ICH Q12 Pharmaceutical Product Lifecycle Management – Part I

Concept and Establishment of the Established Conditions (EC) and of the Product Lifecycle Management (PLCM) Document

Summary

The *ICH Guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management* was published in January 2020. The goal is to harmonize post-approval changes, to facilitate scientific innovation, and help to mitigate drug shortages. The integration of this guideline into European Union (EU) regulatory framework is pending. Some so called *„tools and enablers"* are proposed. Most of them are already implemented in the EU. New instruments are *„established conditions (EC)"* and the *„product lifecycle management (PLCM)"* document. These both instruments are elucidated, and a possible implementation strategy in the context of medicinal product approval and process validation is discussed.

Introduction

The *ICH Q12 Guideline on technical and regulatory considerations for pharmaceutical product lifecycle management*[1] (in short: The ICH Q12 Guideline) was adopted in its final version in January 2020. Now the authorities and the member states involved have to implement it. The ICH Q12 Guideline puts in place framework conditions for the management of post-approval CMC[2] changes. Its goal is to enable technical developments and at the same time to develop regulatory requirements on post-approval changes during the complete life cycle of medicinal products in a harmonised and effective way.

With the implementation of the ICH Q12 Guideline so-called *tools and enablers* are proposed. Their goal is to allow for a uniform and facilitated management of post-approval changes for the involved regulatory authorities and marketing authorisation holders.

The *tools and enablers* include:

- Categorisation of post-approval CMC changes
- Established conditions (ECs)
- Post-approval change management protocol (PACMP)
- Product lifecycle management (PLCM) document
- Pharmaceutical quality system (PQS) and change management
- Relationship between regulatory assessment and inspection

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- Structured approaches for frequent CMC post-approval changes
- Stability data approaches to support the evaluation of CMC

Some of these proposed instruments (*tools and enablers*) are already put into practice for the EU:

- *Categorisation of post-approval CMC changes*: The categories for variations to the terms of marketing authorisations are defined (minor variation of type IA, minor variation of type IB, major variation of type II, extension of a marketing authorisation)[3].
- *Post-approval change management protocol (PACMP)*: The concept of post-approval change management protocol related to active substances and finished products is established in the implementation guidelines to Regulation (EC) No 1234/2008[4], and described in the annexes ID and IE of the ICH Q12 Guideline in its possible forms[5].
- *Pharmaceutical quality system (PQS) and change management*: The pharmaceutical quality management and change management are defined in their different forms in the EU Guidelines to Good Manufacturing Practice and in other regulations[6,7,8,9,10,11]. Further information is contained in the ICH Guideline Q10 *Pharmaceutical Quality System*[12] which is established with Part III of the EU Guidelines to Good Manufacturing Practice.
- *Relationship between regulatory assessment and inspection*: The relationship between assessment of the dossier of the marketing authorisation (*regulatory assessment*) and inspections at manufacturers of active substances, finished products and medicinal products is already regulated on EU level and on national level (cf. articles 111, 122 and 125 of Directive 2001/83/EC[13] as well as §§ 64, 68 AMG[14] and §§ 12, 13 AMG-VwV[15]). A practical example for this is the joint inspection of the responsible federal authority (for Germany: Paul-Ehrlich-Institut) in the case of inspections of manufacturers of blood preparations (second sentence of § 64 (2) AMG).
- *Structured approaches for frequent CMC post-approval changes*: The implementation guidelines to Regulation (EC) No 1234/2008 specify a structured approach for individual or several variation(s) to the terms of marketing authorisations. Any conditions to fulfil and documents to submit are specified for all possible variations. Additionally, a proposal for structurally to be planned post-approval changes of analytical methods is made in Annex II of the ICH Q12 Guideline.
- *Stability data approaches to support the evaluation of CMC*: The implementation guidelines of Regulation (EC) No 1234/2008 as well as Part I Chapter 6.33 of EU Guidelines to Good Manufacturing Practice (on-going stability programme) state the necessity to plan or to submit appropriate stability tests together with variations.

A review and where necessary an adjustment of the rules already applicable in the EU to the philosophy of the ICH Q12 Guideline is still pending.

By contrast, the concept and the legal classification of the ECs and of the resulting PLCM document are not established in the valid EU body of legislation (EUDRALEX[16]).

Established conditions and product lifecycle management (PLCM) in the EU legislative area

The discrepancy between the legal situation in the EU and the requirements of the ICH Q12 Guideline as concerns the ECs and the PLCM document are addressed in the Note on *EU implementation of ICH Q12*[17]:

> *The ICH Q12 Guideline refers to this required or necessary information as 'Established Conditions' (ECs). While this term does not exist in the EU variation legal framework, generally speaking, Established Conditions mirror information and quality characteristics that are subject to a variation, as described in the EU*

Variation Regulation (EC) No 1234/2008 (as amended) and associated EU Variation Guidelines.

However, additional scientific risk-based approaches to defining Established Conditions and associated reporting categories [...] and the Product Lifecycle Management (PLCM) Document [...] are not considered compatible with the existing EU legal framework on variations.

It is important to note that the legal framework always takes precedence over technical and scientific guidelines. More specifically this means that the definition of Established Conditions and their reporting categories must follow the requirements laid down in the current EU Variations Regulation and associated EU Variations Guidelines.

[...]

Irrespective of the above, the tools and concepts in the ICH Q12 Guideline that are not foreseen in the EU legal framework will be considered when this framework will be reviewed. In the meantime, the European Commission, together with the EMA and the National Competent Authorities, will continue to work on the implementation of the ICH Q12 Guideline within the existing EU legal framework.

Hence, this *Note on EU implementation of ICH Q12* is to be understood as a declaration of intent. The Note implies that not legally defined tools and enablers such as ECs or the PLCM document will also be included in the body of laws of the EU concerning pharmaceutical legislation sooner or later. But currently neither the ECs nor the PLCM are applicable in the EU. This raises the question about the form they will take and about the legal adjustments in the EU that will be required for the implementation of the ECs and the PLCM.

Established conditions – definition according to the ICH Q12 Guideline

Established Conditions "*mirror information and quality characteristics that are subject to a variation, as described in the EU Variation Regulation (EC) No 1234/2008 (as amended) and associated EU Variation Guidelines*". This means that here the marketing authorisation has to be considered.

The information to be included in the application for a marketing authorisation are clearly defined[18,19,20]. The *common technical document (CTD)*[21] is the key element of the marketing authorisation – apart from the administrative information about the marketing authorisation holder, the name of the medicinal product etc. This document contains the required information on the manufacture and quality control of the active substances and excipients used and of the medicinal product. A fundamental subdivision of the data is possible in clearly defined material specifications (active substances and excipients, intermediate products, medicinal products), process parameters of manufacture and testing as well as supporting documents (development reports, risk analyses, validation reports etc.).

But what are the *established conditions* in the CTD?

The ICH Q12 Guideline contains the following definition[22]:

ECs are legally binding information considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority.

This binding information relates to product quality. This means that the question from above about the information from the dossier of the marketing authorisation that is part of the ECs remains unanswered. To that end the teleological interpretation of the set of rules makes sense. This is the question "*What is the rule's intention?*". The ICH Q12 Guideline gives the following answer[23]:

References

1 ICH guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management Step 5, EMA/CHMP/ICH/804273/2017, 04. März 2020
2 Chemistry, Manufacturing, Control
3 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.
4 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 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 and on the documentation to be submitted pursuant to those procedures (2013/C 223/01).
5 ICH Q12 Guideline on technical and regulatory considerations for pharmaceutical product lifecycle management – annexes, EMA/CHMP/ICH/831751/2017, 4 March 2020.
6 EU Guidelines to Good Manufacturing Practice Part I Chapter 1 (Medicinal Products for Human and Veterinarian Use).
7 EU Guidelines to Good Manufacturing Practice Part II (Active Substances) Chapter 2 (Active Substances).
8 Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections.
9 Guidelines Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014, C(2017) 8179 final, 08.12.2017.
10 Guidelines dated 22 November 2017, Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products.
11 Leitfaden der Guten Praxis für Standards und Spezifikationen zur Implementierung eines Qualitätssystems in Blutspendeeinrichtungen, BAnz AT 27.12.2017 B3.
12 Pharmaceutical Quality System (ICH Q10), EMA/INS/GMP/79818/2011, 31 January 2011.
13 Directive 2001/83/EG of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67) in the current version.
14 Law on trade in medicinal products (Medicinal Products Act - AMG), date of issue: 24.08.1976, in the version of the Notice of 12 December 2005 (BGBl. I S. 3394), as last amended by article 18 of the law of 20 November 2019 (BGBl. I p. 1626).
15 Allgemeine Verwaltungsvorschrift zur Durchführung des Arzneimittelgesetzes (AMGVwV), Federal Ministry of Health, Federal Gazette No. 63, 30 March 2006 (p. 2287).
16 Legal framework governing medicinal products for human use in the EU, https://ec.europa.eu/health/documents/eudralex_en
17 Note on EU implementation of ICH Q12 (guideline on technical and regulatory considerations for pharmaceutical product lifecycle management), EMA/CHMP/ICH/78332/2020, 4 March 2020.
18 EudraLex - Volume 2 - Pharmaceutical legislation on notice to applicants and regulatory guidelines for medicinal products for human use, https://ec.europa.eu/health/documents/eudralex/vol-2_en
19 EudraLex - Volume 6 - Notice to applicants and regulatory guidelines for medicinal products for veterinary use, https://ec.europa.eu/health/documents/eudralex/vol-6_en
20 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67), Annex I Analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products.
21 EudraLex - Volume 2 - Pharmaceutical legislation on notice to applicants and regulatory guidelines for medicinal products for human use Volume 2B Notice to Applicants Medicinal products for human use Presentation and format of the dossier Common Technical Document (CTD)
22 ICH Q12 Guideline, chapter 3.2.1.
23 ICH Q12 Guideline, chapter 1.3.
24 Failure Mode and Effects Analysis.
25 Hazard Analysis and Critical Control Points.
26 Annex 15 of the EU Guidelines to Good Manufacturing Practice, Qualification and Validation.
27 Pharmaceutical Development Q8(R2), ICH harmonized tripartite guideline, Current Step 4 version, August 2009

The concept of ECs provides a clear understanding between the MAH and regulatory authorities regarding the elements to assure product quality and that involve a regulatory communication, if changed. This guideline describes how ECs are identified as well as what information can be designated as supportive information that would not involve a regulatory communication, if changed. In addition, guidance is included for managing revisions of the ECs.

This means that the ECs have to be understood as the information regarding the quality of the medicinal product agreed upon by the marketing authorisation holder on the one hand and the authority granting the approval on the other hand. Furthermore, variations of the ECs are subject to the rules of Regulation No 1234/2008 ("*Variation Guideline*").

Hence, all information on material specifications, process parameters of manufacture and testing, in-process controls, run times etc have to be understood as ECs. Development reports, risk analyses, validation reports on the other hand are covered by the concept "*supportive information*" according to the ICH Q12 Guideline since they justify the parameters defined for manufacture and quality control and the limits set for these parameters. Annex IA and Annex IB of the ICH Q12 Guideline contain examples for ECs for the manufacturing process.

"Established conditions" in the US American legislative area

A brief digression to the USA shows that the wording for relevant concepts for changes of approvals by the US American FDA already exist.

21CFR314 Applications for FDA approval to market a new drug

§314.70 Supplements and other changes to an approved NDA.

(a) Changes to an approved NDA. (1)(i) Except as provided in paragraph (a)(1)(ii) of this section, the applicant must notify FDA about ***each change in each condition established*** *in an approved NDA beyond the variations already provided for in the NDA.*

The same is applicable to biological drugs falling under the approval of the US American FDA.

21CFR601.12 Changes to an approved application

§601.12 Changes to an approved application.
(a) General. (1) As provided by this section, an applicant must inform the Food and Drug Administration (FDA) (see mailing addresses in §600.2 of this chapter) about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling ***established in the approved license application(s).***

How are "established conditions" defined?

Paramount for the definition of ECs is a risk-based process understanding. This process understanding is based on the fundamental consideration which material attributes of the active substances and excipients used are relevant for the final product quality, which process parameters are critical and which controls (in-process controls, final controls) are required at which steps in the process of manufacture. This assessment can only rarely be deduced from a FMEA[24] risk analysis. A consecutive analysis of each process step (unit operation) following HACCP[25] risk analyses based on the results of development and experience reports is more suitable.

Basis for establishing ECs are thus the definition and identification of the following parameters:

- Critical quality attributes (CQA)
- Critical process parameter (CPP)
- Process control strategy (in-process controls, final controls)

The basic requirement for the definition of CQA and CPP can be found in Annex 15 Chapter 5.21 of the EU Guidelines to Good Manufacturing Practice[26]: "*A process validation protocol should be prepared which defines the critical process parameters (CPP), critical quality attributes (CQA) and the associated acceptance criteria which should be based on development data or documented process knowledge.*"

Corresponding requirements concerning the definition and establishment for the pharmaceutical development can be found in the ICH Guideline Q8 R2 *Pharmaceutical Development*[27].

For the establishment of ECs, the ICH Q12 guideline suggests two basic approaches. These will be presented in the second part of this article in the next issue of the GMP Journal.