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.

ICH Q12 Pharmaceutical Product Lifecycle Management – Part II

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

For the establishment of Established Conditions (EC), the ICH Q12 guideline proposes two basic approaches.

Parameter-based approach

Minimal approach

> *A **minimal approach**, with a limited understanding of the relationship between inputs and resulting quality attributes, will include a large number of inputs (e.g., process parameters and material attributes) along with outputs (including in-process tests). (Chapter 3.2.3.1 ICH Q12 Guideline)*

The minimal approach corresponds to the "traditional"[28] approach of process validation according to which three consecutive production batches are produced. As experience has shown a few more analyses are carried out than is customary in the routine manufacture (such as verification of the mixing homogeneity of the powder mixture before compression). Process knowledge and the testing carried out stem from the experience with the product, from knowledge out of reference books on the formulation processes applied respectively (unit operations) and potentially from developments carried out in the past. Usually, CQA and CPP are not known or not addressed as such. Development reports might be available, but usually it is not possible any more to verify the methodology and the reliability of the results (missing data traceability, obsolete methodologies, performance not according to the currently applicable regulations and legal requirements).

Control strategy: In most cases all collectable input variables (CQA) and process parameters (CPP) are recorded for all batches at 100 % because the empirical evidence on process understanding and knowledge is insufficient. Often the purpose of collection is questioned not from a scientific point of view but only from a commercially one (Motto: *"We have always done it this way."*).

Procedure in the case of an OOS result: In the case of an OOS result it can only be investigated whether the deviation occurred during the manufacture. The effects of this deviation on the OOS parameters often remain a vague assumption, however, since a hypothesis testing is hardly possible due to non-verified relationships and

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dependencies. A targeted (experimental) investigation is difficult to design. The analysis of causes must often remain unfinished and present possible hypotheses.

Figure 1 shows the situation in the case of a minimal approach. This is a fictitious example of a mixing step to visualise the influence of the active substance and the excipient as well as of the process parameters mixing temperature, mixing time and agitation speed on the particle size distribution and mixing homogeneity of the powder mixture obtained from the manufacturing step.

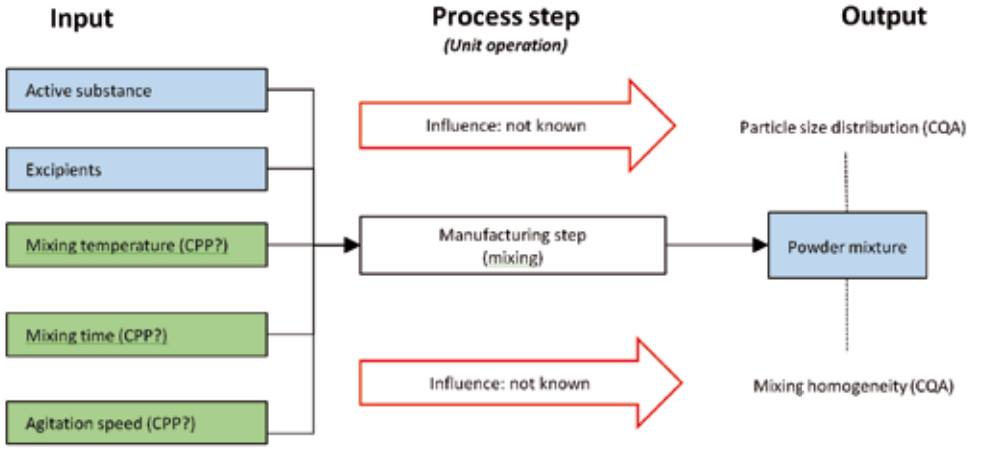

Figure 1: Situation in the case of a minimal approach shown at the example of the mixing step for the manufacture of a powder mixture

Enhanced approach

> *An **enhanced approach** with increased understanding of interaction between inputs and product quality attributes together with a corresponding control strategy can lead to identification of ECs that are focused on the most important input parameters along with outputs, as appropriate. (Chapter 3.2.3.1 ICH Q12 guideline)*

The enhanced approach is characterised by a clear understanding of the relationships between the input variables such as specification of active ingredients and excipients (CQA), the environmental and process parameters (CPP) as well as the output variables (product specification). Process understanding and knowledge is gained by means of systematically structured development approaches that are carried out according to the current guidelines and are completely documented. Available development or transfer reports can be classified and used as reliable basis (supportive information). They establish relationships and set limits for all input and output variables.

Control strategy: Due to this enhanced process knowledge it is not required any more to collect each available information (control) for each batch. It can be dispensed with the collection and recording of non-relevant parameters. On the other hand, there is a high degree of certainty to have collected all really relevant parameters. Since the relationships are known they can be put in relation (mathematically) with each other. The development of control charts is possible that link input and output variables, and a continuous process verification can be carried out.

Procedure in the case of an OOS result: In the case of an OOS result a relationship can be established between the deviations observed and the effects. If no relationship can be established this means that the process understanding for this case of deviation must be further developed. The development department is invited to carry out a targeted investigation of this relationship. This applies even more if a typical OOS result keeps reoccurring.

Figure 2 shows the situation in the case of an enhanced approach. The same example is chosen as in figure 1. In this example it is already known by means of enhanced process knowledge that the active ingredient's particle size distribution has an influence on the particle size distribution of the powder mixture. Consequently, the active ingredient's particle size distribution must be classified as critical quality attribute (CQA). It should be included in the active ingredient's specification and it should be tested in the framework of the control strategy. The particle size distribution of the excipient is irrelevant. Consequently, it is not a CQA and must not be included in the excipient's specification and it needn't be tested.

Moreover, it is known that the parameters mixing time and agitation speed are relevant for the mixing homogeneity and that they must therefore be specified and recorded as critical process parameters (CPP). The mixing temperature is not relevant for the mixing homogeneity. It must not necessarily be recorded and the limits must not necessarily be defined.

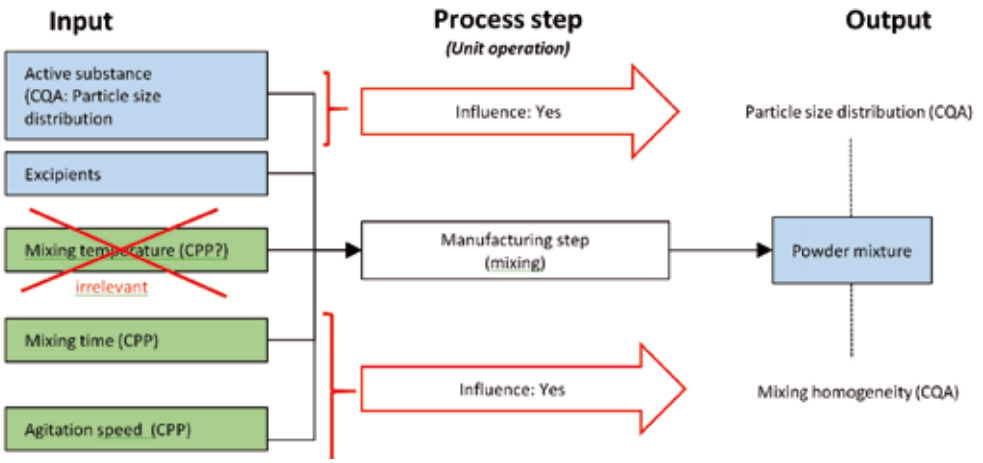

Figure 2: Situation in the case of an enhanced approach shown at the example of the mixing step for the manufacture of a powder mixture

Discussion of the parameter-based approach

In summary, the parameter-based approach consists mainly in a fundamental and generic knowledge of the different steps (unit operations) making part of the manufacture of medicinal products. Specific knowledge often exists only in the form of experience with the product itself. Focus of the approach for assessing the quality of the process is the systematic collection and documentation of all possible quality attributes of active substances and excipients (CQA) und of all collectable process and machine parameters (CPP). The available data pool may undergo a trend monitoring, where appropriate. But the importance of individual collected parameters remains partly unclear.

Performance-based approach

*In a **performance-based approach**, ECs could be primarily focused on control of process outputs (e.g., attributes, measurements, responses) rather than process inputs (e.g., process parameters and material attributes). This is enabled by knowledge gained from an enhanced approach, a data-rich environment, and an enhanced control strategy (e.g., models, Process Analytical Technology (PAT)). For example, a performance-based approach could be considered for manufacturing process steps with in-line monitoring of relevant attributes or with feedback controls or optimization algorithms to achieve the relevant targets for that process step. When considering this approach, it is important to ensure that all relevant parameters and material attributes that have a potential to impact product quality are monitored and equipment used remains qualified in order to assure a stable process. [...] (Chapter 3.2.3.1 ICH Q12 Guideline)*

The performance-based approach is the most progressive approach for gaining process understanding and process knowledge. It requires a systematic and scientific analysis of the process. Individual process steps are well designed and are individually assessed in a process-oriented risk analysis as concerns their criticality. The input parameters CQA and CPP are defined and proven experimentally. Clear, comprehensible and valid development or transfer reports exist.

Initial process validations take account of predetermined areas in their design and are designed in such a way, that worst case conditions are reviewed. Thus, it is guaranteed for the ongoing productions that all batches whose CQA and CPP are within the defined specifications will conform with the end product specification. Concepts such as normal operating range (NOR), design space (DSp), proven acceptable range (PAR), established conditions (EC) are defined and play a role for the process development and for the ongoing production[29].

Design spaces are known and defined in experiments (Design of Experiments (DoE))[30]. It should be noted however that all changes within the design spaces (listed in the marketing authorisation) are neither notifiable nor subject to approval[27]. This means that they can be implemented within the quality system by means of a simply change control procedure and are not relevant for the marketing authorisation.

Control strategy: Altogether the development of the manufacturing process and an individually coordinated control strategy play a central role. Quality by design is the philosophy. This means that the reliable and constant achievement of the desired product quality has priority.

By this it is no longer necessary to collect all collectable variables (input, output) for each batch. A targeted skip-lot strategy can be used, meaning that not all parameters of a specification are tested for each batch.

Not only the data received for the batch to be released play a role for the batch release. Ongoing trend analyses accompany the batch assessment so that the control strategy always contains a continuous and meaningful process verification (continuous Process Verification (cPV)).

Such a profound process knowledge offers the possibility of using process analytical technology (PAT). This means in principle that a batch release is possible solely based on the knowledge of the data pool collected in the course of manufacturing without having to control the end product analytically (real time release testing (RTRT), parametric release). Such a procedure is interesting for products which are administered to the patient immediately after manufacture, for instance radiopharmaceuticals or processed blood preparations and when final quality control of relevant parameters such as sterility is not possible due to time or the required sample quantities[31,32]. The revision of Annex 17 EU Guidelines to Good Manufacturing Practice offers the possibility of such a strategy for the use of parametric release for the routine release of products sterilized in their final container without a final sterility test[33].

OOS: If parameters (CQA, CPP) are outside the validated area (edge of failure) already during production a non-compliance of the batch manufactured with the specification is expectable. And vice versa the following can be expected with a high statistical certainty: if all parameters are within the specified (and validated) area it can be assumed without further testing of intermediate products or end products that the end product complies with the specification.

Discussion of the performance-based approach

In summary, the performance-based approach is based on a control strategy which has been elaborated on the basis of the process knowledge available. Goal is the prediction that the batch will be in compliance with the specification with a high statistical certainty if

all parameters (CQA; CPP) collected during manufacture are in a predefined and by means of development and validation studies ensured area.

Marketing authorisation relevant variation of the established conditions

According to the legal definitions in Article 2 (Definitions) Regulation (EC) No 1234/2008 a variation within the meaning of the Regulation is each variation *"to the contents of the particulars and documents"* which were made in the application for a marketing authorisation. Details of the variations to the terms of marketing authorisations and the categories of variations (minor variation of type IA, minor variation of type IB, major variation of type II, extension of a marketing authorisation) are defined in the relevant implementation guidelines to Regulation (CE) 1234/2008. For each conceivable variation (relevant to the marketing authorisation) specific conditions and documents to be submitted are pre-defined. The documents to be submitted have to be seen as supportive documents (supportive information). These supportive documents contribute to a variation in the manufacturing process or test procedure in so far as suitable batch verifications, stability studies or validations after a variation prove that the proposed variation does not have a negative impact on the quality, safety or efficacy of the medicinal product. In principle these documents have to be seen as supplement to the development studies *"conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the intended use specified in the marketing authorisation application dossier"*[34].

A complete overview over the contents in the CTD that are ECs and the contents which have to be understood as supportive information is given in ICH Q12 Guideline "Appendix 1: CTD sections that contain ECs".

When the ECs are known the question about the way of reporting to the regulatory authority arises for each post-approval change. The ICH Q12 Guideline offers a decision tree (figure 3). This means in principle that all post-approval changes of parameters that have not been identified as ECs are not relevant for the marketing authorisation. They would need to be discussed only in the product quality review (active substances: EU Guidelines to Good Manufacturing Practice, Part II, Chapter 2.6, medicinal products: EU Guidelines to Good Manufacturing Practice, Part I, Chapter 1.10 (v)) as appropriate.

All post-approval changes concerning ECs have to be assessed as concerns their criticality. They need only be notified to the regulatory authority (notification) or be approved ex-ante by the authority (prior approval).

In respect of this proposal in the ICH Q12 Guideline it should be noted that the fundamental categorisation of the post-approval changes to be reported essentially corresponds to EU law but that here EU jurisdiction is relevant (Regulation 1234/2008) and not the ICH Q12 Guideline.

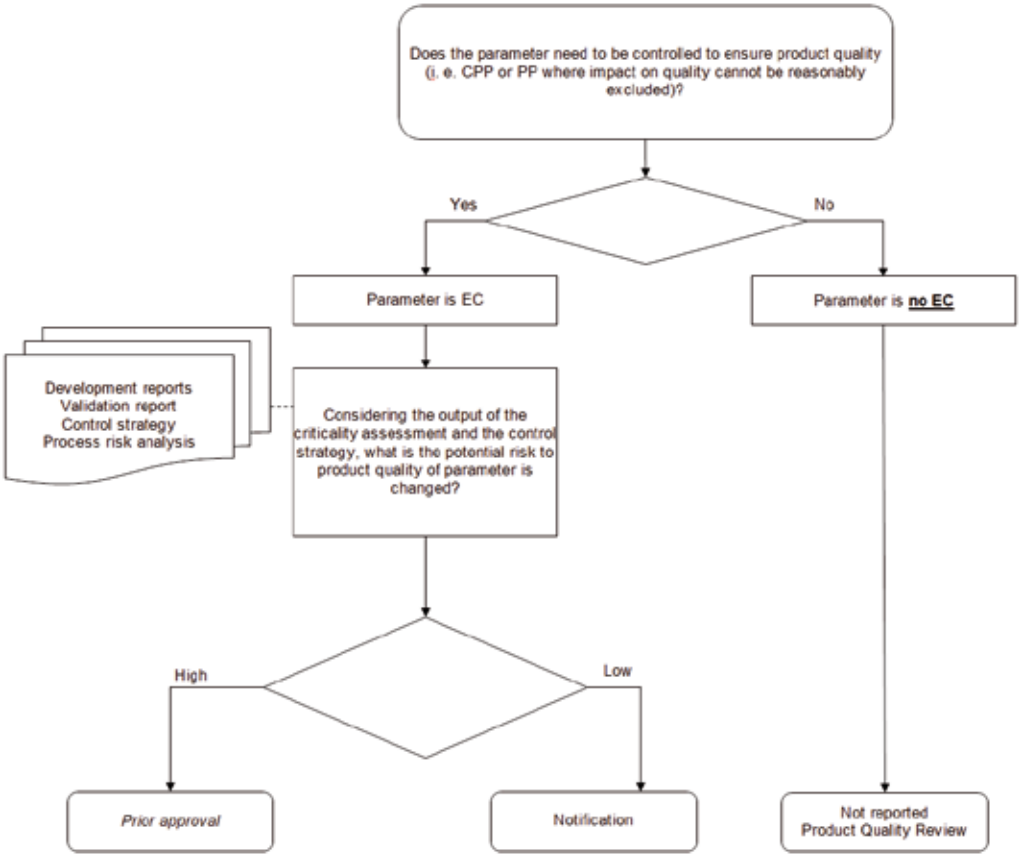

Figure 3: Decision tree for the reporting of post-approval changes of ECs following the ICH Q12 Guideline (cf ICH Q12 Guideline Figure 1: Decision Tree for Identification of ECs and Associated Reporting Categories for Manufacturing Process Parameters).

Product Lifecycle Management (PLCM) Document

The PLCM document outlines the specific plan for product lifecycle management that includes the ECs, reporting categories for changes to ECs, PACMPs (if used) and any post-approval CMC commitments. Its purpose is to encourage prospective lifecycle management planning by the MAH and to facilitate regulatory assessment and inspection. The PLCM document should be updated throughout the product lifecycle as needed.
The PLCM document serves as a central repository in the MAA for ECs and reporting categories for making changes to ECs. (Chapter 5 ICH Q12 Guideline)

The PLCM document is new and not enshrined in EU jurisdiction. This document is supposed to be kept as central register throughout the complete product lifecycle, and it contains all ECS as well as their relevance for the marketing authorisation in the case of a post-approval change (notification or prior approval). Furthermore, the post-approval change management protocol (PACMP) and all relevant explanations of the marketing authorisation holder referring to the product quality and to studies to be carried out after the post-approval changes (post-approval CMC commitments) are supposed to be contained in the document. Annex IF of ICH Q12 Guideline contains an example of a PLCM.

Implementation of the ICH Q12 Guideline into the EU's pharmaceutical regulatory framework

All ICH member authorities and member states are expected to implement the ICH Q12 Guideline. There is already a comprehensive regulatory framework in the EU which would have to be expanded and adjusted to incorporate the ECs as well as the PLCM document. This places the focus on the common technical document (CTD) which has not been changed since its establishment in 2006. A clarification as concerns the distribution of the information on a medicinal product in the dossier for a marketing authorisation application would be helpful in order to be able to distinguish between legally binding between ECs and supportive information.

For the establishment of the PLCM document it is favourable to take over the variation categories defined in the implementation guidelines to Regulation (CE) 1234/2008.

The concept ECs has to be included in all legal requirements for and guidelines on the implementation of process validations. Establishing meaningful process risk analyses is decisive, regardless of the methodology used. These process risk analyses identify CQA and CPP, present a clear control strategy and make a distinction between ECs and supportive information.

But in the end the implementation of the ICH Q12 Guideline in the daily routine of manufacture and testing means the revision of the existing instructions for the change management. Where appropriate it would be convenient to prepare a separate specification for all product related variations that lists all categories for variations concerning process and analyses customary in the EU in one PLCM document. As basis for all contract manufacturing agreements this PLCM document can then lead to clarity between the contract manufacturer and the customer with regard to variations to be carried out.

A revision of the requirements in the EU Guidelines to Good Manufacturing Practice for the design of product quality reviews also makes sense. Practice has shown that often various parameters (in-process-controls, results of the testing of finished products) are reported without their relevance being known. For the future a more systematic reporting of ECs should be pursued, usefully also as trend.

Interestingly, no deadline has been set for the ICH member authorities and member states for the implementation of the ICH Q12 Guideline. Therefore, the question remains unanswered when the harmonisation of the requirements concerning variations to the terms of marketing authorisations can actually be expected.

Part I of this article can be read in the previous issue of the GMP Journal (Nº 32).

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