediate Packaging Materials"[74] became effective in 2005 and replaced the previous version CPMP Guidance 3AQ10a[75]. It applies to applications for new marketing authorisations but also to existing marketing authorisations when there's a new packaging material. Sometimes packaging material is changed when a medicinal product has not been on the market for a while. This may be for marketing reasons but can also be due to non-availability of the packaging from the supplier. Packaging material manufacturers regularly change their packaging material portfolio, constantly developing new materials/ material combinations and presumably to be ahead of competition.

The 2005 Guideline describes in detail the tests to be performed on plastic packaging material and the requirements on leachable/ extractable studies and toxicological assessment of impurities.

Specifically, for plastic materials the information to be provided in 3.2.P.7 has been clarified. In consequence the information provided below might currently not be included in your old product dossier. Usually it should not be a problem to receive the required information on the materials from the packaging material supplier. As the packaging material manufacturers often also manufacture for the food industry, they have to comply Regulation (EU) 10/2011, Article 15 and Annex IV[229]. That means information about the material composition must be provided.

If a specification is already available, it should be checked for compliance with the requirements of the "Guideline on plastic immediate packaging materials" and for compliance with the results from the development studies. For example, are all potentially into the medicinal product migrating additives part of the purity specification tests?

The following recommendations have been described in the 2005 Guideline on immediate primary packaging (see also: Annex A, 3.2.P.7):

EMEA Guideline on plastic immediate packaging materials- Description of materials

All plastic materials

Not only the chemical name for the material but also for any monomer used must be given.

[226] EDQM, Ph.Eur. 10.2 online, History of the chapter 3.2.2
[227] EMA Q&As on Quality, Part II, Packaging, Question 1
[228] Ph.Eur. 10.2, chapter 1. General Notices, 1.3 General Chapters
[229] Regulation (EU) 10/2011, consolidated, Article 15 & Annex IV

Plastic materials used for packaging of non-solid medicinal products for oral/ topical use
The quantitative composition must be given if the packaging material is non-compendial and it is not included in the foodstuff legislation.

Plastic materials used for packaging for inhalation/ parenteral/ ophthalmic use
The name of the material supplier must be included. The quantitative composition must be given if the material is non-compendial.

Plastic materials not described in Ph.Eur. or a pharmacopoeia of the EU member states
The qualitative composition must be given.

EMEA Guideline on plastic immediate packaging materials- Description of the specification

Compendial materials
A reference to the Ph.Eur. monograph and certificate(s) of analysis should be provided.

Non-compendial materials for solid medicinal products
An in-house specification and analytical procedures must be described, which should contain material description test(s), material identification test(s), characteristics tests(s) such as mechanical & physical parameters. Certificate(s) of analysis should be provided.

Non compendial materials for non-solid medicinal products, unless used for oral/ topical applications
The packaging specification should contain additionally identification tests(s) for the main additives (especially those who might migrate in the medicinal product), additional identification test(s) for colorants and qualitative and quantitative test(s) for the extractables identified in 3.2.P.2.4

Food legislation

As mentioned above, materials and containers not included in an EU pharmacopoeia can also be accepted when compliant with EU food legislation. In the following a graph is provided showing the development of the food packaging legislation in the last 20 years. Directive 90/128 for plastic materials in contact with foodstuffs was replaced in 2002 with Directive 2002/72/EC. Again, Directive 2002/72/EC was replaced in 2011 with the current valid Regulation (EU) 10/2011. All of them have been revised at least once. In particular Regulation (EU) 10/2011 has been revised 14 times up to now. Refer to Annex B Additional information on Module 3.2.P.7 for an overview on the revisions.

Mostly new substances have been added in the revisions, but sometimes the legislation became more restrictive. This is the case e.g. for FCM substance 988 where a tighter control of the hydrolysis product was implemented[230]. Another example is the restriction of the specific migration limit of perchlorate used as additive or production aid in order to avoid toxic effects[231]. Thus, references in the dossier to the food legislation might have to be updated to current legislation. This can be done after checking with the foil manufacturer/ supplier compliance with the current legislation, they should provide an updated certificate of compliance (acc. to Article 15 of EU Regulation 10/2011[229]) to QA. For not commonly used packaging materials/ containers there's the risk that the manufacturer/ supplier cannot confirm compliance with current legislation anymore. In general, it is recommended that the information on the compliance is presented in the following way: "complies with EU Regulation 10/2011 and **all amendments**". This prevents that a dossier update is necessary whenever the EU Regulation 10/2011 is revised. However, RA and/or QA (depending on the allocation of responsibilities) and the foil manufacturer have to ensure the compliance of the material with the current revision.

[230] Regulation (EU) 202/2014, recital (3) (3rd revision of Regulation 10/2011)
[231] Regulation (EU) 2018/831, recital (3) (11th revision of Regulation 10/2011)

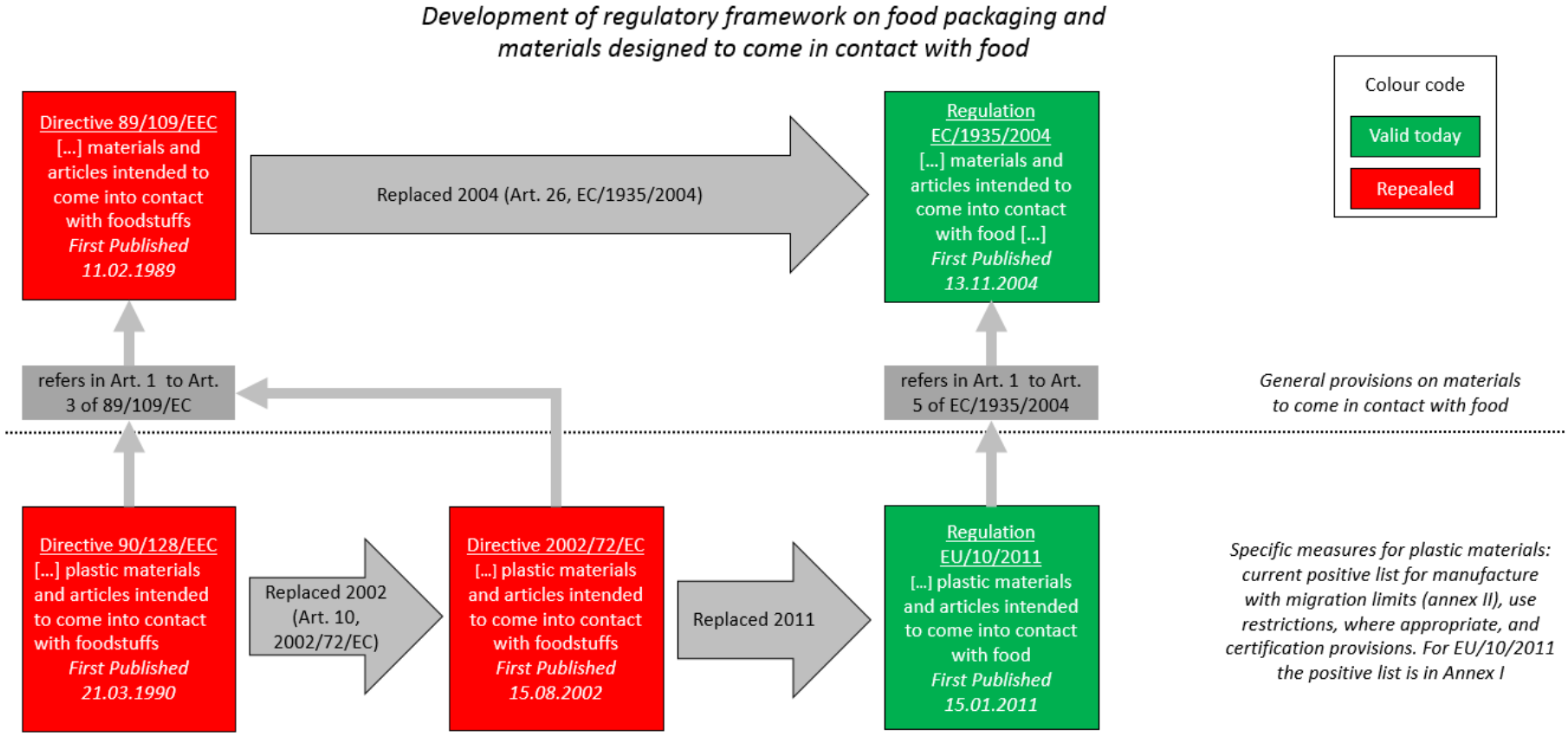

Figure 4: Development of foodstuff legislation in the last 20 years

Other Materials compliant with food law (e.g. Aluminium)

Some materials are not in scope of the above-mentioned regulatory framework on plastic materials but also not included in the pharmacopoeia.

One example is Aluminium, which is frequently used for blisters and sachets. For Aluminium the general food packaging legislation applies (see Figure 4: Development of foodstuff legislation in the last 20 years, section above the spotted line). In 2009 there was a revision of EU Regulation 1935/2004, but it did not concern the requirements on the materials described. The changes were of an administrative nature and referred to the adoption procedure of the EU Commission[232]. The first revision of the former Directive 89/109/EC happened before 2000 already.

For some materials there might be BfR recommendations (refer to 3.2.P.2.4 Container Closure System, Plastic primary packaging materials)

In general, the reference to the food legislation provisions/ BfR recommendations should be updated consummate to the plastic packaging material updates described above, if there was a change in the recommendations or legislation.

Elemental impurities in container closure systems (ICH Q3D(R1)

ICH Q3D (R1) explains that elemental impurities can leach from container closure systems into the medicinal product[233]. If the components of the packaging material are unlikely to contain elemental impurities, no further risk assessment needs to be done. This is the case for solid dosage forms. For semi-solid and liquid dosage forms the risk is higher and recommendations are given on the aspects that should be considered in a risk assessment, which can influence leaching. This information has not changed since introduction of the guideline (first version) in 2014. However, dossiers written before might not contain information on this topic at all.

Depending on the control strategy chosen, information on elemental impurities for liquid and semisolid products may have to be requested from the primary packaging material manufacturer. In case information is already included in the dossier, it should be checked if the risk for elemental impurities has changed. Changes in the packaging material might lead to the need for new leachable/ extractable studies. If new elemental impurities are found, a specification update might be required to include them. In the worst case the packaging material must be changed, because too many elemental impurities leach into the medicinal product. For further information see Development of the regulatory provisions for 3.2.P.5, 3.2.P.5.6 Justification of Specifications, Elemental impurities.

Currently there's also a new draft monograph for a new Ph.Eur. chapter 2.4.35 Extractable Elements in plastic materials for pharmaceutical use published in Pharmeuropa (edition 32.2), which should be considered for updates on elemental impurities in plastic materials as it may become valid soon.

[232] Regulation (EU) 596/2009, recitals (1st revision of Regulation 1935/2004)
[233] ICH Q3D (R1) on elemental impurities, chapter 5.3

3.2.P.8 Stability

Basic provisions on the content of the module 3.2.P.8

The following provisions give some general instruction on the content of 3.2.P.8 today:

Table 23: basic regulatory framework for 3.2.P.8 Stability, sorted by publication date

Type and Title of regulatory framework	Date
EU Directive 2001/83/EC original version from 2001 without amendments[12], Annex 1, Part 2, Section G	Published on 28.11.2001 Effective: 18.12.2001
2nd Amendment to EU Directive 2001/83/EC: 2003/63/EC[3] Annex I, Section 3.2.2.8	Published on: 27.06.2003 Effective: 01.07.2003
EU Commission Notice to Applicants (NTA), Volume 2B, 2008[5], Section 3.2.P.8	May 2008 Info on Module 3 is from July 2004

As this thesis describes dossier updates to medicinal products, which have a marketing authorisation or had a marketing authorisation in the past, the ICH Q1A(R2) "Guideline on stability testing of new drug substances and new drug products"[234] is not relevant within the European Union. Instead the "Guideline on stability testing: Stability testing of existing active substances and related finished products", CPMP/QWP/122/02 Rev. 1 corr" applies.

Table 24: complementary regulatory framework for 3.2.P.8 Stability, sorted by publication date

Type and Title of regulatory framework	Date
EMEA CPMP "Note for guidance on stability testing of existing active substances and related finished products" CPMP/QWP/556/96 *(replaced by the EMA Guideline on stability testing CPMP/QWP/122/02)*	Published: 03/1997 Effective: 10/1998
ICH Q1B "Photostability testing of new active substances and medicinal products", CPMP/ICH/279/95[235]	Published: 01.01.1998 Effective: 01.01.1998
EMEA CPMP "Note for guidance on in-use stability testing of human medicinal products", QPMP/QWP/2934/99[236]	Published: 01.03.2001 Effective: 01.09.2001
ICH Q1D Note for guidance on "Bracketing and Matrixing designs for Stability Testing of Drug Substances and Drug Products" CPMP/ICH/4104/00[237]	Published: 01.02.2002 Effective: 01.08.2002
ICH Q1E "Evaluation of stability data", CPMP/ICH/420/02[238]	Published: 01.08.2003 Effective: 01.08.2003
EMEA CHMP "Guideline on Declaration of Storage Conditions: A. In the product information of medicinal products, B. for active	Published: 19.11.2007 Effective: 01.10.2003 *Initial version from 2003*

[234] EMEA CPMP "Guideline on stability testing: Stability testing of existing active substances and related finished products" Rev. 1 corr
[235] ICH Q1B "Photostability testing of new active substances and medicinal products"
[236] EMEA CPMP "Note for guidance on in-use stability testing of human medicinal products"
[237] ICH Q1D Note for Guidance on "Bracketing and Matrixing designs for Stability Testing of Drug Substances and Drug Products"
[238] ICH Q1E "Evaluation of stability data"

Type and Title of regulatory framework	Date
substances" CPMP/QWP/609/96/Rev 2 [239], "Annex to Note for Guidance on stability testing of new drug substances and products" , "Annex to Note for Guidance on stability testing of existing active substances and related finished product" *The revision of 2007 was only of minor variation for better comprehensibility*	
EMEA CPMP "Guideline on stability testing: Stability testing of existing active substances and related finished products", CPMP/QWP/122/02 Rev. 1 corr.[240] *The initial guideline from 1997 was revised in 2002 and received a new number. The first version of CPMP/ICH/421/02 has been revised again in 2003.*	Published: 17.12.2003 Effective: 01.03.2004 *Initial version from 2002*

Specific provisions on 3.2.P.8

An overview over further regulatory framework to be taken into consideration is provided in Table 25.

Due to the limited volume of this master thesis, they will not be further explained but are listed here in order to make the reader aware of further reading on the provisions in 3.2.P.8. The "Note for guidance on the maximum shelf-life for sterile products for human use after first opening or following reconstitution" is specific for the share of sterile multi-dose/ reconstitution products. The guidelines on stability data to be submitted in variations are specific for variations of the marketing authorization. Although some updates described in this thesis will require the submission of variations when a marketing authorization still exists, these guidelines are not within the focus of this thesis.

Table 25: specific regulatory framework for 3.2.P.8 Stability

Type and Title of regulatory framework	Date
EMEA CPMP "Note for guidance on the maximum shelf-life for sterile products for human use after first opening or following reconstitution" QPMP/QWP/159/96 corr[241]	Published: 28.01.1998 Effective: 01.07.1998
EMEA CPMP Guideline on stability testing for variations to a marketing authorisation, revision 1, CPMP/QWP/576/96 Rev 1[242]	Published: 19.05.2005 Effective: 01.12.2005
EMA Guideline for stability testing for variations to a marketing authorisation, revision 2, EMA/CHMP/CVMP/QWP/441071/2011-Rev.2 [243]	Published: 09.04.2014 Effective: 09.04.2014

Development of the regulatory provisions for module 3.2.P.8

General

In general, this module should be checked for completeness of the stability data provided with regards to the supply chain and the packaging materials used. Either stability data should be provided for each bulk manufacturer or information should be given on the transferability of the results. The same

[239] EMEA CHMP "Guideline on Declaration of Storage Conditions: A. In the product information of medicinal products […]
[240] ICH Q1A(R2) "Stability testing of new drug substances and products
[241] EMEA CPMP "Note for guidance on the maximum shelf-life for sterile products for human use after first opening or following reconstitution"
[242] EMEA CPMP Guideline on stability testing for variations to a marketing authorisation, revision 1, Rev 1
[243] EMA Guideline for stability testing for applications for marketing authorisation, revision 2

applies to packaging material. Exemplarily when two different packaging materials are used but photostability studies have only been done at one packaging material, it can be justified if the medicinal product has proven to be insensitive to light without the container.

The age of the last ICH stability studies should be reviewed, in particular if the change history is known. In case there was a manufacturing process change but stability data are not available from before the change, this should be further investigated. Manufacturing process changes, even minor ones, require new studies[244]. Therefore, a general discussion with QA/ QC about available stability studies makes sense in order to verify them with the data provided in the dossier.

Imprecise wording such as "room temperature" should be replaced by numeric information, e.g. 25°C ± 2°C. It should be checked if it is clear for all stability studies, with which analytical procedures they have been created and with which composition, in case there were changes.

3.2.P.8.1 Stability Summary and Conclusion

EMEA "Guideline on stability testing: Stability testing of existing active substances and related finished products"

An overview over stability studies for the finished product is provided within the guideline. It describes storage conditions to be applied for different types of products and what needs to be considered a significant change. Further information on testing time points, length of stability studies and follow-up actions on significant changes are given.

The initial guideline from 1996 was revised in 2002 in order to comply with the ICH Q1F guideline (initial version) for climate zone III and IV studies (not relevant for EU), the ICH Q1A(R1) and the ICH M4Q Guideline.

The revision in 2003 was done for compliance with the ICH Q1E guideline and the requirements of the ICH Q1A(R2) guideline.

Only the active substance part [245] is concerned by the clarification provided with the correction in 2007.

The revision from 2002 could not be found in the internet anymore for a detailed comparison of the provisions on the specification for shelf life, therefore the initial version and the revision from 2003 were compared (see Annex A, 3.2.P.8, Comparison of recommendations on the stability in the Guideline on stability testing)

In the following, the main changes are listed. Refer to Annex A, 3.2.P.8 Stability, Comparison of recommendations on the stability in the Guideline on stability testing for further details.

Within the revision of the guidance it has been clarified that stability studies must be performed for each strength and container size, except when bracketing or matrixing is applied. If data are not complete for each strength or container size, it should be checked if a bracketing/ matrixing design was used. See subheading Bracketing and Matrixing (ICH Q1D) for further consideration/ actions.

The highest impact change in this guideline was the revision of the storage condition for intermediate condition from 30°C/ 60% RH to 30°C ± 2°C/ 65% RH ± 5%. It happened with the first revision in 2002. Since February 2006 all MA applications should contain data with the new storage condition, if required, according to the Revision History of the current guideline. Thus, it is recommended, that stability studies with the new intermediate storage conditions are started, if it had not been done in the past yet. Of course, if a new marketing authorisation needs to be applied for, it will take at least 6

[244] EU Commission, "variation classification guideline", annex, B.II.b.3 a)
[245] EMEA CPMP "Guideline on stability testing: Stability testing of existing active substances and related finished products, Rev. 1 corr, revision history

months until the required amount of data is available plus time for waiting until the next production slot is available, generating the laboratory stability report and reviewing the data.

Another big change is the introduction of storage recommendations and conditions for impact assessment of significant changes for products to be stored in the freezer and semi-permeable containers (e.g. for aquaeous solutions in plastic packaging). Different storage conditions might be justifiable (e.g. discuss with the stability expert), this option has not been excluded by the (revised) guideline. Data that old should probably supported by recent data, though. When dossiers are more than 15 years old it is not very probable that there have been no changes in the shelf life specification (e.g. change in impurities as described in 3.2.P.5.1) or manufacturing process. Those changes can lead to the necessity of new stability studies. A new, identified degradation product would be an example for a shelf life specification change.

Failure of acceptance criteria of functionality related tests (e.g. hardness, phase separation) has been added to the catalogue for significant changes. The exception are some expected changes in physical parameters (e.g. softening of suppositories). Furthermore, for drug products packaged in semi-solid containers a deviation of minus 5% of water content is also considered a significant change (except for small containers when justified). Consequences of significant changes during accelerated storage have been defined for different types of products. The water loss of more than 5% during accelerated studies would require no significant change in the water loss at 25°C ± 2°C/ 40% RH ± 5% RH throughout the whole shelf life, for the study to be acceptable. If it happens after 3 months accelerated studies, the water content loss becomes a significant change. These changes in the definition of significant change can have an impact on the shelf life when it was defined previous to introduction of the revision. A newly defined significant change might require data at intermediate storage condition that have not been performed. New stability studies would be required then.

Special conditions have been defined for the occurrence of a significant change (accelerated condition) when the product is intended for storage in the refrigerator. The actions depend on occurrence of the change before or after 3 months. In case it happens before 3 months, a risk assessment should be done for opportunities where the product may not be stored within the recommended conditions. This can be done e.g. by stability testing of a batch with more test points than every 3 months acc. to the revised guideline. If the change happens after 3 months, the shelf life will be based on the long-term real time studies only. This means that no extrapolation is possible.

Stability testing of one batch on a higher temperature is recommended by the revised guideline for storage in a freezer. The intention is the assessment of storage outside of the labelled conditions. In general, there is no recommended storage condition for those products in the revised guideline. Shelf life must be based on long-term data only acc. to the revised guideline. If a study on a higher temperature have not been performed yet, it should be organized.

For freezer products it has been recommended to put them on stability on higher temperature (e.g. 5°C ± 3°C or 25°C ± 2°C).

The 1997 version does not provide much information than the possibility of limited extrapolation. In brief, this has been revised in the update. For further information refer to subchapter Evaluation of stability data (ICH Q1E), though.

Photostability studies (ICH Q1B)

The guideline for photostability studies has not changed within the last 20 years. In its preamble (chapter 1.1) the guideline defines that it is applicable only to applications for marketing authorisations for medicinal products with new active substances. However, the guideline still reflects the scientific and technical state of art acc. to Article 23 of Directive 2001/83/EC[4]. Thus, photostability studies should be done for dossier updates if data have not been included so far.

This is substantiated by the "variation classification guideline"[58]. For certain variations the guideline lists photo-stability studies as condition or document to be provided in order to fulfil the requirements of the given variation type (type IA/ type IAIN variations).

Table 26: Variations with photostability requirements

Variation number	Short Description	Type
B.II.a.3 a) 1 &2 B.II.a.3 b) 1.	Changes in the composition (excipients) of the finished product: - Addition, deletion or replacement, increase or reduction of flavours and colorants - Any minor adjustment of the quantitative composition of the finished product with respect to excipients	Listed as condition 4, "where relevant"
B.II.a.4 a)	Change in coating weight (oral dosage forms)/ Change in weight of capsule shells: for solid oral dosage forms	Listed as document 2, "where relevant"

Bracketing and Matrixing (ICH Q1D)

The ICH Q1D for bracketing and matrixing is still in its initial version, introduced in 2002. Bracketing and matrixing has not been a new concept in 2002, it is already described in the initial version of the "Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products" from 1997[246]. Since the 1997 guidance does not elaborate on the concept, old product dossiers with applied bracketing and/ or matrixing should be checked for compliance with ICH Q1D.

Bracketing means that not all samples are tested, but only those considered the worst-case condition or respectively, the lowest and highest unit (the "extremes") of the criteria to be investigated[247]. This can be the highest and lowest strength, or the highest and lowest container size (or both), for example.

Matrixing means that not for all test points all samples are tested. Instead a reduced number of samples are tested, collected by different criteria. Examples are that not all batches per strength are tested at a specific time point or not all container sizes of a strength. Instead of applying the extremes in the choice of samples, it was designed on the assumption that leaving out single samples per test point will still keep the result of the other samples tested representative for all of them[248].

The concepts chosen should be explained for the respective medicinal product. For bracketing it should be justified why the conditions chosen are the extremes. Bracketing should not be applied for strengths when the qualitative composition is different. For matrixing the assumption that the samples left out per test point will not bias the results must be justified. Ideally this is done with data showing the comparability of the characteristic for which the matrixing was applied[247,248].

If bracketing or matrixing has not been justified, the difficulty of creating that justification retrospectively varies. It depends on the characteristic that was applied for bracketing/ matrixing. For example, the matrixing of three different strengths of a solid oral dosage form in blisters does not require a complicated justification. But bracketing on containers for semisolids with different fill volume/ total volume ratio and different container sizes will not be that easy and further data will be needed to assess the comparability of the containers, e.g. thickness of the container, geometry[249].

In the worst case, data for comparability will not be available anymore and a new study without reduced design has to be started or comparability data need to be created first. However; if stability

[246] EMEA CPMP "Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products" CPMP/QWP/556/96, Chapter Finished Product, Section Testing Frequency
[247] ICH Q1D, Chapter 2.3 Bracketing
[248] ICH Q1D, Chapter 2.4 Matrixing
[249] ICH Q1D, Chapter 2.3.1.2

data are from beginning of the 2000s then a new stability study should probably be set up anyway. It is improbable that there were no changes that require a new study or that such changes are not planned.

Evaluation of stability data (ICH Q1E)

As for ICH Q1D, this guideline was introduced in 2003 and has been unrevised since then. The guideline describes principles how the shelf life can be defined and rules for extrapolation of stability results[250]. The possibility for extrapolation has been described in the 1997 version of the "Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products"[251] already. At that time no concrete maximum of extrapolation or further conditions have been included in the guidance. Points recommended to be checked for old dossiers are, for example[252]:

- have assay results been discussed with respect to the target to provide 100% of the label claim of the active substance at release? What are the consequences with regard to interpretation of the stability results if the release assay was higher or lower than 100%?

- has the adequacy of mass balance assessed? E.g. if mass balance is not given, what are the reasons (e.g. different absorption rate of active substance and impurities by the detector)?

- have the results for all quality-critical tests been assessed individually?

- have statistical calculations been explained when used?

- For ongoing studies: are new data available by now? When extrapolation was used, have the assumptions done in the past been confirmed by the stability data available now? If not, what was the cause?

It is assumed that the stability data for the shelf life proposed in the past would already be available for an old product dossier. The maximum period for extrapolation that can be applied at best is 12 months[253]. A decision tree was included as appendix 3 in order to support the determination of the shelf life

In-use stability studies

For medicinal products with containers intended for multiple dose withdrawal, in-use stability studies have to be performed. The necessity for in-use stability studies is described in the since the 1997 version of the "Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products"[251]. By introduction of the “EMEA CPMP “Note for guidance on in-use stability testing of human medicinal products” it has been described, how such studies and the in-use shelf life could be set up. The guideline became effective in 2001. In-use stability data created before should be checked for compliance with this guideline, e.g.

- has the study been performed at least on two batches?

- have the batches been at the end of the shelf life or alternatively has the in-use testing been done at the final time point of one of the already submitted stability studies?

- do the conditions under which the test was performed mirror the instructions on posology and duration of treatment in the labelling? Have those instructions been changed since then?

- have the results been provided in a tabular format and been summarized as well as assessed (has the proposed shelf life for in-use been justified)?

[250] ICH Q1E, Chapter 1.1
[251] EMEA CPMP "Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products" CPMP/QWP/556/96, chapter Evaluation
[252] ICH Q1E “Evaluation of stability data”, Chapter 2.1, 2.2, 2.3
[253] ICH Q1E, Chapter 2.5

If justifications for the study design or conclusions are not complete in the dossier, it can be checked if a protocol and report of the study are still available in the company and provide this information. It can be tried to justify the decisions otherwise retrospectively (in collaboration with a stability/ development expert.)

Should in-use stability studies have not been performed or a new study must be started due a change of the in-use conditions, it might be time-consuming. Studies might be a matter of weeks/ months depending on the duration of the treatment if samples at the end of the shelf life are available. When this is not the case, it must be waited until samples have reached this age, which could take some time.

Intermediate/ Bulk stability studies

The necessity for intermediate or bulk stability studies to support the hold time is described in the EMA guideline on manufacture of the finished dosage form, revision 1 from 2017[222]. Neither this guideline nor the EMA "Q&As on Quality"[254] provide clarification in which dossier module bulk stability data should be provided, if needed. In chapter 4.4 of the guideline on manufacture […] it is recommended: "the maximum holding times of the bulk product or, alternatively, the maximum batch manufacturing time from start of product manufacture to completion of packaging into the final primary container for marketing should be stated, appropriately justified and supported by data in relevant parts of the dossier (e.g. challenging the maximum hold time in process validation studies or providing dedicated stability studies for the bulk storage). Therefore, it is recommended to provide the cross-reference either 3.2.P.8 or 3.2.P.3.4, depending on the module where the data and conclusions have been provided. For example, if intermediate/ bulk stability data are provided in 3.2.P.8.3, in 3.2.P.8.1 should refer to the conclusions provided in 3.2.P.3.4. Vice versa 3.2.P.3.4 should refer to the data provided in 3.2.P.8.3.

In this thesis the requirements on intermediate/ bulk storage are further described in 3.2.P.3 Manufacture, Development of the regulatory provisions for module 3.2.P.3, 3.2.P.3.4 Control of Critical Steps and Intermediates.

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

With the introduction of the 2nd revision of the Directive 2001/83/EC (Directive 2003/63/EC) from 2003 and introduction of the CTD format, the requirement to include information on the post-approval stability protocols and commitments has been added (refer to Annex A, subchapter 3.2.P.8). It has been further elaborated in the revised "Guideline on stability testing of existing active substance and related finished products", either in the first revision (2002) or in the second revision (2003). Exact determination is not possible anymore, since the 1st revision from 2002 is not available anymore. Whenever the stability data does not cover the whole proposed shelf life for 3 production batches at submission (so called primary stability studies), a commitment for completion of the studies needs to be given. Detailed recommendations for different cases were added (for further information see Annex A, subchapter 3.2.P.8). Furthermore, it has been clarified that the stability plan for the commitment batches and the previous (primary) stability studies should be the same. The differences between significant change at accelerated condition for primary stability studies and commitment stability studies has been explained:

When data provided in the old product dossiers call for a stability commitment, it should be easy to add. No new data are required. However, if you find differences between the stability plan for primary stability studies and unfinished commitment studies, this should be carefully evaluated. A risk assessment should be done on the influence of differences on the finished commercial product. It would be difficult to prove that parameters tested within primary studies but not in commitment studies do not need to be monitored for the commercial product, for example. This collides with the fact, that they have been originally evaluated as being relevant for the quality/ safety/ efficacy and in

[254] EMA, Q&As on Quality, Part II, "Stability- Stability issues of pharmaceutical bulk products use in manufacture of the finished product"

addition being subject to change during shelf life. Depending on the case, start of a new commitment study should be considered.

3.2.P.8.3 Stability Data

In general, the completeness of the data and correctness of the shelf life specification given need to be reviewed and potentially revised in the frame of the changes described in module 3.2.P.8.1 and 3.2.P.5.1.

The guidelines describing the dossier content of this module show that there was some change in the requirements when Directive 2003/63/EC became effective (refer to details in Annex A). It describes that the analytical procedures used, and their validation should be described in this module besides the stability data. However, if the analytical methods are the same as used for release, reference to 3.2.P.5.2 and 3.2.P.5.3 can be provided instead. In case analytical methods have been changed within a study, the changes should be described, and it should be assessed, if they the procedures are comparable. Comparative validation studies should be included and ideally stability data should be generated with both, the new and the old method for the remaining shelf life.

Acc. to the BfArM frequent gap list of 2006[1] it is important to give numeric results whenever possible, instead of generic words such as “complies”, “unchanged” etc. If this is the case, it should be corrected in 3.2.P.8.3 based on the stability results in the stability raw data (e.g. calculations, chromatograms).

Excursions

During the process of the dossier update, Quality Assurance and Regulatory Affairs have to collaborate closely. Regulatory affairs is dependent on the scientific information that is required to complete the dossier and fill the existing gaps. Exemplarily QA needs to start stress testing if not done yet for regulatory affairs to be able to include the results in the dossier.

On the other hand, QA is also dependant on a good communication flow from Regulatory Affairs (RA) to QA. RA needs to advice on the regulatory requirements for the respective QA sources documents, e.g. how the batch size should be defined acc. to the guideline on manufacture of the finished dosage form should be communicated from RA to QA.

Further, implementation of details in the dossier that have not been included before, might require actions on QA side. GMP documents should reflect all details that are included in the dossier. The experts from manufacturing operations, quality control teams and quality assurance learn about the contents that must undergo a regulatory variation procedure this way. In practice, the need for a change request may be neglected unintentionally by the staff. The risk that this happens is increased if the GMP documents do not reflect all the information in the regulatory dossier. In general, a change control system must be established in every company[255]. It intends to prevent that changes are implemented without consideration of the need to submit a variation. But it relies on the staff working in GMP areas to recognize the need of a change request.

One example is the exact material composition of plastic foils used for packaging of suspensions. Often GMP documents, e.g. testing instructions, provide the name and material number of the (non-compendial) plastic foil but not the exact material composition. Therefore production /QC staff might conclude that they can change the foil supplier and use a new foil with the same dimension criteria but not the same composition without starting a change control process.
Good training of the operations staff on change control and the need to raise change requests is important, too.

Vice versa, regulatory affairs might not recognize the need to include information on details that are missing in the GMP source documents into the dossier. Examples are additional manufacturing process steps not described in the master batch record, additional test methods applied for tests such as hardness, dimensions, exchange of a reference substance supplier and related change of specification. Therefore, a good quality system is crucial, in particular for 3rd party dossiers. Not only for dossier compilation but also for authority inspections, e.g. for pre-approval inspections if a new marketing authorisation is applied for. The quality system is described in ICH Q10, which is also part of the GMP Guidelines (Part III)[256]. ICH Q12 gives further advice on the handling of CMC change requests within the pharmaceutical quality systems and emphasizes the importance of an effective change management system[257]. In case of 3rd party dossiers an audit should be done at the 3rd party in order to inspect the quality system.
Another source of mistakes in the dossier is misinterpretation of the information provided in the GMP source documents by the RA experts, as they are not the subject matter experts for the topic.

It is recommended, that QA does a compliance check of the GMP source documents that reflect the information to be included in the dossier. This should be done before the dossier update in collaboration with manufacturing and quality control operations. After update of the dossier and before submission it should be reviewed by the relevant departments such as manufacturing

[255] ICH Q10 on pharmaceutical quality system, chapter 3.2.3
[256] ICH Q10 on pharmaceutical quality system
[257] ICH Q12, chapter 1.1 and 1.3

operations, quality control, quality assurance (e.g. change control manager). The reason is, that they are the subject matter experts and know the processes best.

The same principles apply pharmaceutical development and the dossier update of 3.2.P.2. In addition to QA, the R&D (Research and Development) Manager is involved in these topics and a tight collaboration is very important for the success of the dossier update.

Discussion

The topics addressed in this thesis for module 3.2.P.1 to 3.2.P.8 have briefly listed below in form of a gap analysis
The list provides and overview for the reader about the main changes in the regulatory framework within the last 20 years. In most cases dossier updates of old product dossiers create a high workload not only for the involved Regulatory Affairs Manager but also for other related functions within the company, such as Quality Assurance, Manufacturing Operations, Research and Development. Therefore, the contents of the chapter Results have been summarized in an overview list. The list provides information about possible gaps and remediation actions. Further, it gives an indication for the dossiers that might contain this gap, depending on their date of creation.

Summary and assessment of gaps for old product dossiers

A tabular overview was provided in Annex D. The following information has been given:

Module	The module in the chapter Results where the information is from/ which would need to be updated primarily
Topic Category	This is an umbrella term for the topic addressed
Topic	Short description for the discussed regulatory topic
Gap	Description of the possible dossier gap
"This is a risk for dossiers dated ≤"	Year of introduction of the respective change in the regulatory provisions
Modules to be updated (possibly)	Other modules that might have to be updated as a consequence of the gap
Actions	Possible (first) Actions that should be done for remediation of the gap
Effort	A rating of the effort as explained below
Prerequisites	In some cases prerequisites were mentioned for the dossier update of the respective (sub)module

The rating was done in the following way: Topics with the highest effort (rated 3/ 3+ or 4) and were studies are required, should be planned and assessed first. These topics are usually the ones that require most financial, time and often staff resources. In some cases, prerequisites have been listed. They should be completed before the actions can be taken for remediation of the dossier. Yet these prerequisites should not be considered exhaustive. It shall be assessed case by case which actions have to be done and in which order they need to be brought (e.g. a project plan should be created).

In the following the rating for the effort is explained:

1	Information/ data/ conclusions should be available in other dossier parts
2	Information/ data might be available within the company or contracted manufacturers/ laboratories. Conclusions are available or can be drawn by reviewing existing data with experts
3	Internal or external studies required in order to create the required data for review and conclusion with small to moderate effort in time/ costs
3+	Internal or external studies required in order to create the required data for review and conclusion with high effort in time/ costs
4	Conditions of category 3 and additional potential that a large part of the dossier needs to be revised (minimum 3 submodules 3.2.P.X, e.g. 3.2.P.3, 3.2.P.4…)

The dates given in the column "This is a risk for dossiers dated ≤" should hint towards the necessity to check the dossier for this issue. When the creation date of the dossier is known, it can be checked if the change of the regulatory provisions could have been implemented already or not. But it cannot be assumed that dossiers dated later than the year given would be up to date to this regulatory requirement in any case. Reasons for incompliance of the dossier with regulatory requirements of that time have been mentioned in the introduction of this thesis. For 3rd party dossiers it should be verified that the dossier provided was approved by the authority. It might be a draft that was never submitted to the health authority otherwise.

Some regulatory provisions that have been changed several times over the last 20 years and have not been listed in detail in the table above. They are listed with the date "2020". This means that any old dossier falling in the scope of this thesis should be checked for the necessity of changes with regards to that topic.

In the following an assessment has been done for which dossier modules the highest workload can be created when gap applies. For gaps rated with a range, e.g. 2-4 depending on the action taken, the higher rating limit has been chosen (in this case 4).

Table 27: Overview of ratings

Module	**Total No. of topics**	**No of Topics Rated with…**					**Topics requiring new data (3, 3+, 4) in absolute**	**Topics requiring new data (3, 3+, 4) in %**	**Topics with potential update of ≥ 3 sub-modules 3.2.P.X (category 4, in %)**
		1	**2**	**3**	**3 +**	**4**			
3.2.P.1	4	3				1	1	25%	25%
3.2.P.2	18	1	4	5		8	13	72%	44%
3.2.P.3	19	3	11		5		5	26%	0%
3.2.P.4	11		3	6	2		8	72%	0%
3.2.P.5	10		1	2		7	9	90%	70%
3.2.P.6	2	1		1			1	50%	0%
3.2.P.7	2		1	1			1	50%	0%
3.2.P.8	9	1	1	2	5		7	78%	0%
Sum	**76**	**9**	**22**	**17**	**12**	**16**	**45**	**59%**	**21%**

It can be seen that the most topics (18-19), which have changed in the last 20 years are assigned to the modules 3.2.P.2 Development and 3.2.P.3 Manufacture. Some change topics (9-11) have been raised for 3.2.P.3 Excipients and 3.2.P.5 Control as well as for 3.2.P.8 Stability. Not many change topics (2-4) have been addressed for the modules 3.2.P.1 Description and Composition Composition, 3.2.P.6 Reference Standards or Materials and 3.2.P.7 Container Closure System.

Table 28: Total number of change topics per submodule

Category for number of change topics	Most change topics (18-19)	Some change topics (9-11)	Few Change Topics (2-4)
Modules	3.2.P.3 Manufacture 3.2.P.2 Pharmaceutical Development	3.2.P.4 Excipients 3.2.P.5 Control of Drug Product 3.2.P.8 Stability	3.2.P.6 Reference Standards or Materials 3.2.P.7 Container Closure System

It should be mentioned that this assessment could also be done in a different way with regard to the definition of the topics of change in the regulatory provisions. For example, the topic "Compliance Certificates for Compliance with Foodstuff legislation, Ph.Eur., BfR recommendations" could be split up in the subtopics and would then count 3 times instead of once.

However, it was not done this way, because the gap is the same here. Thus, it makes sense to summarize them within one change topic. Furthermore, possible remediation actions to be taken have been considered when the extent of the change topic was defined. Consequently, the changes and resulting possible gaps discussed in the section "Results" have been summarized in a way that makes them easiest to approach the topic, take actions and get the required information/ data for the dossier update.

It has been evaluated how many of the topics have been rated with 3, 3+ or 4. For all of them, active creation of new data is required within the company and therefore they are the topics with the highest effort. Follow-up actions are usually costly and require time. For example, if a new stability study is needed, it will take some time until results are available because this is the nature of stability studies.

If the company does not have the resources to perform the stability study, it must be requested at an external stability laboratory and the related costs must usually be approved internally beforehand. Topics rated one and two, in contrast, do not require new data. Instead already existing data must be reviewed and evaluated. The creation of overview tables, statistics etc. is considered to be part of that evaluation process. The results for the modules in the category "few change topics" have not been considered here. There are too few topics, so that a calculation of the percentage of category 3/3+/4 effort topics does not make sense. They are marked with a grey background in Table 27: Overview of ratings. It is obvious that with such a small total number of topics, the share of high effort topics would be either really high or really low.

Many topics have the potential to require updates in more than one submodule. They have been assigned to the module where the focus of the update is. For example, investigation of the compatibility of the container closure systems with the medicinal product can require update of the following dossier modules:

- 3.2.P.5 when packaging material leachables are found and must be controlled in the finished product specification. Further, analytical procedures must be set up and validated for testing on those leachables.
- 3.2.P.6 when a reference standard for the leachable is required
- 3.2.P.7 for control of the extractable that will turn into a leachable when it migrates into the medicinal product (control in the primary packaging material specification)
- 3.2.P.8 when the amount of leachables must be controlled during stability studies

But mainly this topic will be described in 3.2.P.2.4 and has therefore been listed in the 3.2.P.2 section.

In particular the requirements for the modules 3.2.P.2 Pharmaceutical Development and 3.2.P.5 Control of Drug Product were subject to regulatory changes that can cause the update of more than 3 submodules (3.2.P.X). This is rated as category 4 in terms of effort required for the dossier update.

Changes to regulatory provisions where earlier precursor provisions are not available anymore

For some guidelines specifically the previous versions were sometimes not available in the Internet anymore and could also not be found in other literature archives. One example is the EU Eudralex Volume 2B Notice to Applicants[5]. The document is dated 2008, but the relevant part from this thesis is from 2004[7]. There were earlier versions of this document acc. to its introduction, which could not be found. Therefore, it is assumed that the guidance provided in the current document was published in 2004 already. The contents are also understood as if they were new in 2004 for a) the purpose of comparing regulatory provisions in Annex A in the chronological order and b) establishing the introduction dates of regulatory changes in the gap scenarios above.

There are further examples like the EMEA “note for guidance on stability testing of existing active substances and related finished products” in its 2002 revision. But those examples are also mentioned in the chapter Results.

Non-availability of precursor guidelines can lead to an uncertainty of the introduction of the relevant changes. However, for the purpose of updating dossiers it should always be expected that new regulatory provisions have not been implemented in the dossiers immediately. Consequently, an uncertainty factor is to be considered always.

Regulatory provisions which had been published but had not been effective yet may have been considered for the creation of the old product dossier or not. It is generally advisable to consider published provisions for updates because they will become effective eventually. However, it might not have been done in the past for the old dossier under investigation. In order to find out, there is no other way than checking the dossier contents if they comply with the introduced provisions.

In the introduction to this thesis it has been mentioned that there are various reasons why the contents of an old dossier may not correspond fully to the regulatory requirements of that time. The product might not have been on the market, the writer may have been inexperienced or not up to date to the regulatory developments of that time, or a gap might have been missed by the authority even. Normally dossiers should be timely updated in case the regulatory provisions change, but it is also widely known that this does not work out sometimes.

Lifecycle Changes and other updates

Due to the life cycle of the product there might be changes, which are not due to regulatory provisions but due to the lifecycle. This means that every product is subject to changes during its lifecycle. The supply chain might change due to supply reasons, there might be batch size changes due to a changed market demand or a change of an excipient supplier with consequences on the excipient specification due to unsatisfactory audit results. On one hand it would be expected for old dossiers that there were many changes that require a dossier update due to the product age. On the other hand, investments into the product in form of changes may have been restricted wherever possible. This applies in particular if the product was not on the market for a while or not on the top product list of the company. Old product dossiers also make it probable that different experts were responsible for dossier updates in the last years. Therefore, it should be checked if the changes done during the lifecycle have been consistently implemented in all relevant submodules of Module 3 or if something has been missed.

Furthermore, there are usually data and statements within the dossier, which should be updated in old product dossiers irrespectively of regulatory changes. TSE statements from suppliers might not be up to date even if the guideline itself has not changed since 2011 (refer to 3.2.P.4). The supplier might have changed in this time. Alternatively, they might have changed their manufacturing process and use materials now where absence of a TSE risk cannot be confirmed. Another example is that batch data presented in 3.2.P.5.4 should be updated in general to reflect that the product is currently compliant with the specifications, not e.g. 5 years ago.

Such changes have been mentioned in the section Results but are not included in the Gap list in "Annex D Tabular overview: Summary and assessment of gaps for old product dossiers".

Countries included in the European Union after 2020

For old product dossiers, which had a purely national marketing authorization (only one country), it should be checked if they have been created for one of the countries that has not been an EU member state at that time. It may have not been revised since that time (if marketing authorisation was withdrawn). National legislation could have been different than EU legislation and it cannot be expected that EU legislations introduced before the date of the dossier would be implemented in the dossier.

In the following an overview of the entry data of the member states who joined the EU after 2000[258].

Table 29: Year of entry member states EU

Year of entry (after 2000)	Country/ Countries
2004	Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, Slovenia
2007	Bulgaria, Romania
2013	Croatia

Upcoming changes in the regulatory provisions

Big dossier updates often take a lot of time; thus, it is probable that there will be changes in the regulatory provisions within the time planned for the update.

It is recommended to check the EDQM Pharmeuropa online journal in order to recognize upcoming changes in Ph.Eur. at an early stage and consider their implementation in the dossier update. It may become a mandatory change in the Ph.Eur. monograph, before the updated dossier is ready for submission otherwise.

Further guidelines and directives should always be accessed on the relevant EMA/ EU Commission homepages. This way, always the current version can be seen, instead of an outdated version as it may happen when copies of the provisions are saved. Furthermore, the EMA homepage will also publish draft guidelines for each topic, so that upcoming changes can be recognized in time.

Moreover, there are various expert organisations that send newsletters on planned changes of regulatory provisions if requested and provide another tool to keep updated of regulatory changes. Other service providers have complete databases that inform about changes and summarize the content of regulatory provisions. Some companies established a position "regulatory intelligence" for focussing on regulatory changes or subject matter experts on specific topics. They can support the update of the old product dossier with their knowledge.

[258] EU Commission, Homepage of the European Union, Europa.eu, About EU, Countries, without date

Summary and conclusion

To sum up, the dossier updates that require the creation of new data (studies) are the most work-intensive (refer to Discussion- Summary and assessment of gaps for old product dossiers), not only for regulatory affairs but also for other departments.

The regulatory changes on the provisions done for the modules 3.2.P.2, 3.2.P.4, 3.2.P.5 and 3.2.P.8 have the highest potential for the necessity of additional studies. Thereof, module 3.2.P.2 and 3.2.P.5 have the highest potential for the changes that require revision of large parts of module 3.

Development studies (3.2.P.2) are intended to establish the best possible composition, manufacturing process, analytical methods and packaging material in terms of product quality. Those are the studies that are done first of all and all further developments are based on the knowledge gained in development studies. Consequently, it is not a surprise that if there are gaps within development it often requires product specific new data to gain the knowledge needed. And it is also no surprise, that such new data/ new knowledge can have large-scale impact on the content of other submodules of Module 3. Some changes can be really critical for the capacities that need to be invested in the update. A line extension for the switch to another dosage form more suitable for pediatric use, requires many new studies and therefore high cost as well as much time. Big changes were done with the implementation of ICH Q8 for this module. This is remarkable as the Note for Guidance on Development pharmaceutics is already very detailed for a guideline of that age. And it speaks for the importance of the pharmaceutical development. Care should be taken with old product dossiers developed in the first years of the new century. Such dossiers might be cheap when bought from 3rd parties but the cost of performing missing studies should not be underestimated.

Results of new studies can confirm the assumptions and concepts established during development or afterwards. But they can also result in new findings that do not support those. This is a high risk for old product dossiers and should be taken into account generally. Within gap remediation of old product dossiers, missing development studies should therefore be started first.

It should be considered that a mere minimum amount of knowledge gained in development studies will lead to an increased effort of changes during lifecycle. For every change planned, the more data have to be created, the less knowledge from development is available.

Consequently, the focus of such old dossiers should be set to the development part.

For module 3.2.P.5, control of drug product, most scenarios that cause large-scale changes in module 3 are associated with an update of the specification or control strategy. In particular, new impurities or impurities that exceed new limits in the regulatory provisions are related to a high workload. They must be identified, and the relevant controls established. Other activities that cause a high workload are establishing control strategies where there have been little or none before (e.g. elemental impurities). The risk must be assessed and often the source of the impurities must be investigated in order to set up an appropriate control strategy. As this can be done in several parts of the dossier (excipients, manufacturing process and controls, packaging material control, finished product control, active substance control), the information provided in all dossier parts must be aligned.

The risk of updating module 3.2.P.4 Control of Excipients lies in non-compliance with current specifications and analytical procedures mainly, as given by pharmacopoeias or food-stuff legislation. The related validation/ verification activities can be costly and need time. Further, if there are excipients that are still considered novel, it should be carefully evaluated if the expected return on investment (after MA approval) will be sufficient to cover the effort related to updating this section.

In particular the requirements for the modules 3.2.P.2 Pharmaceutical Development and 3.2.P.5 Control of Drug Product were subject to regulatory changes that can cause the update of more than 3 submodules (3.2.P.X), which is rated as category 4 in terms of effort required for the dossier update.

Module 3.2.P.8 Stability of old product dossiers bears the risk of the need to perform new stability studies due to changes in the regulatory framework implemented between 2000 and 2003. They are probably not relevant for dossiers that have been created some years later. However, life cycle changes -if not carefully evaluated in the past- might also require additional finished product stability studies (e.g. new bulk manufacturer added without stability data but comparability questionable).

For module 3.2.P.3 many changes have been introduced, especially with the new guideline on process validation (2014) and on manufacture of the finished dosage form (2017). Consequently, gaps are also to be expected for dossiers of the newer kind. Most of the changes do not require new studies, just internal evaluation, justification or addition of detail, though. Some of them might require new process validation studies, however, or other new data such as intermediate/ bulk stability studies or transport validation.

Changes in module 3.2.P.7 are mainly related to updates to outcomes of development studies, general specification updates or re-confirmation of compliance with current regulatory provisions (Ph.Eur., foodstuff legislation, BfR recommendations).

Updates to reference standards and materials are mostly related to changes of Ph.Eur. 5.12 or other changes of specifications or analytical methods.

Most changes for module 3.2.P.1 are related to changes in other dossier modules, or information for the updated 3.2.P.1 can be copied from other dossier sections. Besides the general provisions on the dossier content (e.g. Notice to Applicants Module 2B), there is no specific guideline for this module. This explains why there are not many changes with high impact assigned to this module (the gap scenarios have been assigned to the modules with the highest relevance of the change).

For the future it is expected, that the trend to prospective strategies in the development of medicinal products and therefore dossiers will continue. After all, in ICH Q12 the importance of knowledge is emphasized for the performance of post-approval changes. ICH Q14, which is planned, will focus on quality by design principles for analytical methods (refer to Results, chapter 3.2.P.2 Pharmaceutical Development, Development of the regulatory provisions for module 3.2.P.2, General: Approach to development/ Considerations for update of documentation)
Moreover, for the topic process validation the GMP guidelines have been revised some years ago, rendering the prospective approach to process validation mandatory (refer to Results, chapter 3.2.P.3.5 Process Validation).
Hence, further focus will be on the 3.2.P.2 pharmaceutical development and a presentation of the knowledge gained on the product. This knowledge will enable to classify variations as minor, because the studies performed will show that there is only a minor influence on the quality. Manufacturing processes and quality controls will be designed in a way that ensures the quality of the drug product. In this context it must be questioned if old product dossiers with their usually traditional approaches to development and gaps in development will guarantee a long product lifecycle. On the other hand, knowledge can also be gained during the lifecycle. When a dossier has a good foundation in development studies and further resources will be invested in gaining more knowledge at every opportunity, this could be compensated but must be decided case by case. ICH Q9 principles can be applied for the decision in order to see where the gaps in the control strategy are.

It can be anticipated that future guidelines call for more justification and more details to support those justifications in the dossier. This could be observed in the past years already, exemplarily, with the introduction of the revised guideline on manufacture of the finished dosage form (2017).

After the gap analysis of the dossier, it is recommended to make a project plan for the update of the dossier. This project plan should include all activities required for the dossier update and bring them in an order. Milestones can be created to reflect that order. As mentioned above, development studies should be performed first as they lay the foundation for further activities. In the first planning stage, the plan needs to include variables on some points. Where studies have not been performed yet but are

required, the further procedure will rely on the outcome of those studies. Thus, the plan should be updated regularly. Dependencies between certain activities should also be considered. Some have been addressed generally in the discussion of the gap case scenarios. However, they should be discussed specifically for the product dossier under examination. For example, it does not make sense to start process validation activities if the analytical methods are still under discussion. The final analytical methods will be needed for evaluation of the process validation results.

This plan can also be used for a cost and time estimate for the dossier update. A best-case scenario and a worst-case scenario as well as the most probable scenario based on previous experience can be calculated. They might support management on the decision if the dossier should be updated or not.

Planning will have to include collaboration with the submission team of regulatory affairs in order to decide about the submission strategy for the changes done. For new submissions it must be planned when submission can be done and what prerequisites are, e.g. if scientific advice is needed. For existing marketing authorisations, dossier updates must be submitted per variation. The order of submitting the variations and the type of variation (minor, major) should be discussed.

All things considered, it should be carefully evaluated if the costs related to the dossier update are worth the benefits of the planned new marketing authorisation or updated and approved dossier for existing marketing authorisations. Such costs can derive from studies needed for generation of new data, required resources of the Regulatory Affairs team and other related functions and submission costs. This applies in particular, if there are big gaps in the development part and studies might be required. As mentioned above, such studies might show that development decisions in the past must be questioned and the product partially re-developed. This would be very cost intensive. Forecasts for marketing of an old product with an updated dossier should be reviewed thoroughly for products which have been sold poorly in the past. Are the product improvements planned (e.g. new marketing strategy, product optimisations) beneficial enough to cover the costs of the dossier update and subsequent submissions? Finally, it should also be taken into account that evaluation of the gaps in the dossier and creation of a project plan for the update will require substantial resources mainly within Regulatory Affairs that can be missing for other regulatory activities. Hence, the priority of the evaluation of the old product dossier over other activities should be transparent.

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250	EMA, ICH Q1E "Evaluation of stability data", CPMP/ICH/420/02, Chapter 1.1	Published: 01.08.2003 Effective: 01.08.2003	https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-1-e-evaluation-stability-data-step-5_en.pdf	22.05.2020
251	EMEA CPMP "Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products" CPMP/QWP/556/96, chapter Evaluation	Published: 03/1997 Effective: 10/1998	http://www.pharma.gally.ch/cpmp/055696en.pdf	22.05.2020
252	EMA, ICH Q1E "Evaluation of stability data", CPMP/ICH/420/02, Chapter 2.1, 2.2, 2.3	Published: 01.08.2003 Effective: 01.08.2003	https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-1-e-evaluation-stability-data-step-5_en.pdf	22.05.2020

253	EMA, ICH Q1E “Evaluation of stability data”, CPMP/ICH/420/02, Chapter 2.5	Published: 01.08.2003 Effective: 01.08.2003	https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-1-e-evaluation-stability-data-step-5_en.pdf	22.05.2020
254	EMA, Q&As on Quality, Part II, "Stability- Stability issues of pharmaceutical bulk products use in manufacture of the finished product",	n.a.	https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/qa-quality/quality-medicines-questions-answers-part-2#stability---stability-issues-of-pharmaceutical-bulk-products-use-in-manufacture-of-the-finished-product-section	21.05.2020
255	EMA, ICH Guideline Q10 on pharmaceutical quality system, chapter 3.2.3 change management system, EMA/CHMP/ICH/214732/2007	Effective: 06/2008	https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human_en.pdf	30.05.2020
256	EMA, ICH Guideline Q10 on pharmaceutical quality system, EMA/CHMP/ICH/214732/2007	Effective: 06/2008	https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human_en.pdf	30.05.2020
257	ICH Expert Working Group, “ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Life Cycle Management.”, chapter 1.1 and 1.3	Published: 04.03.2020	https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q12-technical-regulatory-considerations-pharmaceutical-product-lifecycle-management_en.pdf	28.03.2020
258	EU Commission, Homepage of the European Union, Europa.eu, About EU, Countries, without date	n.a.	https://europa.eu/european-union/about-eu/countries_en#tab-0-1	30.05.2020

Statutory declaration

English statement:

I hereby declare on oaths that the thesis is written independently and that I have used no other tools/ sources than the specified.

German statement:

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

Stuttgart, 08.06.2020

Kathrin Maria Sugg

Annex

A Comparison tables on regulatory provisions

3.2.P.1 Composition

	2001/83/EC[12] 2001 (not granulated in CTD format yet)	2003/63/EC[3] 2003 (Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	Guideline on **excipients** in the dossier for application for marketing authorisation of a medicinal product[13] 2007
3.2.P.1 Composition Qualitative	To be listed in 3.2.P.1 qualitatively: 1. active substance 2. excipients 3. every substance to be taken orally or to be applied to the patient 4. plus information on the packaging and closure for the pharmaceutical form and **devices** to be provided with the medicinal product The description should be done as follows: - Pharmacopoeia excipients should be listed with the monograph title - the INN (international non-proprietary name) by the WHO or exact scientific name or if not available, a description of the manufacture, other important details can be added	To be listed in 3.2.P.1: 1. active substance 2. excipients 3. every substance to be taken orally or to be applied to the patient 4. plus information on the type of packaging and closure for the pharmaceutical form and **devices** to be provided with the medicinal product **The description of pharmaceutical form and composition for all excipients and the pharmaceutical form should include:** - **function** The description should be done as follows: - Pharmacopoeia excipients should be listed with the monograph title - the INN (international non-proprietary name) by the WHO or exact scientific name or if not available, a description of the manufacture, other important details can be added	To be listed in 3.2.P.1: 1. all components 2. **reconstitution diluents** (in a second P-Part) **3. plus information on the dosage form** 4. plus information on the type of packaging and closure for the pharmaceutical form reconstitution diluents if provided with the product. **The description of medicinal product and composition for all excipients and the pharmaceutical form should include:** - **function** - **the quality standard**	To be listed in 3.2.P.1 (for excipients): 1.common name or brand name with commercial grade **2. For mixtures of compounds: Qualitative information to be provided.** The following should be included: - **function** - **the quality standard**

	2001/83/EC[12] 2001 (not granulated in CTD format yet)	2003/63/EC[3] 2003 (Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	Guideline on **excipients** in the dossier for application for marketing authorisation of a medicinal product[13] 2007
	- For colourants the E number should be given acc. to the Directive 78/25/EEC	- For colourants the E number should be given acc. to the Directive 78/25/EEC **and Directive 94/36/EC**		
3.2.P.1 Composition Quantitative	- For any active substance, the active substance amount should be given as mass/number of units of biological activity, per dosage-unit or per unit of mass or per unit of volume. The description in units of biological activity should be done when there's not the possibility of a molecular description. If there's a unit of biological activity given by the WHO it should be used. If feasible, the biological activity per units should be provided. - Injectables: the mass or units of biological activity for any active substance in the container should be given (incl. the volume of the product to be applied after reconstitution). - Medicinal products applied in drops: mass or units of biological activity of any active substance in the amount of drops which make up 1 ml or 1g of the product. - Syrups/ Emulsions/ Granules and others when applied in a certain measured amount: the	- **the amounts generally should be given on a per-unit basis (including overages) for all components** - For any active substance, the active substance amount should be given as mass/number of units of biological activity, per dosage-unit or per unit of mass or per unit of volume. The description in units of biological activity should be done when there's not the possibility of a molecular description. If there's a unit of biological activity given by the WHO it should be used, **if not another clear expression should be used, if possible in the Ph.Eur. units.**	- **the amounts generally should be given on a per-unit basis (including overages) for all components**	The quantity must be listed for each excipient

	2001/83/EC[12] 2001 (not granulated in CTD format yet)	2003/63/EC[3] 2003 (Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	Guideline on **excipients** in the dossier for application for marketing authorisation of a medicinal product[13] 2007
	mass or units of biological activity of any active substance per measured amount should be given. - For active substance compounds or derivatives the overall mass and the mass of the active entity/entities should be given - For new active substances (first application in any member state) the amount should be listed as mass of the active entity/ entities of the molecule, when the active substance is a salt or hydrate. In all following marketing authorisation dossiers the description should be done in the same way	- For active substance compounds or derivatives the overall mass and the mass of the active entity/entities should be given - For new active substances (first application in any member state) the amount should be listed as mass of the active entity/ entities of the molecule, when the active substance is a salt or hydrate. In all following marketing authorisation dossiers the description should be done in the same way - **Allergen products: the amount should be given in units of biological activity (exception: well defined allergen products, for them the quantity could be described in mass/unit of volume.**		**Mixed compounds: Quantitative information to be provided. Except for flavouring agents the qualitative composition is sufficient.**

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 to 3.2.P.2.6

	CPMP Note for Guidance .on development pharmaceutics 1998	2001/83/EC 2001 (not granulated in CTD format yet)	2003/63/EC 2003 (Update to 2001/83/EC)	NTA Volume 2B 2008 with Module 3 part from 2004	ICHQ8 2009
3.2.P.2.1.1 Drug Substance and Excipients Compat-ibilitity active substance	2.1.1 Compatibility studies of the active substance and excipients as well as the compatibility among active substances in case of multiple-active-substance-preparations should be investigated. Preliminary stability studies should be provided if available	not addressed	3.2.2.2 Discuss the compatibility of active substance and excipients as well as the compatibility among active substances in case of multiple-active-substance-preparations.	3.2.P.2.1.1 Describe the compatibility of active substance and excipients as well as the compatibility among active substances in case of multiple-active-substance-preparations.	2.1.1. Discuss the compatibility of active substance and excipients as well as the compatibility among active substances in case of multiple-active-substance-preparations.
3.2.P.2.1.1 Drug Substance and Excipients Physico-chemical characteristi cs active substance	2.1.2 Trails on preformulations might prove helpful. Physical parameters that are have an influence on the quality if the finished product need to be controlled by the active substance specification, suitable limits and analytical procedures or alternative measures. It can be necessary to perform further physical tests on the active substance depending on the formulation (solid dosage forms, solutions) or pharmacopoeial requirements. Examples mentioned are: - Solubility - Water content - Particle size - Crystal properties? The examples given and their potential influence are further explained in the guidance.	not specifically addressed	3.2.2.2 Explanation required on the physicochemical (and biological, see c)) characteristics of the active substance, if they have an influence on the quality of the finished product and which parameter causes the influence	3.2.P.2.1.1 Explanation required on the physicochemical characteristics of the active substance, if they have an influence on the quality of the finished product and which parameter causes the influence Examples mentioned are: -Solubility - Water content - Particle Size - Polymorphic or solid state form	2.1.1 Explanation required on the physicochemical and biological properties of the active substance, if they have an influence on the quality of the finished product or influence the manufacturing process –irrespective if the active substance has been manufactured specifically to achieve this properties or not. Examples mentioned are: -Solubility - Water content - Particle Size - Crystal properties - Biological activity - Permeability It is mentioned that dependencies between those properties should be included in the discussion. In some cases studies should be performed (reference to ICHQ6A and Q6B) for justification of the active substance specification

	CPMP Note for Guidance .on development pharmaceutics 1998	2001/83/EC 2001 (not granulated in CTD format yet)	2003/63/EC 2003 (Update to 2001/83/EC)	NTA Volume 2B 2008 with Module 3 part from 2004	ICHQ8 2009
	It is mentioned that dependencies between those properties should be included in the discussion.				Examples listed are: - Particle size - Polymorphism
3.2.P.2.1.2 Drug Substance and Excipients	2.2.1 The choice and properties of the excipients should be suitable for the intended use. The criteria for the selection of the excipient quality should be dependent on its purpose in the formulation and the intended manufacturing process. **Sometimes** ("in some cases") a discussion of the quantity of an excipient can be necessary The purpose of adding the excipient should be mentioned. **Sometimes** ("in some cases") study data must be provided in order to justify the necessity of the excipient, e.g. for preservatives data must be provided to justify their use. 2.2.2 Compatibility of excipients with other excipients should be shown, where relevant (e.g. combination of preservatives), supporting stability data can be sufficient. 2.2.3 For novel excipient full information on composition and purpose of the excipient in the formula of the product as well as safety information (comparable to active substance documentation). Examples are mentioned. This applies for novel excipients or excipients that are "administered in an unconventional route" or in high doses. The exception is, when the excipient has been used in certain foods or cosmetics.	Part 2, A.4.1 The choice of excipients should be justified and their intended function described, scientific data should be shown for proof.	3.2.2.2 The choice of excipients (functions, **concentration**) "shall be documented"	3.2.P.2.1.2 The following should be explained for the excipients to be used: **- concentration** -properties that could influence the finished product quality -function	2.1.2: The following should be explained for the excipients to be used: **- concentration** -properties that could influence the finished product quality -function **It is made clear that in this section all substances used must be described, even if they are just supporting the manufacturing process or will be removed later on.** Compatibility of excipients with each other should also be discussed. **It should be shown that the excipients achieve the goal of their intended use** not only up to release but also throughout the shelf life.

	CPMP Note for Guidance .on development pharmaceutics 1998	2001/83/EC 2001 (not granulated in CTD format yet)	2003/63/EC 2003 (Update to 2001/83/EC)	NTA Volume 2B 2008 with Module 3 part from 2004	ICHQ8 2009
3.2.P.2.2.1 Drug Product Formulation Development	The therapeutic activity, the dosage scheme, and the route of administration of the active substance and the intended use of the product should be taken into account when the drug product formulation is developed.	not addressed	A description of the drug product development with respect to the route of administration and use is required	A description of the drug product development with respect to the route of administration and use is required **The differences between the formulation of the investigational product and the current formulation must be justified.** **Results from comparative in vitro studies and comparative in vivo studies should be explained when they are commensurate.**	A description of the drug product development with respect to the route of administration and use is required (summary). **All features that are critical to the quality of the finished product must be named and explained.** Experiments can help to find dependencies in those features. **The description of the formulation development should be linked with the decisions on the properties of the active substance, the choice on excipients, packaging material, dosing devices, and manufacturing process. If applicable, experience from the development of drug products that share certain attributes, shall be described.** The adaptions in the development done step by step should be included and explained. **The differences between the formulation of the investigational product and the current formulation must be justified.** **Results from comparative in vitro studies and comparative in vivo studies should be explained when they are commensurate.** (Study numbers to be mentioned) **All special designs must be listed and the reason for them explained (examples listed, e.g. tablet score line)**
3.2.P.2.2.2 Overages	Overages are discouraged because of the danger of administering too much of the active substance.	Overages must be mentioned and a justification included.	Overages must be justified	Overages must be defended by the applicant.	Overages with the intention to make up for losses in the manufacturing process, in the stability of the product or in order to prolong the shelf life as long as possible are undesirable.

	CPMP Note for Guidance .on development pharmaceutics 1998	2001/83/EC 2001 (not granulated in CTD format yet)	2003/63/EC 2003 (Update to 2001/83/EC)	NTA Volume 2B 2008 with Module 3 part from 2004	ICHQ8 2009
	Description of production and stability overage and related risk of overdosing. Large overages are not accepted when they should cover unstable products, inaccurate analytical procedures or inadequate manufacturing processes. Overages must be justified taking safety and efficacy into consideration.				Overages must be justified taking safety and efficacy into consideration. The overage must be included in the batch formula (3.2.P.3.2) and it must be described by giving the following information: how much overage is needed, what is the justification of the amount of overage and what is the reason for the overage in general.
3.2.P.2.2.3 Physico-chemical and Biological Properties	Chapter 3.2: pH: It should be shown that studies have been done on effect of the pH within the formulation (active substance(s) and where warranted also for excipients Other physico-chemical parameters should be discussed, such as: -dissolution -redispersion -particle size distribution -aggregation -rheological properties The parameters to be considered depend on the formulation Specifically for parenteral products: -tonicity adjustment (parenteral products) -globule size (emulsions) -particle size and shape -changes in crystal form -viscosity - How well the product can be administered with a syringe. Further properties and their influence/ control are explained in special chapters per dosage form (chapters 3.3. to 3.5)	Part A, 4.2 Radiopharmaceuticals: It should be investigated how purity (chemical/radiochemical) correlates to biodistribution	3.2.2.2 d) When a parameter influences how the finished product acts, it should be mentioned here.	3.2.P.2.2.3 All parameters with influence on how the finished product acts (“performance of the drug product acc. to the NTA) Examples are: - pH - ionic strength - dissolution - redispersion - reconstitution - particle size distribution - aggregation - polymorphism - rheological properties - biological activity or potency - immunological activity	All physico-chemical and biological properties that have an influence on the safety, efficacy and the manufacturing process of the drug product should be given here and explained (example given). The analytical method and the measures intended to control the drug release should be explained and justified (information or studies to be provided)

	CPMP Note for Guidance .on development pharmaceutics 1998	2001/83/EC 2001 (not granulated in CTD format yet)	2003/63/EC 2003 (Update to 2001/83/EC)	NTA Volume 2B 2008 with Module 3 part from 2004	ICHQ8 2009
	Chapters 3.4.2, 3.5 For different dosage forms, criteria for the release of the active substance and the analytical method to investigate this have been described. Chapter 2.1.2 Active substance characteristics that influence bioavailability must be controlled and in accordance with results from in vivo studies, specifications must be set.				
3.2.P.2.3 Manufacturing Process Development	Chapter 5: The development of the manufacturing process should be described and the reasons for the choice of this process should be given. **It should be shown that setting up of adequate specifications is possible with the manufacturing process** ("The process should enable the definition of appropriate specifications such that the quality of the finished product can be assured")**.** The following criteria should be considered in the development: microbiological, physical and/ or chemical. Development studies should be the basis for further process optimisation (explanation and examples included). Sterile products: choice of sterilisation method and primary packaging material should be defended.	not addressed	3.2.2.2 f) The choice and further development of the manufacturing process should be described, **Explanation of the differences in the manufacturing process of the investigational medicinal product and the current manufacturing process should be described**	3.2.P.2.3: The choice and further development of the manufacturing process should be described, especially when it comes it its **critical aspects.** Sterile products: the sterilisation process or the aseptic process must be described **Explanation of the differences in the manufacturing process of the investigational medicinal product and the current manufacturing process should be described and the impact on the quality of the product ("performance") should be evaluated.**	Chapter 2.3: The development of the manufacturing process **and its controls** should be described. **For the choice of the manufacturing process, the process options and the critical attributes of the formulation should be taken into consideration** ("It is important to consider the critical formulation attributes, together with the available manufacturing process options") Such critical properties could be of a microbiological, physical and/ or chemical nature. Development studies should be the basis for further process optimisation (explanation and examples included). Critical process parameters must be described and the controls explained and justified. Sterile products: choice of sterilisation method and primary packaging material should be defended. **Explanation of the differences in the manufacturing process of the investigational medicinal product and the**

	CPMP Note for Guidance .on development pharmaceutics 1998	2001/83/EC 2001 (not granulated in CTD format yet)	2003/63/EC 2003 (Update to 2001/83/EC)	NTA Volume 2B 2008 with Module 3 part from 2004	ICHQ8 2009
					current manufacturing process should be described and the impact on the quality of the drug product should be evaluated ("performance, manufacturability and quality"). The same applies to manufacturing **changes that happened after the primary stability studies**. Information given should be e.g. batch number, manufacturing site, batch size, important equipment changes **Data collected can be helpful for further process development/ optimisation. Where it was found that the process can be performed under varying conditions (conditions must be named) and still result in a drug product of appropriate and predetermined quality this should be described.**
3.2.P.2.4 Container Closure System	Chapter 4: The (primary) packaging material chosen should be justified in relation of -safety for patients/ medical staff when the product is applied -children (necessity for child-resistant packaging) -integrity (are there interactions between the packaging material and the drug product? This needs to be considered as well for reconstitution products that are prepared in a separate container) -the type of product (depending on the manufacturing process), e.g. sterile products	Part 2, A 4.1 The decision for this specific container must be justified Part 2, G.1 Interaction studies product- container required when there's a risk for interaction, e.g. for parenteral medicinal products or aerosols	3.2.2.2 g) It needs to be addressed if the packaging material is sufficient for storing of the product, transport and for the application of the medicinal product. The possibility of physicochemical reactions between container closure system and drug product should be included in the discussion.	3.2.P.2.4: It needs to be addressed if the packaging material is sufficient for storing of the product, transport and for the application of the medicinal product. The considerations should include: -the decision on the material of the container -protection from humidity and light -interactions of the container closure with the medicinal product (e.g. leakage, adsorption)	Chapter 2.4: The (primary) packaging material chosen should be justified in relation of -the foreseen use -suitability for storage and transportation -integrity (are there interactions between the packaging material and the drug product? Criteria to be assessed (exemplary): -choice of materials -protection from humidity and photo-protection -compatibility drug- packaging

	CPMP Note for Guidance .on development pharmaceutics 1998	2001/83/EC 2001 (not granulated in CTD format yet)	2003/63/EC 2003 (Update to 2001/83/EC)	NTA Volume 2B 2008 with Module 3 part from 2004	ICHQ8 2009
	Criteria to be assessed: -Sorption to the packaging material (for liquid or semi-solid formulations) -Leaching for the duration of the shelf life, when safety is not given for liquid or "finely divided solid" formulations -accuracy of the dosage (for dosing devices)			**-innocuousness of the container closure materials** -does the container closure system/ dosing device fulfil its intended purpose (e.g. does a device always deliver the same dose?)	**-safety of packaging materials** -accuracy of the dosage (for dosing devices)
3.2.P.2.5 Micro-biological attributes	Chapter 3.3.1.1: Explain and justify/demonstrate: -If applicable, the choice and performance of the preservative measurements (lowest effective amount to be applied). The following criteria should be considered: storage conditions, reconstitution, and dilution before use, in case of multi-dose containers: frequency of opening. -The length of the shelf life and the influence of the pack size must be discussed for products requiring a preservative.	Not addressed	3.2.2.2 h) The microbiological purity should be given in accordance with the criteria of the Ph.Eur.	3.2.P.2.5 The microbiological properties of the medicinal product should be explained and it should be justified if no microbial limit test for non-sterile products is done. The choice and decision for a preservative system as well as its ability to fulfil the intended purpose should be documented as well. **Sterile products: The ability of the container closure system to protect the product against microbial impurities should be shown**	Chapter 2.5: Explain and justify/demonstrate: -If applicable, the choice and performance of the preservative measurements (lowest effective amount to be applied) or the evidence of the anti-microbiological activity of a drug product (further explanation given in guideline) **-packaging material integrity in the sense of protection from microbial contamination for sterile products.**
3.2.P.2.6 Compatibility (reconstitution diluents/ dosage devices)	Chapter 3.3.2: Compatibility (chemical/ physical) with reconstitution diluents and dosage devices should be discussed with regards to the in-use- shelf life the storage temperature and the point of extreme concentration. Chapter 3.5.1	Part 2, A 4.1 The decision for the constituents chosen must be justified	3.2.2.2. i) Compatibility with reconstitution diluents and dosage devices should be discussed	3.2.P.2.6 Compatibility with reconstitution diluents or dosage devices should be discussed with regards to the storage, sorption to the injection	Chapter 2.6: Compatibility with reconstitution diluents should be discussed with regards to the in-use- shelf life, the storage temperature and the point of extreme concentration.

	CPMP Note for Guidance .on development pharmaceutics 1998	2001/83/EC 2001 (not granulated in CTD format yet)	2003/63/EC 2003 (Update to 2001/83/EC)	NTA Volume 2B 2008 with Module 3 part from 2004	ICHQ8 2009
	For transdermal patches: compatibility with matrix patch and the adhesive component must be shown. Chapter 3.5.3 Dry powders for inhalation: it must be shown that the dose delivery is sufficient for the intended use: e.g. air flow rate/ part of the active substance remaining in the device			system and precipitation of the solved active substance)	Discuss the possibility of segregation of the mix/dilution before the product is applied on the patient.

Comparison of the recommendations on Bioequivalence

The comparison was done on the topic the similarity of in-vitro dissolution profiles.

	EMEA CPMP Note for guidance on the investigation of bioavailability and bioequivalence (replaced) 2001/2002	EMEA CPMP Guideline on the Investigation Bioequivalence 2010
Sampling Times	Appendix II Low solubility and high permeability products: adequate sampling shall be done until 90% dissolution or the asymptote is achieved.	Appendix 1: Sampling time points should be sufficient to obtain meaningful dissolution profiles, and **at least every 15 minutes**. More frequent sampling during the period of greatest change in the dissolution profile is recommended. For rapidly dissolving products, where complete dissolution is within 30 minutes, generation of an adequate profile by sampling at 5- or 10-minute intervals may be necessary.
Non-Rapidly dissolving medicinal products	-	For products for which 85% of the dissolution is reached before 30 min but after 15 min, the following criteria apply: - min. 3 time points to be tested - 1st test (time) point before 15 min - 2nd test (time) point at 15 min - 3rd test (time) pint at approximately 85% release
Similarity calculation (Weibull/ f2 function/statistics)	Appendix II The following criteria apply for the relative standard deviation for each product: < 10% from the 2nd to the last test point	Appendix I The following criteria apply for the relative standard deviation or variation coefficient for each product: **< 20% for the first time point** < 10% from the 2nd to the last test point The criteria for acceptance may not be > 10% difference. Variability of the the dissolution of the products to be compared should be similar.
Appendices	-	Additional appendixes were provided: Appendix II: provisions for different pharmaceutical forms Appendix III on BCS based Biowaivers

3.2.P.3 Manufacture

3.2.P.3.1 to 3.2.P.3.4

	EMEA CPMP Note for Guidance on Manufacture of the Finished dosage form CPMP/QWP/486/95 1996	2001/83/EC[12] 2001 (not granulated in CTD format yet)	2003/63/EC[3] 2003 (2nd Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	Guideline Manufacture of the finished dosage form 2017
GMP and Dossier contents	Chapter 2 of the Note for Guidance: 3.2.P. should only contain medicinal product-specific information and not general information which are covered by the GMP rules. Examples for non-specific information not to be included in the marketing authorisation dossier: personnel qualification, production equipment and room cleaning as well as final packaging and labelling procedures.	not addressed	not addressed	not addressed for Module 3.2.P.3	Chapter 4: Only information specific to the product to be included, no general GMP topics.
3.2.P.3.1 Manu-facturers	Chapter 5 of the Note for Guidance: Only sites to be mentioned that do - manufacturing operations (incl. packaging) - final market release For companies with operations/release at different sites the addresses must be listed separately.	not addressed	Annex I, Part 1, Module 3, 3.2.2.3 a):: Each manufacturer **and contractor** for manufacturing sites **and testing sites**: Name Address **Responsibilities**	3.2.P.3.1 Each manufacturer **and contractor** for manufacturing sites **and testing sites**: Name Address **Responsibilities**	Chapter 4.1: Each manufacturer **and contractor** for manufacturing sites (incl. packaging) **and testing sites incl. on-going stability testing sites, if they are not the same as the manufacturing sites)**: Name Address **Responsibilities** **+ EU site** for batch release
3.2.P.3.2 Batch Formula	Chapter 3 of the Note for Guidance: <u>Batch size</u> Batch size to be provided including explanation for more than one batch size or batch size ranges.				Guideline Chapter 4.2: <u>Batch size</u> a) <u>Determination of the batch size</u> **- Justification for batch size needed (no negative influence on quality allowed, to be shown in process validation)** **- To be defined by the production equipment** **- Batch size must be large enough for commercial manufacturing (exceptions to be justified), for solid oral dosage forms min. 100,000 units** **- Continuous manufacture:** **Definition of the batch size to be explained**

	EMEA CPMP Note for Guidance on Manufacture of the Finished dosage form CPMP/QWP/486/95 1996	2001/83/EC[12] 2001 (not granulated in CTD format yet)	2003/63/EC[3] 2003 (2nd Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	Guideline Manufacture of the finished dosage form 2017
	Manufacturing Formula The manufacturing formula must include: - quantities of all substances used. Exact quantities do not have to be listed when they cannot be given for reasons of the pharmaceutical form -overages - all components, incl. substances that are removed again or substances that are only used if needed. - factorisation, if applied - in case of factorisation: substances used to level the higher/lower quantity of the active substance for keeping the total mass	Annex 1, Part II B 1. Manufacturing Formula The manufacturing formula must include: - quantities of all substances used. Exact quantities do not have to be listed when they cannot be given for reasons of the pharmaceutical form -overages - all components, incl. substances that are removed again or	Annex I, Part 1, Module 3, 3.2.2.3 a):: Manufacturing Formula A detailed batch formula	3.2.P.3.2 Manufacturing Formula The manufacturing formula must include: - quantities of all substances used (per batch) -overages **- quality standards**	**- For packaging of one bulk in different presentations/packs the batch size is the size before the bulk is divided. For the process steps that follow the worst case should be applied for description of the length of these steps, if critical.** b) If more than one batch size shall be used/ batch size ranges - Explanation needed, why more than one batch size is used or for a batch size range **- Batch formula to be given for at least the smallest and largest size for ranges**. c) Sub-batches **The manufacture of sub-batches:** **-must be justified** **- batch formula must be given** **- batch size for sub batch to be included** **- further division of sub-batches must be described, if applicable** **- number of sub-batches must be given** Manufacturing Formula The manufacturing formula must include: - quantities of all substances used. -overages - all components, incl. substances that are removed again **(can be listed in ranges)** or substances that are only used if needed. **- quality standards** - factorisation, if applied - in case of factorisation: substances used to level the higher/lower quantity of the active substance for keeping the total mass -Acceptance limits for the quantities of the excipients can be stated but must be justified

	EMEA CPMP Note for Guidance on Manufacture of the Finished dosage form CPMP/QWP/486/95 1996	2001/83/EC[12] 2001 (not granulated in CTD format yet)	2003/63/EC[3] 2003 (2nd Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	Guideline Manufacture of the finished dosage form 2017
	- Acceptance limits for the quantities of all substances must be given and should not be wider than 95-105% for APIs and 90-110% of excipients. Wider limits must be explained and batch results for batches where the excipient is at the upper/lower limit must be shown in order to prove that the results are still within specification.	substances that are only used if needed.			
3.2.P.3.3 Description of Manufacturing Process and Process Controls	Chapter 1 and 4 of the Note for Guidance: <u>General provisions and Description</u> The manufacturing steps must be described Description of the equipment used, if relevant **No detailed descriptions of manufacturing process, equipment IPCs should be provided in order to avoid variations.** **Parameters where the final batch control cannot ensure the quality for all units of the lot** (such as content uniformity or sterilisation): Other control parameters (process parameters, IPCs etc) need to be described in the dossier (in sufficient detail).	Annex 1, Part II B 1. : <u>General provisions and Description</u> The manufacturing steps must be described	Annex I, Part 1, Module 3, 3.2.2.3 a): <u>General provisions and Description</u> The manufacturing steps must be described	3.2.P.3.3: <u>General provisions and Description</u> The manufacturing process must be documented and described as follows: -The manufacturing steps **specific for the batch size** - **Packaging process** *(explicitly mentioned)* **- All Equipment to be described by type** **- Equipment capacity, if necessary** - P**rocess parameters with numeric criteria (ranges possible). Justification to be presented in 3.2.P.3.4** **- Scientifically/ Technically new (novel) aspects such as processes/technologies/ operations to be described in detail** **- If critical, environmental conditions should be given**	Chapter 4.3: <u>General provisions and Description</u> The manufacturing process must be documented and described as follows: -The manufacturing steps **specific for the batch size** **- All Equipment to be described by type.** **- Equipment capacity, if necessary** **- <u>All</u> process parameters with numeric criteria (ranges possible). Non-criticals and parameters necessary for the process to be described, that is "supportive" to be included, but no expectation for detail is given by the guideline** **- If critical, environmental conditions should be given** **- the operating principle for each step** - The steps, where IPCs, Intermediate Tests or final product controls are performed **The need for sufficient detail in the manufacturing process is expressed as finished product testing solely cannot prevent a varying product quality. How detailed the description has to be, is dependent on the criticality of the relevant aspect.**

	EMEA CPMP Note for Guidance on Manufacture of the Finished dosage form CPMP/QWP/486/95 1996	2001/83/EC[12] 2001 (not granulated in CTD format yet)	2003/63/EC[3] 2003 (2nd Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	Guideline Manufacture of the finished dosage form 2017
	Flow Chart Flow chart with manufacturing steps, and IPCs required Alternatives: In case of alternative manufacturing steps, it must be should be data that they are equivalent (product to be always within specification) Sterile products and other special items The following topics are described further in the note for guidance: - Sterilisation methods (and reference to 3.2.P.2 for the choice of the method) **- Reprocessing (residual products) shall not be part of the dossier** - Removal of solvents or gases - Cleaning and sterilisation of primary primary container closuring systems **- Production surroundings (should usually not be described unless requested)**	Sterile products: Description of sterilization and/or the aseptic process	Annex I, Part 1, Module 3, 3.2.2.3 a): Sterile products: Description of sterilization and/or the aseptic process	**- If reprocessing is done it should be mentioned and justified.** Flow Chart Flow chart with manufacturing steps (in particular critical steps), and IPCs as well as **final product controls** required Sterile products: *not explicitly mentioned*	*The guideline includes an Example for a manufacturing process description in the Annex* Flow Chart Flow chart with manufacturing steps, and IPCs **as well as all materials and where they enter the process needed**. **If applicable, design spaces should be included.** Alternatives **The same manufacturing process should be applied by all sites. Exceptions in the form of technical adaptions, e.g in equipment are possible:** **-Justification needed** **- Justification also needs to be targeted at the IPCs and finished product quality.** **- Data to support the justification needed.** **- For each technical model a flow chart needs to be presented** **- The models need to be compared** **- Technical adaptions possible but not different manufacturing principles** *Examples are given in the guideline* Sterile products: *not explicitly mentioned*
3.2.P.3.4 Controls of Critical Steps and	Chapter 1 and 4 of the Note for Guidance:	Annex 1, Part II B 1. : Description of in-process controls if	Annex I, Part 1, Module 3, 3.2.2.3 b)	3.2.P.3.3: Justification for acceptance criteria for process parameters to be included in 3.2.P.3.4.	Chapter 4.4. General provisions

	EMEA CPMP Note for Guidance on Manufacture of the Finished dosage form CPMP/QWP/486/95 1996	2001/83/EC[12] 2001 (not granulated in CTD format yet)	2003/63/EC[3] 2003 (2nd Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	Guideline Manufacture of the finished dosage form 2017
Intermediates	Description of in-process controls if relevant and at which manufacturing step they are performed Continuous manufacturing: measurements for control of the homogeneity of the finished product should be described	relevant and at which manufacturing step they are performed Continuous manufacturing: measurements for control of the homogeneity of the finished product should be described Annex 1, Part II E. : Controls performed **on an intermediate** must be described	Controls performed **on an intermediate** or in-process-controls must be described. Annex I, Part 1, Module 3, 3.2.2.3 a): Continuous manufacturing: measurements for control of the homogeneity of the finished product should be described	3.2.P.3.4: **Inclusion of tests and specifications for the critical steps in the manufacturing process, including justification and data to support the specification** For intermediates which are isolated in the process, quality and the control should be described.	To be listed: A) **all critical manufacturing steps and intermediates -justification on criticality to be included, for data the link to 3.2.P.2 could be provided** **- for the non-critical steps, a monitoring concept should be explained, specifications must be set up for those parameters**. B) In-process controls **with test methods and specifications -for complex control models and continuous manufacturing the frequency of IPCs and the correlation to finished product release testing and release decisions in the frame of ensuring a consistent quality should be explained for the criteria. Example: handling of unexpected variations** <u>Intermediate/ Bulk Storage</u> **A) Intermediates** **Information on the storage of intermediate, transportation and testing must be given** **B) Bulk** **Is storage required before final packaging? If this is the case the following information needs to be given:** **- Temperature** **- Humidity** **- Other environmental conditions, if applicable** **- Maximum hold time of the bulk or maximum time needed for manufacturing (start of the manufacture until completion of the packaging in the primary packaging material), if relevant** **- Justification for max. hold time bulk or max. manufacturing time plus reference to data in relevant dossier parts.** **- Reasons for longer storage/ manufacturing time as time needed should normally be as short as possible. Prolonged storage: > 30 days for solid oral products and >24h for sterile products.** **- Bulk stability studies in case of prolonged storage to be performed at 2 batches at the intended storage conditions**

	EMEA CPMP Note for Guidance on Manufacture of the Finished dosage form CPMP/QWP/486/95 1996	2001/83/EC[12] 2001 (not granulated in CTD format yet)	2003/63/EC[3] 2003 (2nd Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	Guideline Manufacture of the finished dosage form 2017
					C) Shelf Life Calculation **The Product shelf life shall be calculated acc. Note for Guidance on the start of shelf life of the finished dosage form. Other types of calculation are to be explained and justified.** D) Bulk or Intermediate Transport **The following information should be given, in case bulk is transported between sites:** **-Within the bulk transportation acc. to GMP Annex 15 cases where the temperature reaches values not within the intended storage conditions are to be discussed and if needed, data must be provided.** E) Packaging of Bulk/ Intermediates **Reference to other parts of the dossier where the packaging material/ specification is described**

3.2.P.3.5

	EMEA CPMP Note for Guidance on Manufacture of the Finished dosage form CPMP/QWP/486/95 1996	EMEA CPMP Note for guidance on process validation 2001	2001/83/EC[12] 2001 (not granulated in CTD format yet)	2003/63/EC[3] 2003 (Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	Guideline on process validation for finished products- information and data to be provided in regulatory submissions 2014
3.2.P.3.5 Process Validation and/or Evaluation: A)Traditional Process Validation	Chapter 6 of the note of Guidance: Validation studies for the development of non-standard processes to be included in development part Part IIA (in CTD 3.2.P.2) Validation of non-standard processes and standard processes to be described in this chapter only if it cannot be assured that the finished product specification criteria will be fulfilled for the whole batch with an appropriate statistical safety. Process validation does not replace the relevant finished product release and shelf life testing (e.g. sterility, content uniformity).	Chapter 4 and 5: Validation data needed from all production sites. For batch size ranges, it must be proven that the batch size all batch sizes can guarantee the finished product quality by validation studies. Chapter 4: Validation studies for the development of non-standard processes to be included in the dossier, for standard processes it must not necessarily be available at the time of submission. Chapter 4: <u>Extent of validation data to be provided is dependent on:</u> - type and complexity of the finished product - type and complexity of the active substance - type and phase of development of the manufacturing process Chapter 4.2, 4.4 and Annex 1: <u>Size of the Process Validation Batches</u> - Pilot Batch Size Validation studies are not sufficient at the time of submission for products with non-standard method of manufacture or **which belong to certain modified release dosage forms.** - Definition of Pilot Size: min. 10% of the commercial batch sizes and for solid oral dosage forms min. 100,000 units or 10% of the commercial batch size (the bigger number has to be applied) - If no commercial scale validation data are submitted, pilot scale batches and a validation	Annex 1, Part II B 1. : Validation studies for the development of non-standard processes to be included or if required for the control of the quality of the finished product	Annex I, Part 1, Module 3, 3.2.2.3 a): Validation studies for the development of non-standard processes to be included or if required for the control of the quality of the finished product Annex I, Part 1, Module 3, 3.2.2.3 c): Explanation and data to be provided on the validation of critical manufacturing steps or assays to be included	3.2.2.3 a) and c) Validation studies must be shown and included if the process is non-standard or for any critical step.	Chapter 4: Validation data needed from all production sites **and all strengths.** **Bracketing could be possible in respect of strengths, batch sizes and pack sizes.** Chapter 5.1: <u>Extent of Validation Activities/ Number of validation batches</u> to be provided is dependent on: - complexity of the finished product - complexity of the manufacturing process - previous knowledge from development **- consistency of the process** **- amount and quality of data available from commercial manufacture (e.g. technical transfers and experience of the manufacturer)** <u>Size of the Process Validation Batches</u> - Pilot Batch Size Validation studies are not sufficient at the time of submission for products with non-standard method of manufacture. - Definition of Pilot Size: min. 10% of the commercial batch sizes and for solid oral dosage forms min. 100,000 units or 10% of the commercial batch size (the bigger number has to be applied). **If these criteria are not met, it must be justified.** - If no commercial scale validation data are submitted, pilot scale batches and a validation plan for 3 consecutive batches commercial scale are required for marketing authorisation application. 1-2 batches can be enough, when

	EMEA CPMP Note for Guidance on Manufacture of the Finished dosage form CPMP/QWP/486/95 1996	EMEA CPMP Note for guidance on process validation 2001	2001/83/EC[12] 2001 (not granulated in CTD format yet)	2003/63/EC[3] 2003 (Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	Guideline on process validation for finished products- information and data to be provided in regulatory submissions 2014
		plan for 3 consecutive batches commercial scale are required. The content of the process validation plan is described in Annex 1. <u>Number of validation batches (only for non-standard processes), Chapter 4:</u> -1 to 2 batches: if pilot scale batches have been done, the product is manufactured with basically comparable processes and has been consistently manufactured - 3 batches for aseptic processes or non-standard sterilisation procedures <u>Focus of the studies, Chapter4</u> Critical stages, **where quality cannot be fully ensured by the finished product specification solely** (justification to be included for the proposed plan) Annex 1: Process validation plan *For a full list of provisions refer to Annex I of the guideline.* Annex II: <u>Non-standard processes</u> - Information if a process considered is standard or not needs to be included in 3.2.P.3.5 (and justified) *For a full list of non-standard processes refer to Annex II of the guideline.*				pilot batches are available and with appropriate justification. - Chapter 5.1: The content of the process validation plan is described in Annex 1 and the content of the plan must be justified. <u>Focus of the studies, Chapter 5.1</u> Critical stages (justification to be included for the proposed plan) **<u>Scale up and Batch Size Ranges (Chapter 6):</u>** **- The critical aspects for scale up should be included in the validation concept** - For batch sizes ranges it must be shown that the product quality is not negatively influenced by an additional batch size (exception: it has been already proven that the process is independent from the batch size) Annex 1: Process validation plan *For a full list of provisions refer to Annex I of the guideline. No changes have been performed in comparison to* EMEA CPMP Note for guidance on process validation 2001. Annex II: <u>Non-standard processes</u> *For a full list of non-standard processes refer to Annex II of the guideline.* *In the following only the topics that have been changed compared to the* EMEA CPMP Note for guidance on process validation 2001 *are listed*: **- nanoparticulate preparations have been added**

	EMEA CPMP Note for Guidance on Manufacture of the Finished dosage form CPMP/QWP/486/95 1996	EMEA CPMP Note for guidance on process validation 2001	2001/83/EC[12] 2001 (not granulated in CTD format yet)	2003/63/EC[3] 2003 (Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	Guideline on process validation for finished products- information and data to be provided in regulatory submissions 2014
						- standards methods of sterilisation with related application for parametric release have been deleted
3.2.P.3.5 Process Validation and/or Evaluation: B)Continuous Process Verification	not adressed	not adressed	not adressed	not adressed	not adressed	**<u>Continuous Process Verification</u>** Chapter 4: Validation data needed from all production sites **and all strengths.** **Bracketing could be possible in respect of strengths, batch sizes and pack sizes.** *Explanation of continuous process verification included* <u>Chapter 5.3:</u> <u>Extent of validation activities/ number of batches</u> to be provided is dependent on: - complexity of the finished product - complexity of the manufacturing process - previous knowledge from development **- consistency of the process for products where those data are already available** **- amount and quality of data available from commercial manufacture e.g. experience of the manufacturer with similar products)** **- use of automation of the process and analytical technology used.** The relevant data generated matching the concept explained and justified in 3.2.P.2 must be included **<u>Scale up and Batch Size Ranges (Chapter 6):</u>** **- The critical aspects for scale up should be included in the validation concept**

	EMEA CPMP Note for Guidance on Manufacture of the Finished dosage form CPMP/QWP/486/95 1996	EMEA CPMP Note for guidance on process validation 2001	2001/83/EC[12] 2001 (not granulated in CTD format yet)	2003/63/EC[3] 2003 (Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	Guideline on process validation for finished products- information and data to be provided in regulatory submissions 2014
						Annex 1: Process validation plan *For a full list of provision refer to Annex I of the guideline. The criterial for continuous process verification schemes have been included..*
3.2.P.3.5 Process Validation and/or Evaluation: C)Hybrid validation	not adressed	not adressed	not adressed	not adressed	not adressed	**<u>Hybrid approach</u>** **It must be clarified for when traditional validation and when continuous process verification has been used (for different manufacturing steps)** **Batch Size and Number of batches:** **- depends on the level of application of the continuous process verification** **For non-standard processes:** **- If continuous verification does not cover the critical quality aspects, then the validation should be done on the criteria for the traditional process validation**
3.2.P.3.5 Process Validation and/or Evaluation: D)Design Space						**Chapter 5.4:** **Verification of the design space to be provided if within development (3.2.P.2) a design space has been established but it has not been proven that it is valid for all batch sizes and if traditional validation has been done.** **If a design space is used and continuous process verification is done, the design pace verification must be part of the continuous process verification concept.**

3.2.P.4 Control of Excipients

	EU Commission Guideline on Excipients in the dossier for application for marketing authorisation of a medicinal product, 1st version 1994	2001/83/EC[12], Annex I, Part II 2001, (not granulated in CTD format yet)	2003/63/EC [3] 2003 (2nd Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	EMEA CHMP Guideline on Excipients in the dossier for application for marketing authorisation of a medicinal product, Revision 2 2007/2008
3.2.P.4.1 Specifications	Chapter 2.1.1 Compendial excipients: **- the specifications applied in routine must be described** -reference to the pharmacopoeia sufficient except if impurities exist that are not controlled by the pharmacopeia→ a specification must be set up for those and it must be proven that the pharmacopoeia quality requirements are fulfilled. - In case the monograph describes a group of substances, only the specification for the excipient used should be included. - the specification should include, if required, additional tests and specifications to the monograph for proof of the function. Chapter 2.1.2 and 2.2 Non-compendial excipients The specification must include tests of the following category: - Physical - Identification - Purity (at least single and total impurities) - content or limit tests if required - Other tests, for example relevant for the performance of the pharmaceutical form - microbiological purity for excipients used in sterile filtration processes for parenteral application forms	Chapter 1.1: Compendial starting materials **- the specifications applied in routine must be described** -reference to the pharmacopoeia sufficient except if impurities exist that are not controlled by the pharmacopeia→ a specification must be set up for those and it must be proven that the pharmacopoeia quality requirements are fulfilled (that is equivalence). -3rd country pharmacopoeia monographs might be accepted if the starting material is not described in a pharmacopoeia of the EU member states Chapter 1.2 Non-compendial starting materials The following information should be given:	Chapter 3.2.2.4 a) and b) The following must be listed for excipients - specifications - all substances needed for manufacturing of the excipients with a information, where those are used in the manufacturing process of the excipient - Explanation of quality and control of the excipient - if the excipient is a colourant, compliance with Directive 78/25/EEC and/or 94/36/EC as well as the purity requirements from 95/45/EC must be confirmed	3.2.P.4.1 Specifications to be included	Chapter 4.3 a) and b) Compendial excipients: **- it should be referred to the current edition of the pharmacopoeia** -reference to the pharmacopoeia sufficient except if impurities exist that are not controlled by the pharmacopeia→ a specification must be set up for those and it must be proven that the pharmacopoeia quality requirements are fulfilled **(refer to Ph.Eur. 1.1 General statements).** - In case the monograph describes a group of substances, only the specification for the excipient used should be included **(with justification).** - the specification should include, if required, additional tests and specifications to the monograph for proof of the function. -3rd country pharmacopoeia monographs might be accepted if the starting material is not described in a pharmacopoeia of the EU member states **(justification required). The specification must then fulfil the requirements of the Ph.Eur. monograph "Substances for pharmaceutical use"** Chapter 4.3.c) Non-compendial excipients The specification must include tests of the following category: - Physical - Identification - Purity (at least single and total impurities) - Content or limit tests if required **(to be validated)** - Other tests, for example relevant for the performance of the pharmaceutical form General

	EU Commission Guideline on Excipients in the dossier for application for marketing authorisation of a medicinal product, 1st version 1994	2001/83/EC[12], Annex I, Part II 2001, (not granulated in CTD format yet)	2003/63/EC [3] 2003 (2nd Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	EMEA CHMP Guideline on Excipients in the dossier for application for marketing authorisation of a medicinal product, Revision 2 2007/2008
		-name of the substance - chemical definition - identification tests - purity tests - for complex substances with several properties with similar activities an overall assay can be stated - if special conditions for the storage are required, they should be listed with the retesting time			-If the excipient is a colourant, compliance with Directive 78/25/EEC and/or 94/36/EC as well as the purity requirements from 95/45/EC must be confirmed - For sterile products: microbiological purity, except it is tested on the bulk before sterilisation **- For sterile products: Endotoxin limits to be included, except it is tested on the bulk before sterilisation** **Information and data on residual solvents must be included in the dossier.**
3.2.P.4.2 Analytical Procedures	not addressed	Chapter 1.1 Compendial starting materials: Reference to the pharmacopoeia sufficient except if impurities exist that are not controlled by the pharmacopeia→ an analytical test procedure must be set up.	Chapter 3.2.2.4 b): Analytical procedures to be included	3.2.P.4.2 Analytical procedures to be included, where relevant	not addressed
3.2.P.4.3 Validation of Analytical Procedures	not addressed	not addressed	Chapter 3.2.2.4 b): Validation of Analytical Procedures to be described	3.2.P.4.3 Validation of Analytical Procedures to be described, including data.	*not specifically addressed, it is only said that the validation parameters for the assay or limit tests must be given for non-compendia excipients (see section 3.2.P.4.1)*
3.2.P.4.4 Justification of Specifications	Chapter 2.2.1: - Specifications set up specifically to verify the function of the excipient ad described in the development part must be explained. Chapter 2.1.1	not addressed	Chapter 3.2.2.4 b): Justification for the specifications to be included.	3.2.P.4.4 Justification for the specifications to be included.	Chapter 4.4.: - Specifications set up specifically to verify the function of the excipient and described in the development part must be explained (in particular, if critical).

	EU Commission Guideline on Excipients in the dossier for application for marketing authorisation of a medicinal product, 1st version 1994	2001/83/EC[12], Annex I, Part II 2001, (not granulated in CTD format yet)	2003/63/EC [3] 2003 (2nd Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	EMEA CHMP Guideline on Excipients in the dossier for application for marketing authorisation of a medicinal product, Revision 2 2007/2008
	- Specifications have to be based on scientific considerations. Only for well-known excipients (incl. EU pharmacopoeia excipients) those data may not be required.				- For pharmacopoeia excipients from Ph.Eur. or another EU pharmacopoeia explanation is usually not required - For well-known excipients justification may also not be required
3.2.P.4.5 Excipients of Human or Animal Origin	Annex: - For those excipients, which are of human or animal origin, the risk needs to be assessed and supported by data on the handling, control of tissues and body fluids) - name and address of excipient manufacturer needs to be listed for excipients of animal or human origin	Chapter 1.2.f)	Chapter 3.2.24 c): For those excipients, which are of human or animal origin, it must be confirmed that they are manufacture acc. to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products & updates to this Note for Guidance. This can be done by including a certificate of suitability for the Ph.Eur. monograph on Transmissible Spongiform Encephalopathies or by providing data that prove the compliance.	3.2.P.4.5 For those excipients, which are of human or animal origin, an explanation with regard to adventitious agents should be included.	Chapter 4.5: Safety in respect of viruses and the TSE risk must be addressed acc. to Ph.Eur. 5.1.7 Viral Safety and Ph.Eur. 5.2.8 Minimising the risk of Transmitting Animal Spongiform Encephalogphathy Agents via Human and Veterinary Medicinal Product.
3.2.P.4.6 Novel Excipients	*A list of recommendations is included in chapter 2.2.2 for novel excipients*	not specifically addressed	Chapter 3.2.24 c): The following info needs to be provided in accordance with the requirements on active substances: -description of the manufacturing process -characterisation - how it is controlled (incl. references to the clinical and non-clinical safety data, toxicity studies to be provided in module 4) - chemical/ pharmaceutical and biological information should be given in the structure of the 3.2.S.	Chapter 3.2.P.4.6: The following info needs to be provided in accordance with the requirements on active substances: -description of the manufacturing process -characterisation - how it is controlled (incl. references safety data)	Chapter 4.6: The following info needs to be provided in accordance with the recommendations on active substances: -description of the manufacturing process -characterisation - how it is controlled (incl. references safety data) *A list of provisions is provided in chapter 4.6. Only the differences to the* EU Commission Guideline on Excipients in the dossier for application for marketing authorisation of a medicinal product, 1st version 1994 *will be explained further:* **- Data to be provided on novel excipients has to follow the criteria given in the CPMP Guideline on the Chemistry of New Active Substances (CPMP/QWP/130/96)* instead of the Note for Guidance Chemistry of Active Substances**

	EU Commission Guideline on Excipients in the dossier for application for marketing authorisation of a medicinal product, 1st version 1994	2001/83/EC[12], Annex I, Part II 2001, (not granulated in CTD format yet)	2003/63/EC [3] 2003 (2nd Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	EMEA CHMP Guideline on Excipients in the dossier for application for marketing authorisation of a medicinal product, Revision 2 2007/2008
					- stability data have to be provided as explained for active substances in the "Note for Guidance on Stability Testing of New Drug Substances and Products (CHMP/ICH/2736/99)- ICH Q1A(R2) **was replaced by the Guideline on the chemistry of active substance EMA/454577/2016, 2016* ******

3.2.P.5 Control of Drug Product

3.2.P.5.4, 3.2.P.5.5, 3.2.P.5.6

	EU Commission "Specifications and Control Tests on the Finished Product" 3AQ11a 1991/1992	2001/83/EC[12], Annex I, Part II 2001, (not granulated in CTD format yet)	2003/63/EC[3] 2003 (2nd Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004 Chapter 3.2.P.5.4-3.2.P.5.6
3.2.P.5.4 Batch Analysis	Chapter 3: Batch analysis *For provisions on data to be provided it is referred to the notice of applicants* Further provisions: -Data provided must cover all release specifications, even if not tested on every batch. -Consecutive batch results to be provided - Commercial scale batches preferred - Data from all manufacturing sites to be included	Not addressed	Not addressed	The batches and results of the analysis should be described.
3.2.P.5.5 Characterisation of Impurities	Not addressed	Not addressed	Not addressed	The characterisation of impurities should be described, if not already done in 3.2.S.3.2 Impurities
3.2.P.5.6 Justification of Specifications	Not specifically addressed.	Not addressed	Chapter 3.2.2.5: The specification set-up must be justified for release and shelf life specification	A justification should be included in this module.

Comparison of recommendations on the shelf life specification

Guideline on stability testing of existing active substances and related finished products, initial version from 1997 and revision 1 in 2003 (Finished product)

	First version (1997) CPMP/QWP/556/96	**Revision 1 (2003) CPMP/QWP/122/02**
Specification	Chapter Test Procedure and Test Criteria: <u>Stability tests to be included in the shelf life specification:</u> -all properties that might change during shelf life and can influence quality/ safety/ efficacy -analytical procedures should be fully validated, the assays shall be indication for stability. - Testing should include physical/ chemical/ biological/ microbiological properties, preservative content Chapter Specifications: <u>Setting of acceptance criteria</u> -Acceptance criteria should be set up related to the release specification (if applicable) and based on stability results. -The shelf life specification can be different to the release specification if results of stability studies show changes. - Upper limits for degradation products required, and they must be justified in terms of safety/ efficacy - Setting limits for some tests (e.g. particle size, dissolution) needs to include a reference to bioequivalence/ bioavailability studies. - Antimicrobial preservatives: differences between release and shelf life specification to be supported by data from preservative efficacy testing	Chapter 2.2.5 <u>Stability tests to be included in the shelf life specification:</u> -all properties that might change during shelf life and can influence quality/ safety/ efficacy - Testing should include physical/ chemical/ biological/ microbiological properties, preservative content **and functionality related tests (e.g. dose delivery)**. Extent of studies is conditional upon the results of validation studies. <u>Setting of acceptance criteria</u> -Acceptance criteria should be set up based on stability results. -The shelf life specification can be different to the release specification if results of stability studies show changes. - Antimicrobial preservatives: differences between release and shelf life specification to be supported by data from preservative efficacy testing **The dependency of the chemical content and the preservative effectiveness should be demonstrated and validated during development for the commercial finished product. Additionally one primary stability batch should be tested on preservative content and preservative effectiveness in any case if an antimicrobial preservative is used.**

Comparison of ICH Q3B first version and Revision 2

	ICH Q3B first version (1997)	**ICH Q3B Revision 2 (2006)**
1. Introduction	*no relevant change*	
Rational for Reporting and Control of Impurities/ Degradation Products	Chapter 2.2.: Degradation product to be identified when they are **equal to** or more than the identification threshold	Chapter 2: Degradation product to be identified when they are more than the identification threshold *Information included when alternative thresholds for impurities can be justified*
Analytical procedures	Chapter 2.1: -	Chapter 3: As part of the validation of analytical procedures stress studies should be conducted: light, heat, humidity, acid/ base hydrolysis and oxidation.
Reporting Impurity Content of Batches/ Reporting Degradation Products Content of Batches	Chapter 2.3 The reporting level should be < than the identification threshold - - Chromatograms with peaks (named) from batch analysis **and stability studies needed**.	Chapter 4: - Reporting of degradation products: 1. Each degradation product > reporting threshold 2. Total degradation products (this includes all degradation products > reporting threshold) Description of Degradation Products: *Rules for the number of decimal places have been added and instruction on rounding of numbers.* -Degradation products should be described by code number or other measures, such as the retention time. -Results should be reported in numbers, not in words, if applicable Chromatograms with peaks (named) from **batch analysis and validation studies needed**. Further information on the degradation product analysis must be provided on request.
Specification Limits for Impurities/ Listing of Degradation Products in Specifications *(completely revised)*	Chapter 2.4: -	Chapter 5: *It is explained how the degradation products should be included in the specification (specified and identified or unidentified) and how the limit should be set, as well as the need for a justification for including them or not including them as well as the requirements for such a discussion. Acceptance criteria for unspecified degradation products are given .How unidentified degradation products shall be presented in the specification and recommendations on the justification for not identifying them are given.*
Qualification of impurities (& New impurities)	Chapter 2.5/2.6 It can be possible to defend a higher amount of degradation products than those used in the safety studies. Alternative thresholds are under certain circumstances possible, decision case-by-case: *the circumstances are described* - -	Chapter: It can be possible to defend a higher amount of degradation products than those used in the safety studies **when a comparison of the actual dose administered in the safety studies and the proposed dose in the medicinal product is done.** Alternative thresholds are under certain circumstances possible, decision case-by-case: *no circumstances given* It can be easier to reduce degradation products to lower or equal of the threshold than creating safety data. *Comments on clinical development added.*
Attachment 1 Thresholds	Identification Threshold for a Maximum Daily Dose of >2 g→ 0.1% Qualification Threshold for a Maximum Daily Dose of > 2g → 0.1% Qualification Threshold for a Maximum Daily Dose of > 100 mg on – 2 g→ 0.2% or 2 mg TDI whichever is lower	Identification Threshold for a Maximum Daily Dose of >2 g→ 0.1**0**% Qualification Threshold for a Maximum Daily Dose of > 2g → 0.15% Qualification Threshold for a Maximum Daily Dose of > 100 mg on – 2 g→ 0.2% or **3** mg TDI whichever is lower
Attachment 2		*Attachment 2 has become attachment 3 (updated). Attachment 2 is an example for calculation of the threshold*

3.2.P.6 Reference Standards or Materials

	EU Commission "Specifications and Control Tests on the Finished Product" 3AQ11a 1991/1992	ICH Q2(R1) 1995/2005	ICH Q6A 2000	2003/63/EC [3] 2003 (2nd Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004
3.2.P.6 Reference Substances	Chapter 2. Test procedures Analytical Procedure description shall include: - description of reference substances used has to be included (with specification) Official reference substances (Ph.Eur., pharmacopoeias of the EU member states, WHO) to be use or alternatively a working standard (which has to be standardised against an official standard)	Part II, Introduction, revision 2: Reference materials for analytical procedure validation should be well-characterized and their purity should be determined ("documented").	Chapter 2.11 Definition of reference standard: -substance used for assay, identification and purity tests - should be qualified for its use - Characterisation and Investigation for the intended use is frequently done by further procedures than used in routine testing - when used for assay tests, impurities must be identified and/ or controlled appropriately. Investigation of purity to be done with a quantitative analytical procedure.	Chapter 3.2.2.6: -Reference Standards must be identified - they must be described thoroughly (under the condition that this information has not already been provided in the active substance part).	Chapter: 3.2.P.6 Information must be included in this module (under the condition that this information has not already been provided in 3.2.S.5 Reference Standards or Materials).

3.2.P.7 Container Closure System

	2001/83/EC[12], Annex I, Part II 2001, (not granulated in CTD format yet)	2003/63/EC[3] 2003 (2nd Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004	Guideline Manufacture of the finished dosage form 2017		EMEA- CHMP Guideline on **plastic immediate** packaging materials 2005
3.2.P.7 Container Closure System	Chapter A:1.1 To be provided with the qualitative/ quantitative composition: - relevant data on container - if adequate, the closure and - a description of devices for use/ administration if provided with the product Chapter C.1 Starting Materials: - Starting materials include containers **- test results are needed** The description provided in Chapter C 1.1 and 1.2 is not specific for packaging material but applies to all "starting materials": Chapter C.1.1: <u>Compendial starting materials</u> **- the specifications applied in routine must be described** -reference to the pharmacopoeia sufficient unless impurities exist that are not controlled by the pharmacopeia→ a specification must be set up for those and it must be proven that the pharmacopoeia quality requirements are fulfilled (that is equivalence). -3rd country pharmacopoeia monographs might be accepted if the starting material is not described in a pharmacopoeia of the EU member states Chapter C.1.2 <u>Non-compendial starting materials</u> The following information should be given: -name of the substance - chemical definition - identification tests **- purity tests** - if special conditions for the storage are required, they should be listed with the retesting time Chapter 1.1:	Chapter 3.2.2.7 The following information should be included: - Description of the container closure system For primary packaging: - Description of the materials of the packaging (identity) for primary packaging - Description of the specification of the primary packaging. The specification must include description and identification test(s) - Analytical procedure description and validation for non-compendial procedures For secondary packaging: A. Non-functional secondary packaging: -Brief description B. Functional secondary packaging: - Description + Additional information	Chapter 3.2.P.7: The following information should be included: - Description of the container closure system For primary packaging: - Description of the materials of the packaging (identity) for primary packaging - Description of the specification of the primary packaging. The specification must include description and identification test(s) **and critical dimension (with drawings, if adequate)** - Analytical procedure description and validation for non-compendial procedures For secondary packaging: A. Non-functional secondary packaging: -Brief description B. Functional secondary packaging: - Description + Additional information	Chapter 4.4 **Information on bulk or intermediate container closure system:** **The following information should be included:** **- Description of the materials of the packaging** **- Description of the specification of the primary packaging.**		<u>Description of materials (chapter 3.1)</u> <u>-</u> chemical name of the material & chemical name of any monomer used **- For non-solid medicinal products: material supplier name (for inhalation, parenteral or ophthalmic use)** **- For non-solid medicinal products the qualitative composition must be given, if used…** ***for inhalation, parenteral or ophthalmic administration** ***and material not described in Ph.Eur./ EU member states pharmacopoeia** ***and when the pharmacopoeia monograph allows more than one additive** **- for non-solid medicinal products for oral and topical administration with non-compendial primary packaging materials not included in the foodstuff legislation** <u>Description of the specification (chapter 3.2)</u> **- compendial materials: reference to monograph + CoA** **- non-compendial materials: in-house specification & analytical procedures containing material description test(s), material identification test(s), characteristics such as mechanical & physical parameters & CoA needed** **- packaging specifications for non-compendial non-solid medicinal products should contain additionally identification tests(s) for main additives (especially those who might migrate in the medicinal product), additional identification test(s) for colorants and qualitative and quantitative test(s) for the extractables identified in 3.2.P.2.4**

	If non-compendial analytical procedures are used, they must be described					

3.2.P.8 Stability

	2001/83/EC[12], Annex I, Part II 2001, (not granulated in CTD format yet)	2003/63/EC[3] 2003 (2nd Update to 2001/83/EC)	NTA Volume 2B[5] 2008 with Module 3 part from 2004
3.2.P.8.1 Stability Summary and Conclusion	Chapter G*: Description should be provided of: -Studies done Conclusions to be given -on storage conditions -on shelf life -on the results of the studies	Chapter 3.2.2.8 Summary should be provided on: **-Study Type** **- Study Plan (Protocol)** - Results of the studies	Chapter 3.2.P.8.1: Summary should be provided on: **-Study Type** **- Study Plan (Protocol)** - Results of the studies Conclusions to be explained -on storage conditions -on shelf life **- on in-use storage conditions and shelf life (if applicable)**
3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment	not addressed	Chapter 3.2.2.8 Post-approval… -stability protocol - commitment …to be included	Chapter 3.2.P.8.1: Post-approval… -stability protocol - commitment …to be included
3.2.P.8.3 Stability Data	Chapter G*: - Stability data to be included.	Chapter 3.2.2.8 - Stability data to be included. - Information on analytical procedures used - Information on validation of the analytical impurities Vaccines: Information on cumulative studies (where appropriate) The form of presentation of the data should be adequate	Chapter 3.2.P.8.3 - Stability data to be included. - Information on analytical procedures used - Information on validation of the analytical impurities The form of presentation of the data should be adequate, e.g. tabular, graphical, narrative

*Chapter G is only partially applicable to 3.2.P.8, because it also contains the requirements on the finished product shelf life specification

Comparison of recommendations on the stability in the Guideline on stability testing

[Stability testing of existing active substances and related finished products, initial version from 1997 and revision 1 in 2003 (Finished product)]

In the following the abbreviation "M" means "month(s)"

A) For 3.2.P.8.1 Stability summary and conclusion

	First version (1997) CPMP/QWP/556/96	**Revision 1 (2003) CPMP/QWP/122/02**
Selection of Batches	Chapter selection of batches: Type of testing Long term and accelerated studies Pilot/ commercial scale batches for marketing authorisation application a) 2 pilot scale batches when - conventional dosage form (e.g. immediate release solid dosage form or solutions) and - stable active substance b) 3 batches with 2 of them min. pilot scale, the 3rd could be smaller - critical dosage forms (e.g. prolonged release) or - unstable active substance c) further conditions: - manufacturing process for pilot/ small size batches should be similar to the commercial process (same quality specifications, same overall quality) - it is recommended to use different batches of the active substance for different finished product batches **- same stability plan to be used as for the commercial scale product** - results to be submitted to the authority	Chapter 2.2.3: Type of testing Long term and accelerated studies Pilot/ commercial scale batches for marketing authorisation application a) 2 pilot scale batches when - conventional dosage form (e.g. immediate release solid dosage form or solutions) and - stable active substance b) 3 batches with 2 of them min. pilot scale, the 3rd could be smaller - critical dosage forms (e.g. prolonged release) or - unstable active substance c) further conditions: - manufacturing process for pilot/ small size batches should be similar to the commercial process (same quality specifications, same overall quality) - it is recommended to use different batches of the active substance for different finished product batches **- studies must be performed on each strength and container size (except if bracketing or matrixing is used)**
Container Closure	Chapter: Packaging/ Containers Containers and closures used for stability studies should be the same as for marketing Studies with product without container closure can be supportive as part of the stress testing studies	Chapter 2.2.4: Container Closure System Containers and closures used for stability studies should be the same as for marketing Studies with product without container closure can be supportive as part of the stress testing studies
Storage conditions general	Chapter Storage conditions Minimum data at submission in general Long term testing: 25°C ± 2°C/ 60% RH ± 5% for 6M (option a) 25°C ± 2°C/ 60% RH ± 5% for 6M (option b) Accelerated Testing 40°C ± 2°C/ 75% RH ± 5% for 6M Chapter Evaluation - Evaluation of stability after reconstitution and dilution required, data for in-use shelf life to be provided.	Chapter: 2.2.7: Storage conditions Minimum data at submission in general Long term testing: 25°C ± 2°C/ 60% RH ± 5% **or 30°C ± 2°C/ 65% RH ± 5%** for 6M (option a) 25°C ± 2°C/ 60% RH ± 5% for 6M (option b) **Intermediate testing:** **30°C ± 2°C/ 65% RH ± 5% for 6M** Accelerated Testing 40°C ± 2°C/ 75% RH ± 5% for 6M Alternative storage conditions can be used but their choice must be explained. Products after reconstitution/ dilution: Stability testing to be performed through in-use-period initially and at the final time point

	First version (1997) CPMP/QWP/556/96	Revision 1 (2003) CPMP/QWP/122/02
	Chapter Storage conditions Significant change: - Assay ± 5% from initial value - one or more degradation products not in specification - specifications cannot be met for appearance, physical properties - out of specification results for pH or dissolution for 12 capsules/ tablets (level 2 of dissolution testing) What are the consequences if significant change occurs? Within 6 month accelerated studies: additional testing at **30°C/ 60% RH required** for 12M: min. 6M data to be submitted at MA application ***(intermediate condition relative humidity deviates from revision 1 from 2003)***	**Effect of short-term excursions outside label storage conditions:** **Data from intermediate/ accelerated conditions can be used for the assessment** Significant change: - Assay ± 5% from initial value - one or more degradation products not in specification - specifications cannot be met for appearance, physical properties, **functionality tests** (**except some changes in physical attributes that can be expected, such as softening of suppositories, melting of cremes and partial loss of adhesion for transdermal products)** - **Depending on the dosage form**: out of specification results for pH or dissolution for 12 dosage units (level 2 of dissolution testing) What are the consequences if significant change occurs? Within 6 month accelerated studies: additional testing at intermediate condition required for 12M: min. 6M data to be submitted at MA application
Storage conditions-impermeable containers	Chapter Storage conditions Permanent barrier products: temperatures and moisture conditions as described above	Chapter 2.2.7.2 Finished products packaged in impermeable containers Stability studies can be performed under any humidity condition
Storage conditions semi-permeable containers	Chapter Storage conditions Semi- permeable containers low relative humidity can alter the product negatively. This should be considered.	Chapter 2.2.7.3 Finished products packaged in semi-permeable containers **Assessment on water loss needs to be done in addition for prove that water based finished products are stable under low humidity conditions.** **Storage conditions added:** Long term testing: 25°C ± 2°C/ 40% RH ± 5% RH or 30°C ± 2°C/ 35% RH ± 5% RH for 6M **(option a) or 12 M (option b)** Intermediate testing: 30°C ± 2°C/ 65% RH ± 5% RH Accelerated Testing 40°C ± 2°C/ nmt 25% RH for 6M **Alternative approach for storage is included (by performing studies for long-term or accelerated conditions under higher relative humidity and calculating the water loss at the labelled storage condition)** **Significant change:** All as listed above (general) plus the following: **- Water content - 5% from initial value after 3M accelerated studies except for small containers when adequately justified** **What are the consequences if significant change occurs?**

	First version (1997) CPMP/QWP/556/96	Revision 1 (2003) CPMP/QWP/122/02
		-Within 6 month accelerated studies **(any significant change except water loss):** additional testing at intermediate condition required for 12M: min. 6M data to be submitted at MA application **- When water loss within 6 month accelerated studies happens, no significant water loss may occur at studies at 25°C ± 2°C/ 40% RH ± 5% RH throughout the whole shelf life** **- After 3M accelerated studies: water loss of more than 5% is a significant change**
Storage conditions refrigerator	Chapter Storage conditions Heat-sensitive products Long term testing: 5°C ± 3°C for 6M Accelerated Testing 25°C ± 2°C/ 60% RH ± 5% for 6M	Chapter 2.2.7.4 Finished products intended for storage in a refrigerator Long term testing: 5°C ± 3°C for 6M **(option a)** **5°C ± 3°C for 12M (option b)** Accelerated Testing 25°C ± 2°C/ 60% RH ± 5% for 6M **Assessment on water loss needs to be done in addition if packed in semi-permeable packaging material** Significant change: *no special conditions besides those as listed generally defined* **What are the consequences if significant change occurs?** **-Significant change within 3M accelerated stability: evaluation of the effects on storage outside the labelled conditions must be done, additional data can be provided on a further batch with more frequent testing points. The accelerated study can be stopped at 3 months.** **- Significant change after 3 but within 6 months of accelerated stability testing: Shelf life based on long-term studies only, but no extrapolation possible.**
Storage conditions freezer	not addressed	**Chapter 2.2.7.5 Finished product intended for storage in a freezer** **Long term testing:** **-20°C ± 5°C for 6M (option a)** **-20°C ± 5°C for 6M (option b)** Significant change: *no special conditions besides those as listed generally defined* **Shelf life shall be based on data from long-term conditions. No accelerated storage conditions available. For evaluation of short term storage outside labelled conditions one batch should be put on stability at a higher temperature (e.g. 5°C ± 3°C or 25°C ± 2°C)**
Storage conditions products stored below 20°C	not addressed	**Chapter 2.2.7.6 Finished product intended for storage below -20°C** **Storage conditions to be defined case by case**
Testing frequency	Chapter testing frequency: General: Every 3 months in the fist year, every 6 months in the second year, afterwards: every year	Chapter 2.2.6 Testing Frequency General : Every 3 months in the first year, every 6 months in the second year, afterwards: every year **Specifically for intermediate studies:**

	First version (1997) CPMP/QWP/556/96	Revision 1 (2003) CPMP/QWP/122/02
		Intermediate studies are usually done when there's a significant change at accelerated condition. A 12 month study should be performed. **<u>Specifically for accelerated studies:</u>** **Studies need to be conducted for 6 months. If it can be foreseen based on experience from development, that there will be a significant change, either add a fourth test point or increase the number of samples at the final time point.** **Bracketing and Matrixing can be applied, but must be justified**
Evaluation	<u>Chapter Evaluation</u> For evaluation of shelf life and storage conditions the following data must be considered: - physical, chemical, biological and microbiological tests as well as special properties of the dosage form (e.g. dissolution for solid oral dosage forms) - The higher the degree of variability between the batches the lower the reliability that the commercial batches in the future will meet the specification during the whole shelf life. <u>Further recommendations are given on:</u> - Determining the batch variability - Different regression types for degradation effects - When statistical analysis is not required - not only assay evaluation but also degradation products and other properties must be evaluated. - mass balance of degradation products and assay may have to be considered - Evaluation of stability after reconstitution and dilution required, data for in-use shelf life to be provided.	<u>Chapter 2.2.9 Evaluation</u> For evaluation of shelf life and storage conditions the following data must be considered: - physical, chemical, biological and microbiological tests as well as special properties of the dosage form (e.g. dissolution for solid oral dosage forms) - The higher the degree of variability between the batches the lower the reliability that the commercial batches in the future will meet the specification during the whole shelf life.
Extrapolation	<u>Chapter Evaluation</u> - Extrapolation requires a predicable statistical behavior and needs to be justified - Limited extrapolation possible	Annex II: Extrapolation of data is possible based on accelerated data. Maximum extrapolation: 2x length of real-time studies Not more than 12 months extrapolation beyond real-time data. *A decision tree for the choice of the shelf life has been provided* *Evaluation and Extrapolation is further addressed in ICH Q1E*

B) For 3.2.P.8.2 Post-approval Stability Protocol and Commitment

	First version (1997) CPMP/QWP/556/96	Revision 1 (2003) CPMP/QWP/122/02
Stability commitment	not addressed	**Chapter 2.2.8 Stability Commitment:** **A commitment should be included to complete the stability studies until the end of the proposed shelf life when the stability data does not cover the whole proposed shelf life at submission for 3 production batches** ***3 options are presented for the stability commitment for the following cases for different scenarios*** **The stability plan for commitment batches and the stability batches already included in the dossier should be the same.** **In case of significant change at accelerated condition:** **- batches included for application of marketing authorization (primary batches): studies at commitment batches to be performed at either immediate or accelerated condition** **- commitment batches: studies at intermediate condition mandatory**

B Additional information on Module 3.2.P.7

In the following, the revisions of the EU Directives/ Regulations on food packaging are listed.

A) General food packaging

Directive 89/109/EEC, published 11.02.1989		
Rev.No.	Regulation/ Directive No.	Published
M1	Regulation EC/1882/2003	11.2.1989

Regulation EC/1935/2004, published 13.11.2004		
Rev.No.	Regulation/ Directive No.	Published
M1	Regulation EC/596/2009	18.07.2009

B) Plastic packaging for foodstuffs

Directive 90/128/EEC, published 21.03.1990		
Rev.No.	Regulation/ Directive No.	Published
M1	Directive 92/39/EEC	18.07.1992
M2	Directive 93/9/EEC	14.04.1993
M3	Directive 95/3/EC	23.2.1995
M4	Directive 96/11/EC	12.03.1996
M5	Directive 1999/91/EC	04.12.1999
M6	Directive 2001/62/EC	17.08.2001

Directive 2002/72/EC, published 15.08.2002		
Rev.No.	Regulation/ Directive No.	Published
M1	Directive 2004/1/EC	13.01.2004
M2	Directive 2004/19/EC	10.03.2004
M3	Directive 2005/79/EC	19.11.2005
M4	Directive 2007/19/EC	31.03.2007
M5	Directive 2008/39/EC	07.03.2008
M6	Regulation EC/975/2009	20.10.2009

Regulation EU/10/2011, published 15.01.2011		
Rev.No.	Regulation/ Directive No.	Published
M1	Regulation EU/321/2011	02.04.2011
M2	Regulation EU/1282/2011	10.12.2011
M3	Regulation EU/1183/2012	12.12.2012
M4	Regulation EU/202/2014	04.03.2014
M5	Regulation EU/865/2014	09.08.2014
M6	Regulation EU 2015/174	06.02.2015
M7	Regulation EU/2016/1416	25.08.2016
M8	Regulation EU/2017/752	29.04.2017
M9	Regulation EU/2018/79	19.01.2018
M10	Regulation EU/2018/213	14.02.2018
M11	Regulation EU/2018/831	06.06.2018
M12	Regulation EU/2019/37	11.01.2019
M13	Regulation EU/2019/988	18.06.2019
M14	Regulation EU/2019/1338	09.08.2019

C Correlation Table for the EU CTD and NTA format (Module 3)

MODULE 3 – QUALITY			
CTD	**EU CTD (NTA, Vol. 2B, Edition 2001)**	**NTA, Vol. 2B (Edition 1998)**	**NTA**
3.2.S.4.3	Validation of analytical procedures	Development Chemistry: Analytical Validation	II C 1.2.5
3.2.S.4.4	Batch analyses	Batch analysis	II C 1.2.7
3.2.S.4.5	Justification of Specification	Development Chemistry: Comments on the choice of routine tests and standards	II C 1.2.5
3.2.S.5	Reference Standards or Materials	Development chemistry: Full characterization of the primary reference material Batch analysis: Reference material	II C 1.2.5 II C 1.2.7
3.2.S.6	Container Closure System	---	
3.2.S.7	Stability	Stability Tests on Active Substance(s)	II F 1
3.2.P	DRUG PRODUCT		
3.2.P.1	Description and composition of the drug product	Composition and container (brief description)	II A1 II A2
3.2.P.2	Pharmaceutical Development	Development Pharmaceutics and clinical trial formulae	II A 4 II A3
3.2.P.2.4	Controls and critical steps and intermediates	Manufacturing process (including in-process control and phamraceutical assembly process) Control tests on intermediate products	II B3 II D
3.2.P.3	Manufacture	Method of Preparation	II B
3.2.P.3.1	Manufacturer(s)	Administrative Data	I A
3.2.P.3.2	Batch formula	Manufacturing Formula	II B 1
3.2.P.3.3	Description of Manufacturing Process and Process Controls	Manufacturing Process (including In-process Control and Pharmaceutical Assembly Process)	II B 2
3.2.P.3.4	Controls of critical steps and intermediates	Manufacturing Process (including In-process Control and Pharmaceutical Assembly Process)	II B 2
3.2.P.3.5	Process validation and / or evaluation	Validation of the Process	II B 3
3.2.P.4	Control of excipients	Excipients(s)	II C 2
3.2.P.4.1	Specifications	Specifications and routine tests	II C 2.1
3.2.P.4.2	Analytical procedures	Specifications and routine tests	II C 2.1
3.2.P.4.3	Validation of analytical procedures	Scientific data	II C 2.2
3.2.P.4.4	Justification of specifications	Scientific data	II C 2.2
3.2.P.4.5	Excipients of human or animal origin	---	
3.2.P.4.6	Novel Excipients *(ref to A 3)*	Excipient(s) not described in a pharmacopoeia Scientific data	II C 2.2.1 II C 2.2
3.2.P.5	Control of drug product	Control Tests on the Finished Product	II E
3.2.P.5.1	Specification(s)	Product specifications Quality specifications for the proposed shelf life	II E 1.1 II F 2
3.2.P.5.2	Analytical Procedures	Control Methods	II E 1.2
3.2.P.5.3	Validation of Analytical Procedures	Analytical validation of methods	II E 2.1
3.2.P.5.4	Batch analyses	Batch analysis	II E 2.2
3.2.P.5.5	Characterisation of Impurities	---	
3.2.P.5.6	Justification of specification(s)	Comments on the choice of routine tests and standards	II E 2.1
3.2.P.6	Reference Standards or Materials	Batch analysis: Reference material	II E 2.2
3.2.P.7	Container Closure System	Packaging Material (Immediate Packaging)	II C 3
3.2.P.8	Stability	Stability Tests on the Finished Product	II F 2
3.2.A	APPENDICES		
3.2.A.1	Facilities and Equipment	---	
3.2.A.2	Adventitious Agents Safety Evaluation	---	
3.2.A.3	Excipients	---	
3.2.R	REGIONAL INFORMATION	Validation of the process	-II B3--
3.3	LITERATURE REFERENCES	OTHER INFORMATION	II Q

Figure 5: EU CTD (2001) and NTA (1998) format correlation table

Source: EU Commission Eudralex, Volume 2, Notice to Applicants Volume 2B, page 28

D Tabular overview: Summary and assessment of gaps for old product dossiers

3.2.P.1 Description and Composition

Table 30: Gap scenarios 3.2.P.1

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
3.2.P.1	Composition	Function of excipients	Function of excipients not described	2003	3.2.P.1	Look up information in 3.2.P.2.1.1 (Development Part)	1	The function of excipients in 3.2.P.2 should be proven
3.2.P.1	Composition	Overages	Overages not listed	2003	3.2.P.1	Look up information in 3.2.P.2.2.2 (Development Part)	1	Overages must be justified in 3.2.P.2.2.2
3.2.P.1	Composition	Quality standard of components	Quality standard not listed	2004	3.2.P.1	Look up information in 3.2.S.4.1 (Active substance) or 3.2.P.4.1 (Excipients)	1	-
3.2.P.1 3.2.P.2.1 3.2.P.4	Composition	Qualitative/ Quantitative Composition of Mixes	Supplier does not want to reveal information of composition (the supplier is the only supplier known for this excipient as the composition is unclear).	2007	3.2.P.1 3.2.P.2 3.2.P.4	Refer to quality agreement if available/ switch supplier/ discuss revealing composition to authority only with authority and supplier	2-4 (4 in case of composition change)	An exchange of the excipient might require new development studies and testing of specificity of the analytical method

3.2.P.2 Pharmaceutical Development

Table 31: Gap scenarios 3.2.P.2

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
3.2.P.2.1.2	Development/ Excipients	Choice of excipients, e.g. for paediatric use, for the elderly, colorants/ flavours not compliant with current Regulations	Excipient not suitable and must be exchanged	2020	All of 3.2.P.	Discuss requirements of new excipient, perform research on a suitable component, potentially perform development studies	4	An exchange of the excipient might require new development studies and testing of specificity of the analytical method
3.2.P.2.1.2	Development/ Excipients	Justification of quantities used (excipients)	Information on trials performed not available in development report or other internal source, no complete justification based on literature possible	2003	3.2.P.2.1.2	New development studies with different quantitative compositions required.	4	All excipients used in the past are still on the market
3.2.P.2.1.2	Development/ Excipients	Proof of the function of excipients	The available data in development report, dossier (control strategy) and literature/ company knowledge have gaps/ are not sufficient to prove the function.	2005/2006	3.2.P.2.1.2, 3.2.P.4.1-3.2.P.4.5, 3.2.P.3.4 3.2.P.5.1, 3.2.P.5.6	Tests must be done on some functionalities and potentially included in the control strategy of the medicinal product	3-4	The justification of the quantities of the excipients should be established
3.2.P.2.1.2	Development/ Composition	Completeness of excipients	Excipients used in the manufacturing process have not been mentioned, e.g. processing aids	2005/ 2006	3.2.P.1, 3.2.P.2, 3.2.P.4.1-3.2.P.4.5	A justification for the use of the excipients must be done, their quality/ safety assessed, development studies possibly required e.g. for compatibility, proof of function	2-4	-
3.2.P.2.2.1	Development/ Formulation	Suitability of formulation (administration, dosage scheme,	e.g. Change of the pharmaceutical form required (line extension)	2020	All of 3.2.P (in particular 3.2.P.2.2.1)	Partially new development studies	4	Collect data on suitability, e.g. review EU

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
		duration of use, volume/size of each unit/ measuring devices) for certain age groups (children, elderly)						guidance, customer complaints
3.2.P.2.	Development/ Formulation	Critical quality attributes	Critical quality attributes have not been discussed and information must be collected from other dossier parts (e.g. manufacturing process development, justification of specifications) and possibly development data	2005/ 2006	3.2.P.2 3.2.P.4.1- 3.2.P.4.4, 3.2.P.5.1- 3.2.P.5.4 3.2.P.5.6	Review of all data available	2	-
3.2.P.2.2	Development/ Formulation	Development formulation vs. Clinical formulation	Studies, e.g. Bioequivalence studies should be available as MA already exists, so the information just has to be added in this module	2004	3.2.P.2.2.1	Review of the available data in other dossier parts or development report and inclusion in 3.2.P.2.2.1	1-2	-
3.2.P.2.2	Development/ Formulation	Special design features	Supportive studies not available, e.g. subdivision of tablets has not been investigated	2005/ 2006	3.2.P.2.2.1	Perform the required studies	3	-
3.2.P.2	Development/ Overages	Overage not justified at all (in terms of quality, safety and efficacy should be justified in the preclinical and clinical sections of the dossier)	Product optimisation required in order to eliminate production/ stability overage (e.g. new manufacturing equipment, reduced hold times, optimised formulation in terms of compatibility,	Products developed before 2000	3.2.P.2 3.2.P.3 3.2.P.7	Check product optimisation possibilities and perform the required studies/ changes	4	-

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
			better packaging material…)					
3.2.P.2.2	Development/ Bioequivalence	In-vitro dissolution profiles for solid oral dosage forms	Old Dissolution profiles deviate from the requirements in the revised guideline for bioequivalence (e.g. sampling or evaluation criteria)	2010	3.2.P.2.2.3	Case by case decision: in some cases it might be possible to justify gaps as minor, in rare cases previous formulations will have to be manufactured again for investigation of comparability acc. to the current guideline	1-3	Discriminatory properties of in-vitro dissolution method have been proven
3.2.P.2.2	Development/ Bioequivalence	Demonstration of knowledge: Development of in-vitro-dissolution method for solid oral dosage forms	Discriminatory properties of the in-vitro dissolution method have not been demonstrated and no data are available anymore	2005/ 2006	3.2.P.2.3	Studies need to be done retrospectively	3	-
3.2.P.2.3	Development/ Manufacturing Process	Changes between manufacturing process current product and process for investigational medicinal product	Changes not described/ justified	2003	3.2.P.2.3	Data need be reviewed and a comparison of the processes done. It must be tried to justify the differences in collaboration with a development/clinical expert	2	-
3.2.P.2.3	Development/ Manufacturing Process	Changes in manufacturing process and their impact	Little data are available on this topic	2005/ 2006	3.2.P.2.3	Post-approval changes can be reviewed for their impact, e.g. technical transfers, manufacturing process optimisations etc.. Results can be included in the dossier. It should be described which parameters are critical.	2	-
3.2.P.2.4	Development/ Container Closure	Intermediate/ Bulk material packaging	Bulk material packaging not described; no innocuousness discussed	2017	3.2.P.2.4, 3.2.P.3.4 or 3.2.P.7	Review existing data, e.g. stability data if available, request information about	1-3	

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
						compliance with current regulatory provisions from supplier, perform leachable/ extractable studies if needed		
3.2.P.2.4	Development/ Container Closure	Innocuousness of the container closure system	Studies are required but have not been done (e.g. leachable/ extractable studies), sterilisation of the packaging material is performed but the impact on the packaging material has not been addressed	2004	3.2.P.2.4, 3.2.P.7	Review existing data, e.g. stability data if available, request information about compliance with current regulatory provisions from supplier. Depending on the type of product (solid/ semisolid) and packaging (compendial/ non-compendial) can be either just be discussed or must be supported by studies (e.g. leachable/ extractable studies)	2-3	
3.2.P.2.4	Development/ Container Closure	Results of compatibility of the packaging material with the medicinal product	Innocuousness cannot be confirmed- studies (e.g. leachable/ extractable studies) prove that the material is not suitable	2004	3.2.P.2.4 3.2.P.5 3.2.P.6 3.2.P.7 3.2.P.8	Change of container/ closure system. The proposed container closure system must be reviewed for suitability, too.	4	
3.2.P.2.4	Development/ Container Closure	Suitability of the packaging material for elderly population (if not excluded in the indication)	The packaging is not suitable, e.g. it is difficult to open for elderly people with dexterity problems (customer complaints) but the medicinal product is intended for self-administration for patients with gout	2017	3.2.P.2.4 3.2.P.5 3.2.P.6 3.2.P.7 3.2.P.8	Change of the container closure system (new development studies required)	4	
3.2.P.2.5	Development/ Microbiology	Protection of packaging material from microbial growth	For sterile medicinal products the protective properties of the packaging	2004	3.2.P.2.5	Could by shown by referring to finished product stability data with testing of the	1	The microbiological purity was tested at the end of the shelf

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
			material have not been shown.			microbiological purity at the end of the shelf life.		life for production batches

3.2.P.3 Manufacture

Table 32: Gap Scenarios 3.2.P.3

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
3.2.P.3.1	Manufacturers	Completeness of manufacturing sites and information about their responsibilities	Sites are missing or responsibilities not clear	2017	3.2.P.3.1	Add responsiblities after check with QA	2	External manufacturing sites are appropriately qualified by QA.
3.2.P.3.2	Batch Formula	Quality standard of components	Quality standard not listed	2004	3.2.P.3.2	Look up information in 3.2.S.4.1 (Active substance) or 3.2.P.4.1 (Excipients)	1	-
3.2.P.3.2	Batch Formula	Justification of batch size	Justification missing	2017	3.2.P.3.2 3.2.P.2.3	Check e.g. 3.2.P.2/ development report/ process validation report or discuss with manufacturing operations experts	1-2	-
3.2.P.3.2	Batch Formula	Batch size definition	Batch size definition not in line with guideline on manufacture of finished dosage form, e.g. batch size has been given for the number of units after split up for different presentation/ packs	2017	3.2.P.3.2 3.2.P.2.3	File a variation for redefinition of the batch size	2	-
3.2.P.3.2	Batch Formula	Sub-batches	The use of sub-batches has not been described in the dossier but is applied	2017	3.2.P.3.2 3.2.P.3.3 3.2.P.3.5	Information about batch formula, batch size, number of sub-batches, justification	2	The use of sub-batches must be validated.

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
						can be requested from QA or manufacturing operations		
3.2.P.3.2	Batch Formula	Amounts of components added as manufacturing aids but shall be removed later in the process, e.g. water	Amounts are not given or with a variable	2004	3.2.P.3.2 3.2.P.3.3	Amounts can be expressed as ranges but must be given. Amounts to be clarified with QA/ manufacturing operations	2	Clarification of excipients used as manufacturing aids
3.2.P.3.3	Manufacturing Process Description	Details in the manufacturing process description	(Numeric) Detail is missing, e.g. equipment capacity, sieve sizes, mixing times, critical environmental conditions, reprocessing per batch size	2017	3.2.P.3.3	Information can be copied from master batch record (consult QA/ manufacturing operations)	2	Updated master batch record available (if changes are planned, a draft new master batch record should be provided)
3.2.P.3.3	Manufacturing Process Description	Flow Chart	Detail in the flow chart is missing (e.g. material flow)	2017	3.2.P.3.3	Information should be already present in 3.2.P.3 as narrative process description	1	-
3.2.P.3.3	Manufacturing Process Description	Alternative manufacturing steps/ methods/ equipment	Alternative manufacturing steps/ operations with a significant different nature are included in the dossier (not merely equipment differences)- although the use of alternatives except for technical adaptions is not recommended (the manufacturing principle should be the same).	2017	3.2.P.3.3 3.2.P.3.4 3.2.P.3.5	If both processes have been validated in the past and the results are comparable as well as a sound justification is available, it can be tried to justify it. It is not recommended to invest into studies on a process alternative with a different manufacturing principle if data are not already available due to the regulatory risk.	2	-
3.2.P.3.4	Manufacturing Critical Steps	Description of critical steps and their control	Critical control steps are not discussed and justified, e.g. IPCs are not complete with test, acceptance	2017	3.2.P.3.4, 3.2.P.2.3	Obtain the required data from QA e.g. complete IPCs according to the master batch record, check critical process	2	Minimum data on influence of different parameters on the

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
			criteria, test method, justification for limits, critical process parameters not discussed			steps in validation protocols/ development reports/ manufacturing risk assessments		product quality should be available from development or life cycle activities
3.2.P.3.4/ 3.2.P.8	Manufacturing Bulk/Intermediates	Storage of Intermediates or Bulk	Prolonged storage happens but is not described in the dossier. No stability studies available.	2017	3.2.P.3.4, 3.2.P.7, 3.2.P.8	Investigate max. required hold times (QA& Operational Planning) and perform stability studies or include data in dossier if available	3+	Update of the finished product specification, if needed.
3.2.P.3.4	Manufacturing time	Total time needed for manufacture	The way of expiry data calculation is unclear/ not addressed	2001	3.2.P.3.4	Research total manufacturing time and ensure the expiry date is calculated in accordance with the regulatory provisions (QA)	2	New data about total manufacturing time needed in case production was discontinued (potentially different staff, different degree of capacity utilisation)
3.2.P.3.4	Manufacturing Bulk/Intermediates	Transportation	No information on transport validation provided when different manufacturing sites are involved	2015	3.2.P.3.4	Perform transport risk assessment and perform validation (QA) if transport is critical.	2-3+	-
3.2.P.3.4/ 3.2.P.7	Manufacturing Bulk/Intermediates	Packaging	Intermediate/ Bulk storage is performed but no information on the packaging material is given and compliance with current regulatory requirements has not been checked recently	2017	3.2.P.3.4 3.2.P.7	Request information from QA/ manufacturing operations the packaging material supplier, perform check and include in the dossier.	2	It is assumed that suitability of the packaging material has already been proven in 3.2.P.2.4 and no changes to the container/ materials have been done since.
3.2.P.3.5	Manufacturing Process Validation	Scale up	Critical aspects of scale up not mentioned	2014	3.2.P.3.5	Information available in 3.2.P.2. It can be copied or referred to.	1	Reports from development/ post-approval process

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
								validation reports are still available
3.2.P.3.5	Manufacturing Process Validation	Reduced validation approaches, e.g. validation of less than 3 batches for a non-standard process or bracketing	The new criteria (1.) consistency of the process and (2.) previous experience (amount and data available) from commercial manufacturing are not met	2014	3.2.P.3.5	Recommended revalidation	3+	-
3.2.P.3.5	Manufacturing Process Validation	Nanoparticulate preparations	Only pilot batch validation data on Nanoparticulate preparations provided	2014	3.2.P.3.5	Production batch size validation to be performed	3+	-
3.2.P.3.5	Manufacturing Process Validation	Retrospective process validation	Only retrospective process validation data available	2014	3.2.P.3.5	Check if prospective process validation was performed meanwhile. If not, it should be done.	2-3+	-

3.2.P.4 Control of Excipients

Table 33: Gap Scenarios 3.2.P.4

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
3.2.P.4.1 3.2.P.4.2	Excipients	Compliance of compendial excipients with current monographs	Pharmacopoeia specifications/ analytical procedures have been copied into the dossier or reference to a specific (outdated) version of the monograph is provided	2020	3.2.P.4.1 3.2.P.4.2 3.2.P.4.3 3.2.P.4.4	Update of specifications/ analytical procedures/ analytical procedure verifications	2-3	-
3.2.P.4.1 3.2.P.4.2	Excipients	Non-compendial excipients and excipients	Excipient specification and/ or test procedures do not comply with Ph.Eur.	2008	3.2.P.4.1 3.2.P.4.2 3.2.P.4.3	Update specification and analytical procedures perform	3	-

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
		described in 3rd country pharmacopoeias	monograph substances for pharmaceutical use		3.2.P.4.4 3.2.P.4.5	analytical procedure verification/ validation		
3.2.P.4.1	Excipients	Colorants/ compliance with foodstuff regulations	Specification not in accordance with Regulation EC 231/2012	2020	3.2.P.4.1 3.2.P.4.2 3.2.P.4.3 3.2.P.4.4	Update specification and analytical procedures perform analytical procedure verification/ validation	3	-
3.2.P.4.1 3.2.P.4.2	Excipients	Formerly non-compendial excipients now described in a EU member state pharmacopoeia/ Ph.Eur.	Compliance with Ph.Eur./ EU member state pharmacopoeia not given	2020	3.2.P.4.1 3.2.P.4.2 3.2.P.4.3 3.2.P.4.4 3.2.P.1 3.2.P.3.2	Update specification and analytical procedures perform analytical procedure verification	3	-
3.2.P.4.1	Excipients	Microbiological purity risk	Not addressed, no evaluation done so far for non-compendial excipients or compendial excipients without this test in the monograph	2008/2009	3.2.P.4.1 3.2.P.4.2 3.2.P.4.3 3.2.P.4.4 3.2.P.2.5	If there is a risk for microbiological purity should be assessed and when it cannot be excluded a test for microbiological purity should be done (incl. verification)	3	-
3.2.P.4.1	Excipients	Endotoxins	Sterile medicinal products: There's no endotoxin removal step in manufacture and endotoxin test has not been included in the Ex. specification or is not compliant with the revised Ph.Eur. 5.1.10	2016	3.2.P.4.1 3.2.P.4.2 3.2.P.4.3 3.2.P.4.4	Update excipient specification / analytical procedures and perform analytical procedure verification	3	-
3.2.P.4.5	Excipients	Viral Safety Human/ Animal origin	Viral Safety has not been addressed	2008	3.2.P.4.5	Risk Assessment to be done and absence to be confirmed	2	Data from suppliers required
3.2.P.4.5	Excipients	TSE risk	Absence of risk is not addressed	2020	3.2.P.4.5	Request information from excipient suppliers if risk for TSE can be excluded	2	Data from suppliers required

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
3.2.P.4.6	Excipients	Novel excipients	Novel excipient not described as extensive as an active substance	2008	3.2.P.4.6	Perform a gap analysis, organize the required studies	3+	The required information is available at the manufacturer of the excipient
3.2.P.4.6	Excipients	Novel excipients	Novel excipient not described in accordance with the current provisions on active substances	2020	3.2.P.4.6	Perform a gap analysis, organize the required studies	3+	The required information is available at the manufacturer of the excipient
3.2.P.4.6	Excipients	Novel excipients	The excipient has been included in the Ph.Eur./ a EU member state pharmacopoeia	2020	3.2.P.4.1 3.2.P.4.2 3.2.P.4.3 3.2.P.4.4 3.2.P.4.5 3.2.P.4.6	Update specification/ analytical procedures to pharmacopoeia monograph.	2	-

3.2.P.5 Control of Drug Product

Table 34: Gap Scenarios 3.2.P.5

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
3.2.P.5.1	Specification Related Substances	Changed related substances specification	New degradation products or existing products exceed ICH Q3B identification/ qualification limit	2020	3.2.P.5.1 3.2.P.5.2 3.2.P.5.3 3.2.P.5.4 3.2.P.5.5 3.2.P.5.6 3.2.P.6 3.2.P.8	Revise specification, if required also the analytical procedure description and validation. Perform a toxicological assessment (medical affairs) in case of new degradation product or excess qualification limit	4	-
3.2.P.5.3	Analytical procedure validation, Stress Tests	Stress testing	No stress testing done	2006	3.2.P.5.3	Perform stress testing	3	Related substance specification to be updated to ICH

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
								Q3B(R2) requirements
3.2.P.5.5	Characterisation of impurities	Characterisation general	Characterisation has not been addressed	2003	3.2.P.5.5 3.2.P.5.6	Provide reference to 3.2.S.3.1, but if there are impurities in the drug product other than derived from the drug substance they must be characterized (requires studies)	3	-
3.2.P.5.5	Characterisation of impurities	Characterisation unidentified impurities	No justification given for unidentified impurities above identification limit	2006	3.2.P.5.5 3.2.P.5.1 3.2.P.5.2 3.2.P.5.4 3.2.P.6 3.2.P.8	Impurities must be investigated, and it must be tried to characterize them. If not successful, the trials must be described	4	-
3.2.P.5.6	Control strategy	General control strategy with its components control of excipients, control of manufacturing process, control of critical steps and intermediates, finished product control	General control strategy not addressed, when checked there are gaps	2008	3.2.P.4 3.2.P.3 3.2.P.5 3.2.P.8	Setting up of a control concept: Available knowledge needs to be reviewed e.g. from development or changes performed post-approval. Where needed, gaps must be closed by introducing the required controls or changing the frequency.	4	Review of all controls in the relevant dossier parts for compliance with current regulatory requirement.
3.2.P.5.6	Control Strategy	Residual solvents	Triethylamine can be present in the finished product as result of the risk analysis or PDEs must be updated	2020	3.2.P.3.4 3.2.P.4.1 3.2.P.4.2 3.2.P.4.3 3.2.P.4.4 3.2.P.5.1 3.2.P.5.2 3.2.P.5.3 3.2.P.5.4 3.2.P.5.6	Update the control strategy, review if the specification controls in the excipients/ manufacturing process/ finished product specification are still sufficient or if specifications must be revised, analytical procedures changed and verification/	2-4	-

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
						validation activities performed		
3.2.P.5.6	Control Strategy	Elemental impurities	No elemental impurities are discussed in the dossier, instead the test "heavy metals" is applied for excipients/ finished products	2014	3.2.P.3.4 3.2.P.4.1 3.2.P.4.2 3.2.P.4.3 3.2.P.4.4 3.2.P.5.1 3.2.P.5.2 3.2.P.5.3 3.2.P.5.4 3.2.P.5.6 3.2.P.7	Evaluate the occurrence of elemental impurities acc. to one of the options described in ICH Q3D(R1). Set up appropriate limits	2-4	-
3.2.P.5.6	Control Strategy	Mutagenic impurities	Topic not addressed	2014	3.2.P.4 3.2.P.5.1 3.2.P.5.5 3.2.P.5.2 3.2.P.5.3 3.2.P.5.4 3.2.P.5.6 3.2.P.7 3.2.P.8	Assess risk for mutagenic impurities and if present, perform follow up activities (see below). Information from suppliers of the active substance and excipients will be required.	2	Information on presence of mutagenic impurities from suppliers of the active substance and excipients might be required.
3.2.P.5.6	Control Strategy	Mutagenic impurities	Tightening of limits for mutagenic impurities due to introduction of revision 1 of ICH M7 but the recommended limits are exceeded.	2017	3.2.P.4 3.2.P.5.1 3.2.P.5.5 3.2.P.5.2 3.2.P.5.3 3.2.P.5.4 3.2.P.5.6 3.2.P.7 3.2.P.8	Perform optimisation of the manufacturing process/ materials used e.g. purging steps in order to reduce the amount	4	Data are available on genotoxic impurities: which impurities can be present, in which amount and what is the source
3.2.P.5.6	Control Strategy	Mutagenic impurities	New mutagenic impurities are suspected/ found incl. Nitrosamines	2020	All of 3.2.P	Perform confirmatory testing, in case of suspicion. Check if ICH M7 PDE is exceeded or not. Find root cause and	4	-

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
						optimize the manufacturing process and/ or materials used in case of Nitrosamines or if PDE is exceeded.		

3.2.P.6 Reference Standards or Materials

Table 35: Gap Scenarios 3.2.P.6

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
3.2.P.6	Reference standards and materials	Compliance with Ph.Eur. 5.12	It is referred to a specific version of the updated Ph.Eur. monograph 5.12 or text passages have been copied and included in the dossier	2014	3.2.P.6	Dossier update only, qualification of the standard should not be affected.	1	-
3.2.P.6	Reference standards and materials	Change of reference standards due to change of the standard supplier, analytical procedures or specifications (e.g. new impurities)	The reference material specification, analytical procedures used for qualification, certificates of analysis have not been updated to the changes.	2020	3.2.P.6	Request the required documents from QA. A new qualification or partial re-qualification might be required	3	-

3.2.P.7 Container Closure System

Table 36: Gap Scenarios 3.2.P.7

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
3.2.P.7	Container Closure System	General update	No tabular specification for incoming good control at the finished product manufacturer has been provided, only a technical data sheet.	2020	3.2.P.7	Check with QA if a specification for incoming good release is available. If not, it must be set up. CoAs will be required and verification or validation of the analytical procedures.	3	It is assumed that compatibility of the packaging material has been proven in 3.2.P.2.4
3.2.P.7	Container Closure System	Compliance Certificates for Compliance with Foodstuff legislation, Ph.Eur., BfR recommendations	Compliance certificates reference to regulatory provisions/ recommendations are outdated	2020	3.2.P.7	Request up-to-date compliance certificates	2	It is assumed that compatibility of the packaging material has been proven in 3.2.P.2.4

3.2.P.8 Stability

Table 37: Gap Scenarios 3.2.P.8

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
3.2.P.8.1 3.2.P.8.3	Stability Summary/ Data	Compliance of the intermediate condition with the guideline on stability testing for existing drug substances/ drug products	The intermediate condition is 30°C/ 60% RH	2003	3.2.P.8.1 3.2.P.8.2 3.2.P.8.3	Perform new stability studies with the intermediate condition 30°C/ 65% RH	3+	Updated specifications and stress testing on degradation products completed as well as fully validated analytical procedures.
3.2.P.8.1 3.2.P.8.3	Stability Summary/ Data	Compliance with recommended	Compliance with the updated guideline for drug	2003	3.2.P.8.1 3.2.P.8.2	Either the differences between the revised guideline	3+	Updated specifications and

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
		storage conditions for products to be stored in semi-permeable containers or freezer	products with existing drug substances is not given		3.2.P.8.3	and the storage conditions can be justified or a new stability study must be started (new stability study recommended due to the age of the studies)		stress testing on degradation products completed as well as fully validated analytical procedures.
3.2.P.8.1 3.2.P.8.3	Stability Summary/ Data	Change of criteria for significant change in the guideline for drug products with existing drug substances, e.g. for functionality related tests/ water content for storage in semi-permeable containers	According to the new criteria the data from the accelerated stability study are out of specification, but no study at intermediate condition has been performed	2003	3.2.P.8.1 3.2.P.8.2 3.2.P.8.3	Perform a new stability study (it is recommended to put batches on intermediate condition stability immediately)	3+	Updated specifications and stress testing on degradation products completed as well as fully validated analytical procedures.
3.2.P.8.1 3.2.P.8.3	Stability Summary/ Data	Photostability	Photostability studies have not been performed	2020	3.2.P.8.1 3.2.P.8.3	Perform photostability studies acc. ICH Q1B	3	Updated specifications
3.2.P.8.1 3.2.P.8.3	Stability Summary/ Data	Bracketing/ Matrixing	Bracketing or Matrixing is performed is not in line with ICH Q1D	2002	3.2.P.8.1 3.2.P.8.2 3.2.P.8.3	Perform new stability studies. A different concept as described in ICH Q1D can be tried to justified	3+	Updated specifications and stress testing on degradation products completed as well as fully validated analytical procedures.
3.2.P.8.1 3.2.P.8.3	Stability Summary/ Data	Evaluation criteria acc. to ICH Q1E, e.g. discussion of assay results	Stability data provided have not been discussed.	2003	3.2.P.8.1	The data should be reviewed and discussed together with a stability expert	2	-
3.2.P.8.2	Stability Commitment	On-going stability studies	There are ongoing studies but no/ inadequate stability commitment has been given	2003	3.2.P.8.2	Add stability commitment according to the requirements of the guideline on stability	1	-

Module	Topic Category	Topic	Gap	This is a risk for dossiers dated ≤…	Modules to be updated (possibly)	Actions	Effort	Prerequisites
						testing for drug products with existing drug substances		
3.2.P.8.3	Post-approval stability protocol	Stability plan primary stability studies vs. commitment batches	There are differences between the stability protocol for primary stability studies and the commitment stability studies that cannot be justified	2003	3.2.P.8.1 3.2.P.8.2	Start a new commitment stability study immediately	3+	Updated specifications and stress testing on degradation products completed as well as fully validated analytical procedures
3.2.P.8.3	Stability Data	Analytical methods and method validation used for stability studies	The analytical method has been changed within in the history of stability studies and the effect on stability data has not been discussed. No data for comparability of the analytical procedures are included in the dossier.	2003	3.2.P.8.3	Search internally for comparability data. If they cannot be found, perform comparative validation studies between the previous and the current analytical procedure for stability studies. In case of minor changes, try to justify them with the help of an analytical expert.	2- 3+	-