Post-Approval Change Management Systems in the ICH Region with Focus on "Established Conditions"

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

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Bonn 2017

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Abbreviations

ANDA	Abbreviated New Drug Application
BLA	Biologics License Application
CAPA	Corrective action and preventive action
CBE	Changes being effected
CMA	Critical Material Parameter
CMC	Chemistry, Manufacturing and Control
CP	Comparability Protocol
CPP	Critical Process Parameter
CQA	Critical Quality Attributes
CTD	Common Technical Document
DP	Drug Product
DS	Drug Substance
EC	Established Conditions
eCTD	Electronic Common Technical Document
EU	European Union
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GMP	Good Manufacturing Practice
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IPC	In-process control
J-NDA	Japan New Drug Application
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MCN	Minor change notification
PAC	Post-Approval Change
PACMP	Post-Approval Change Management Protocol
PCA	Partial change application

PMDA	Pharmaceutical and Medical Device Act
PPPQM	Process performance and product quality management
PQS	Pharmaceutical Quality System
PSLCM	Product-Specific Lifecycle Management
QbD	Quality by Design
QRM	Quality risk management
QTTP	Quality target product profile
NDA	New Drug Application
US	United States
SUPAC	Scale-up and post-approval changes

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Summary

The management of post-approval changes on a global scale is complex, unpredictable and time consuming. Even in the ICH region different systems are existing. In the US, Japan and Europe are established different national procedures of handling post-approval changes. In 2015, the FDA drafted the guidance on established conditions to clarify which CMC changes need to be reported to the FDA. Established conditions are defined as the description of the product, manufacturing process, facilities and equipment and elements of the control strategy whereas certain CMC changes can be made solely under the pharmaceutical quality system (PQS) and its enablers, as described in the guidance for industry Q10. The PMDA has already a similar system since 2005 when the Pharmaceutical Affairs Law in Japan was revised, resulting in an enhancement of post-marketing measures. In Japan, different to the EU and US, module 1 of the NDA contains a summary of the most important elements of the application. The contents, that is described in that summary, is legally binding approved matters. On the contrary, the EU introduced the concept of the post-approval change management protocol in 2010, a two-step approach in the assessment of changes. Using a post-approval change management protocol might result in a lower categorization of changes than they would have been categorized under the traditional approach. Currently, the international council for harmonization of technical requirements for pharmaceuticals for human use is working on a harmonization of post-approval changes for marketed products within the ICH regions. This guideline, the ICH Q12, is not yet publicly available. Among others, the current working draft of the ICH Q12 guideline contains chapters on categorization of changes, established conditions and post-approval change management protocols. If the guidance come into force it could result in a paradigm shift in terms of the processing of post-approval changes on a global scale.

1 Scope

The presented master thesis provides information on different post-approval change management procedures in the ICH region before the ICH Q12 guideline on Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management comes into force. The main focus of this thesis is on the application of established conditions in the US and in Japan, however, also the concept of post-approval change management protocol in Europe is described.

In a second step the planned contents of the ICH Q12 guideline is described, according to the state of knowledge in June 2017. At that time, no draft version of the guideline was available.

Special characteristics for biological products are not included, thereof this master thesis is written with focus on small molecule products.

Please keep also in mind that the presented master thesis covers aspects for medicinal products for human use only.

2 Introduction

2.1 Background

Currently, the management of post-approval changes on a global scale is complex, unpredictable and time consuming [1] Even within the ICH region different systems are existing and also the classification of the reporting categories do not correspond in the different countries. The US, Japan and Europe, thus all three foundation members of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), have established their own national risk-based post-approval change management system.

2.2 The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)

The ICH concept is an approach of the authorities and the industry for the harmonization of drug regulatory requirements. ICH founders are following three regions: Europe (EU), United States (US) and Japan, the so-called TRIADE. The regions are represented by their Health Authorities and Associations.[2] Further country members are Canada, Switzerland, Brazil and South Korea.[3]

The mission of the ICH is a greater harmonization worldwide in drug registration with the aim that safe, effective and high quality drugs are developed and registered. This is achieved by the development of the ICH guidelines, written by industry and regulatory experts side-by-side.[4]

Besides the three founding regulatory and industry members the ICH association comprises more regulatory and industry members and observers.[2]

The formal harmonization process for the completion and implementation of an ICH guideline consists of five steps:

1. In the first step an established expert working group prepares a consensus draft of the technical document.[5]

2. In the second step the regulatory members take the required actions for the development of the draft guideline, as soon as consensus is confirmed.[5]

3. The third step consists of three different stages: regulatory consultation in the ICH regions, discussion of comments resulted from consultation and finalization of a step three experts draft guideline.[5]

4. In the fourth step the experts draft guideline which was finalized in step three is submitted to the regulatory members of the assembly for the adoption of an ICH harmonized guideline.[5]

5. The final step five of the process is the regulatory implementation of the harmonized guideline. This is carried out according to the same procedures that apply to other regional regulatory guidelines.[5]

Until now guidelines have been harmonized on four main topics, safety (S-guidelines), quality (Q-guidelines) efficacy (E-guidelines) and multidisciplinary (M-guidelines). Chemistry, Manufacturing and Control (CMC) topics for medicinal products are regulated in the quality-guidelines. Achieved harmonization includes, among others, the definition of impurity thresholds, the conduct of stability studies and risk management.[6]

Despite the implementation of harmonized guidelines and standards on various topics in the ICH member states, they still have their own national regulations on a variety of topics and harmonization is ongoing.

2.3 Lifecycle Change Management

Lifecycle management of a pharmaceutical product may be described as a process of managing the product's lifecycle from its development through commercial manufacturing to product discontinuation. During their lifecycle, medicinal products change due to cost reduction, quality improvement, process optimization, or workflow standardization. Despite many years of drug development, the most work-intensive phase in a medicinal product's lifecycle is the post-approval time (see Figure 1), because companies must ensure that they meet regulatory requirements by submitting changes and remain compliant.[7]

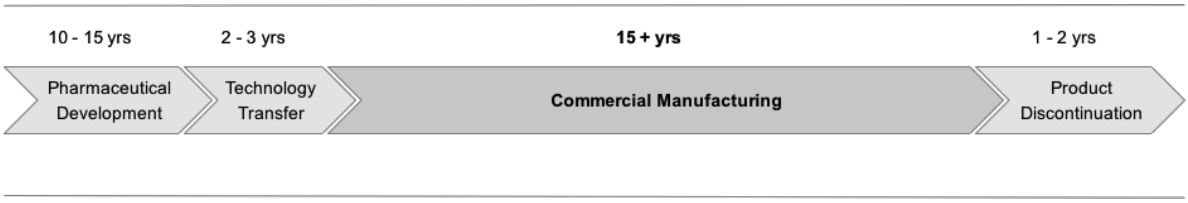

Figure 1: Key Elements of a Product Lifecycle of a Medicinal Product (following Michor 2008)

Lifecycle change management is a complex and challenging field. The current regulatory post-approval change processes vary between countries with regard to terminologies of change categories, requirements for documentation and timelines for approval. And although ICH is proceeding, the specific requirements of each region are still remaining.

Change management is a systematic approach to proposing, evaluating, approving, implementing and monitoring changes to a validated process.[8]

The purpose of change management is the prevention of unwanted and unapproved changes to validated processes.[9] This can be reached by the creation of structured procedures to assure that the changes do not impact the quality of the product negatively.[9]

In pharmaceutical change management it is differentiated between various change types: planned changes, unplanned changes and temporary changes.[9]

Planned changes are permanent or temporary chances which are known in advance.[9] Out of that reason such a change is approved and the potential impact can be evaluated prior to implementation. Unplanned changes, on the other hand, arise out of emergency cases during production process. They are not approved and cannot be evaluated prior to implementation. In general, unplanned changes should be handled and investigated the same as deviations are. The third change type are temporary changes. Temporary changes are approved prior to implementation, but only for a certain time or a described number of batches. Already at the time of implementation there is the intention of returning the system back to its former condition.

Manufacturing changes may have a possible impact on the identity, strength, quality, purity or potency of the medicinal product. As the properties of the medicinal product relate to its safety and effectiveness, current guidelines recommend the assessment of effects on these properties.[10]

3 Established conditions

3.1 Established Conditions in the United States

3.1.1 Background

In 2015, the Food and Drug Administration (FDA) developed the draft guidance “Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products” intended for applicants submitting either new drug applications (NDAs) or abbreviated new drug applications (ANDAs) or also biologics license applications (BLAs). With this guidance FDA wants to clarify which CMC changes can be made solely under the pharmaceutical quality system and which CMC changes need to be reported to FDA.[11]

In the national regulations (21 CFR 314.70 (a)(1)(i)) is stated that an applicant has to notify the authority about every change in every condition that is established in an approved application. Although this phrase has been described in a number of ways since the revision of the post-approval change regulations since 1997, there has not been a shared understanding of the meaning. The phrase has often been used synonymously with the term “regulatory commitment”, which allows various interpretations.[11]

The FDA is of the opinion that there is a lack of clarity regarding which elements are considered established conditions and have to be reported to FDA. This confusion leads to unnecessary submissions of post-approval changes and also to incompliance regarding changes that should have been but have not been reported to FDA. With the help of the new guidance FDA intends to increase clarity and transparency on established conditions and what constitutes established conditions.[11]

3.1.2 Definition of Established Conditions

The draft guidance for industry of the FDA defines established conditions as the description of the product, manufacturing process, facilities and equipment and as elements of the control strategy. These conditions are defined in a new drug application (NDA) and assure both, the process performance and the quality of an approved medicinal product. Every change to an established condition has to be reported to the FDA.[11] In the guidance document a table is provided identifying those sections of a CTD-formatted application typically containing information to be considered to meet the definition of established conditions. In the table examples are listed of established conditions for each section of the module 3. A copy of the table can be found in Annex I (see 9.1) of this Master Thesis.

In the application, adequate detail should be provided concerning the suggested established conditions. The provision of inadequate details for suggested established conditions will be addressed during application review.[11] If an

applicant fails in the provision of sufficient details, this could delay the review process or rather preclude approval of the submitted application.[11]

3.1.3 How to Establish "Established Conditions"

3.1.3.1 Elements of a Pharmaceutical Quality System

Changes to non-established conditions can be made solely under the pharmaceutical quality system (PQS), as described in the guidance for industry ICH Q10, without the need to report these changes to the FDA.[11]

Achieving product realization, establishment and maintenance of a state of control and the facilitation of continual improvement are the main objectives which can be achieved by the implementation of the ICH Q10 model, also enhancing the regional GMP (good manufacturing practice) requirements.[8]

Per ICH Q10, the following quality system elements are used for the identification and management of post-approval changes: process performance and product quality monitoring (PPPQM), corrective and preventive action (CAPA), change management and management review.[12]

In each stage of a product's lifecycle, continual improvement of process performance and product quality is required. Therefore, a monitoring system should be planned and executed providing assurance of the continued capability of the processes and controlling that the product produced has the desired quality. Additionally, with the implementation of the system the company should be able to identify areas for continual improvement. During pharmaceutical development knowledge is generated on product and process. Monitoring during the development phase can help in the establishment of an effective control strategy for the later manufacturing phase. Monitoring during the technology transfer and scale up activities can help to obtain further knowledge very useful for the further development of the control strategy.[8] During commercial manufacturing a well-

defined system assures performance within a state of control and identifies improvement areas. Also when manufacturing is stopped, monitoring should be continued, especially on marketed products according to regional regulations.[8]

The pharmaceutical quality system should use a quality risk management for the establishment of the control strategy (see 3.1.3.3). The use of the control strategy should facilitate appropriate corrective and preventive action. The system should also provide the tools needed for the measurement and analysis of the parameters identified by the use of the control strategy and also analyse these parameters for the verification of a continued operation. The identification of sources where process performance and product quality is affected can reduce or control variations by continual improvement. Also feedback from different sources (internal and external) on product quality should be implemented into the process performance and product quality monitoring system.[8]

The CAPA system results from investigations and trends from process performance and product quality monitoring. The use of such a system should result in product and process improvements as well as in enhanced product and process understanding.[8]

Innovation and process improvements lead to changes. For the evaluation, approval and implementation of these changes, an effective change management system is necessary. A proposed change should be evaluated by utilizing quality risk management relatively to the marketing authorization. All changes should be evaluated by the change management system and by an expert team, and it should be assessed if regulatory filing is to be done under regional requirements. When the change has been implemented, an evaluation should take place confirming that the change objectives were achieved and that there was no impact on the product quality.[8]

The fourth element of the pharmaceutical quality system, the management review, includes various levels of management in a series of reviews. The review process should include a timely and adequate escalation process where quality issues are raised up to senior management for review.[8]

3.1.3.2 Knowledge Management and Quality Risk Management

Quality risk management (QRS) and knowledge management are the enablers of a pharmaceutical quality system (PQS).[12]

Knowledge management is the acquisition, analyzation, storage and dissemination of information referred to a medicinal product and its processes and components.[8] Knowledge can be gained from various sources, including pharmaceutical development, manufacturing experience, innovation and continual improvement studies, technology transfer activities and change management activities.[13] The knowledge about a product and its process should be managed through the whole lifecycle of a product, including its discontinuation.[8] An effective knowledge management can support the advancement of product and process understanding, because the expertise grows and evolves through the entire lifecycle of a product.[13]

The ICH Q9 guideline provides principles and tools for a quality risk management which are applicable to several aspects of pharmaceutical quality, including development, manufacturing, distribution as well as the inspection and review processes throughout the product's lifecycle. There are two fundamental principles of quality risk management. First, the evaluation should be based on scientific knowledge and second, the level of effort, formality and documentation should be proportionately to the level of risk. By the implementation of a quality risk management process, the quality of the medicinal product can be assessed, controlled, communicated and reviewed through the lifecycle of the product.[14] Usually, risk assessment is performed in the development process. As more information becomes available and greater knowledge is obtained, the risk assessment is repeated.[15] An overview of a typical quality risk management process, shown in Figure 2, is provided by the ICH Q9 guideline:

Risk assessment is the identification of sources of danger and the subsequent analysis and evaluation of the risks that are associated to those sources of

danger.[14] The result of the risk assessment can either be a numerical probability of the risk or a defined qualitative description, such as “low”, “medium” or “high”.[14]

Risk control is the decision making if the identified risk should be reduced or can be accepted.[14]

The result of the risk management process should be shared by communicating and documenting the results appropriately. It should also be reviewed or monitored permanently for considering new knowledge and experiences.[14]

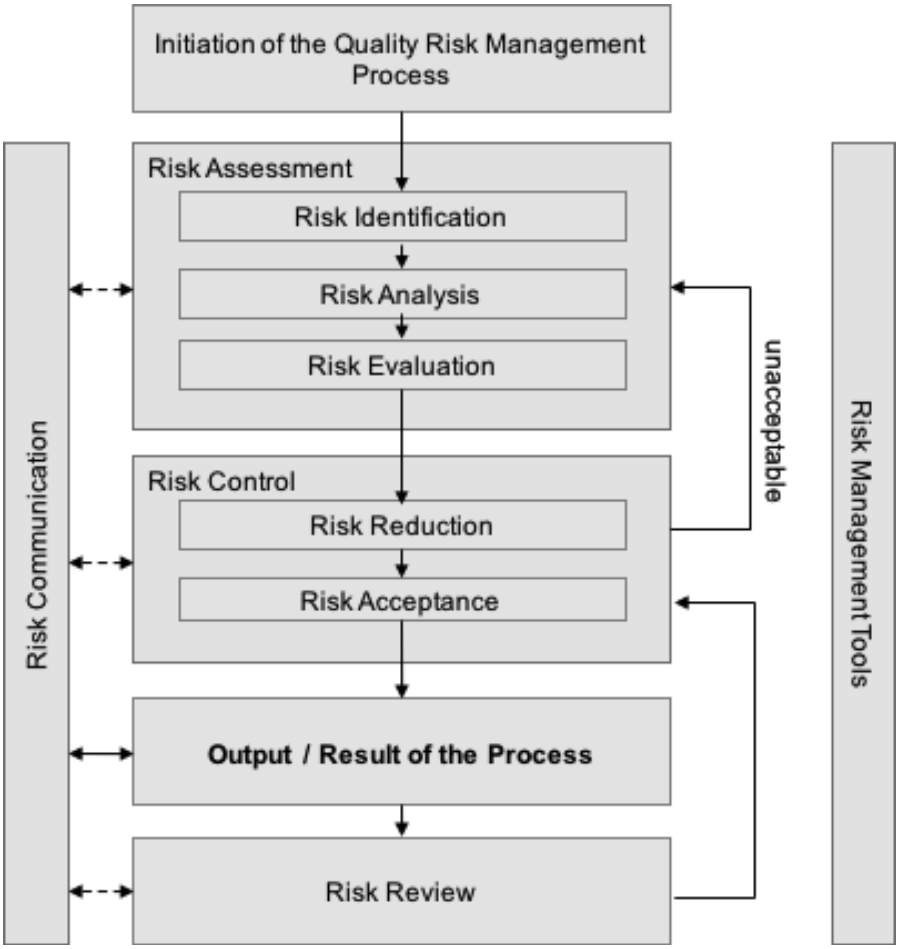

Figure 2: Model of a Typical Quality Risk Management Process (following ICH Q9)[14]

The information obtained from pharmaceutical development studies can also be used as a basis for quality risk management. During development, properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality can be assessed.[15] These critical quality attributes (CQAs) are mainly associated with the drug substance, excipients, intermediates and the drug product and can be modified as product knowledge and process understanding increases. Subsequently, by applying an iterative process of quality risk management, relevant CQAs can be identified.[15] Risk management is also used to identify critical material attributes (CMAs) and critical process parameters (CPPs), that can have an impact on the product CQAs.[15]

CQAs as well as CPPs build the basis for the control strategy[16] (see 3.1.3.3).

The implementation of both, knowledge management and quality risk management together enable a company to implement ICH Q10 effectively and successfully.[8] When implemented successfully, they will support an effective change management system[12] by providing tools for science and risk based decisions.[8]

3.1.3.3 Control Strategy

A control strategy, defined in ICH Q11, is a planned set of controls assuring process performance and product quality as defined in ICH Q10. The planned set of controls should derive from current product and process understanding [17] and should be based on product, formulation, and process understanding. At a minimum, they should include the control of the critical process parameters and material attributes.[15]

Every manufacturing process of a drug substance is accompanied by a control strategy, irrelevant if the process was developed by a traditional or an enhanced approach.[17] The control strategy of a manufacturing process should assure the

drug substance quality by making sure that the critical quality attributes (CQA) of the drug substance is within the appropriate range, limit or distribution.[17]

Several controls are included into a control strategy of a manufacturing process. This includes, but is not limited to, controls on the properties of materials used in the manufacturing process, controls included in the design of the manufacturing process, such as the order of reagent addition, in-process controls (IPC) and controls on drug substances, such as release testing.[17]

There are different strategies for the development of a control strategy, the traditional approach and the enhanced approach.

In the traditional approach the set points and operating values are set very narrow on the observed data in the manufacturing process. This strategy assures consistency in the manufacturing process. The assessment of critical quality attributes at the stage of the drug substance, such as end-product testing, is a higher emphasized feature in this approach. But at the end this approach offers a limited flexibility in the operating values.[17]

A better process and product understanding is generated by using the enhanced approach for developing a control strategy. The control strategy provides a greater flexibility in the operating values to address variability in process parameters. In turn, sources of variability can be identified in a more systemic way because the development by using this approach generates a better process and product understanding.[17]

One part of the overall control strategy is the drug substance specification. There are three different possibilities to include the critical quality attributes (CQA) into this specification. Either they can be included in the specifications and verified by final drug substance testing, or they can be included in specifications and verified by in-process controls (IPC) or measurement of critical process parameters (CPP), so called upstream controls.[17]

The control strategy reflects the current product and process understanding of a product and is submitted within the initial application.[11] It can be developed and

revised as new knowledge is derived around the lifecycle of the concerned product.[11]

The overall drug control strategy can be filed in the CTD section of the drug product specification P.5.6 of the application. But information about input material controls or process controls have to be provided in the appropriate sections.[15]

3.1.3.4 Components of the Control Strategy that can be Considered Established Conditions

The controls of the control strategy are derived from current process and product understanding and can include different types of CMC parameters and attributes. Established conditions are only a part of an overall control strategy and there are elements that may be managed only under the pharmaceutical quality system. Control strategy elements, that are reported in an application, have only supportive character, whereas established conditions are necessary elements assuring process performance and product quality.[18]

The guideline on established conditions includes, but does not limit to, the following elements of a control strategy, that could be established conditions described in an application.[11]

- Drug substance (DS) / drug product (DP) manufacturing (includes packaging and labeling operations, testing and quality control of DP) and testing facilities[11]
- Specifications for and source of starting materials for biological products[11]
- Process (including in-process tests and work sequence), equipment, and process parameters and their ranges[11]

- Specifications for the drug substance, other components, in-process materials and the drug product (also the tests, analytical procedures and acceptance criteria) [11]
- Container closure system, components, and specifications[11]
- Maintenance strategy for models (chemometric and/or multivariate) having an impact on product quality[11]

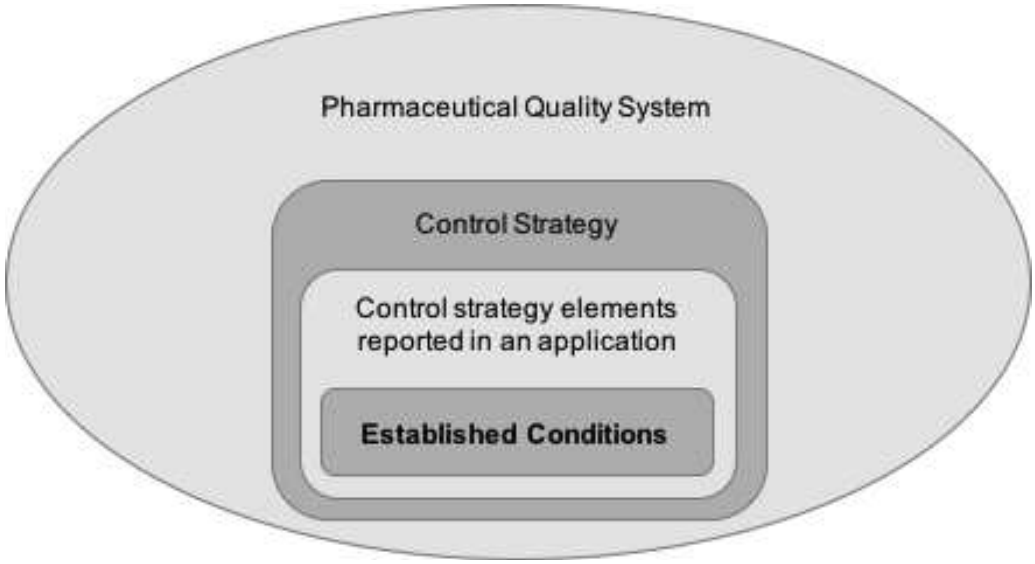

Figure 3: Established Conditions within a Control Strategy
(following guideline on "established conditions, FDA, 2015 [19])

Sometimes the relevance of the established conditions is dependent on manufacturing site specific capabilities, and therefore elements of established conditions may need to be specific to one or more manufacturing sites.[11]

Batch records are generally not considered established conditions. They reflect the current manufacturing process as well as the in-process controls (IPC) ensuring the product quality.[11] Not every change to batch records have to be

reported to the FDA, but in case of a change to the control system, impacting the batch record, a current batch record should be submitted to the FDA, although validation activities are also not considered established conditions. They are supporting the approved manufacturing process and the analytical methods, and a change should be supported by validation data. Also development data, characterization data and batch analysis data are not considered established conditions.[11]

3.1.4 Submission of Established Conditions as Part of NDA

In Annex I the table from the FDA guidance document is shown which identifies the sections of a CTD-formatted (common technical document - formatted) application normally containing established conditions. But even when the information is placed in another CTD-section and then specified in the table, it would still be considered as an established condition.[11]

For proposing established conditions for a medicinal product, the applicant should provide a summary of the established conditions in the application. It is recommended to submit the summary in Module 2, section 2.3 of the CTD (introduction to the quality overall summary) as a table. The summary should also contain a short description or identification of the established conditions and it should also refer to the specific location of the established condition in Module 3 of the CTD, or to a hyperlink in an eCTD (electronic common technical document).[11]

After submission, the proposed established conditions are assessed together with the risk assessment plan, the control strategy and the product and process knowledge of the applicant. The assessment of the proposed established conditions will be finalized at application approval. For particular parameters normally considered established conditions a greater flexibility is allowed. When the applicant can demonstrate a risk mitigation, it may be that such parameters are not considered established conditions. In this case they can be changed under

the pharmaceutical quality system of the applicant and no submission or notification to FDA is needed.[11]

In the case the FDA assesses that provided supportive information is inappropriate and thus the applicant lacks the ability of appropriate change management, the proposed established conditions may be reassessed by the FDA as soon as the applicant submitted corrected and accurate information.[11]

3.1.5 Changes to Established Conditions

As written above, established conditions are part of the control strategy of the marketing authorization holder (MAH) (see 3.1.3.4). The control strategy of a product should be updated as new knowledge is obtained or new risks occur. As soon as new knowledge is obtained during commercial manufacturing, the MAH should provide an updated summary of the established conditions together with supportive information for the new or modified established condition. This summary is to be submitted in a supplement or together with the next annual report. It is also possible to remove an established condition by submitting an annual report or supplement. Therefore, the applicant should determine that it is no longer required for the assurance of the process performance or the product quality. In the submission, the MAH should clearly explain the way of his determination. He should also explain the elements of the control strategy providing sufficient or improved control.[11]

Parts in an approved application that are not identified as established conditions would not require reporting to the FDA if post-approval changes were made. But if there is any change to an established condition requiring reporting per definition, supportive elements such as validation data should also always be submitted to support the change”[11]

3.1.6 Post-Approval Changes according to Regulations of the FDA

Reporting categories are defined in section 506A of the Federal Food, Drug, and Cosmetic Act[20] (FD&C Act), added by section 116 of the Food and Drug Modernization Act[21] and 21 CFR 314.70.[20]

The FDA guidance document “Guidance for Industry: The Changes to an Approved NDA or ANDA” clarifies the reporting categories and provides recommendations on them. Exceptions are reporting categories on components and composition. As the guidance does not provide recommendations on them, the recommendations in the SUPAC (scale-up and post-approval changes) guidance document apply.[20]

The categorization is based on the impact the change could have on the identity, strength, quality, purity or potency of the medicinal product as well as the relationship to the safety and effectiveness of the product.[20]

Minor changes are defined in 21 CFR 314.70 (d). They have a minimal potential to have an adverse effect on the identity, strength, quality, purity or potency of the drug product.[20] They are annual reportable by the applicant according to §314.81 (b)(2).[22] Further recommendations on notifications by annual reports are provided in the FDA guidance document “CMC post-approval manufacturing changes documented in annual reports”.[21]

Moderate changes are defined in 21 CFR 314.70 (c). They have a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of the drug product.[21] If a change is considered to be moderate, a supplement must be submitted at least 30 days before the drug product made using the change is distributed (paragraph (c)(1)) or, in some cases, a supplement has to be submitted at least at the time of distribution (paragraph (c)(6)).[22]

Major changes are defined in 21 CFR 314.70 (b). They have a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of the drug product.[21] If a change is considered to be major, it must be

submitted and an approval is needed prior to distribution of the product made after the change was established. This reporting category includes, but is not limited to, changes in the qualitative or quantitative formulation of the drug product or in the specifications (see Figure 4).[22]

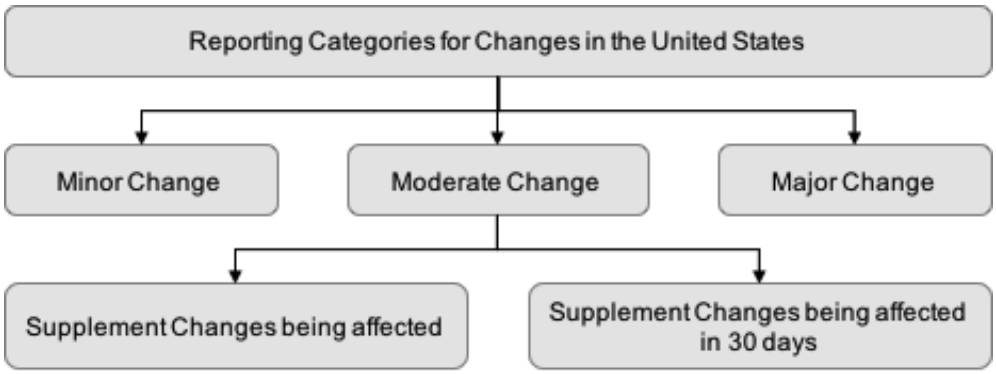

Figure 4: Change Classification in the United States.

3.2 Approved Matters as Established Conditions in Japan

3.2.1 Background

Effective in April 2005, the Pharmaceutical Affairs Law in Japan was revised.[23-24] The revision resulted in an enhancement of post-marketing measures. Additionally, the responsibility of the marketing authorization holder (MAH) with regard to quality management was clarified.[24]

The Japanese system regarding new drug applications is unique,[24] the Japanese approach of module 1 in the NDA is the most apparent difference between the module 1 in the other ICH countries. In the US and in Europe module 1 of the NDA is seen as an administrative section whereas in Japan module 1 contains a summary of the most important elements of the application.[25]

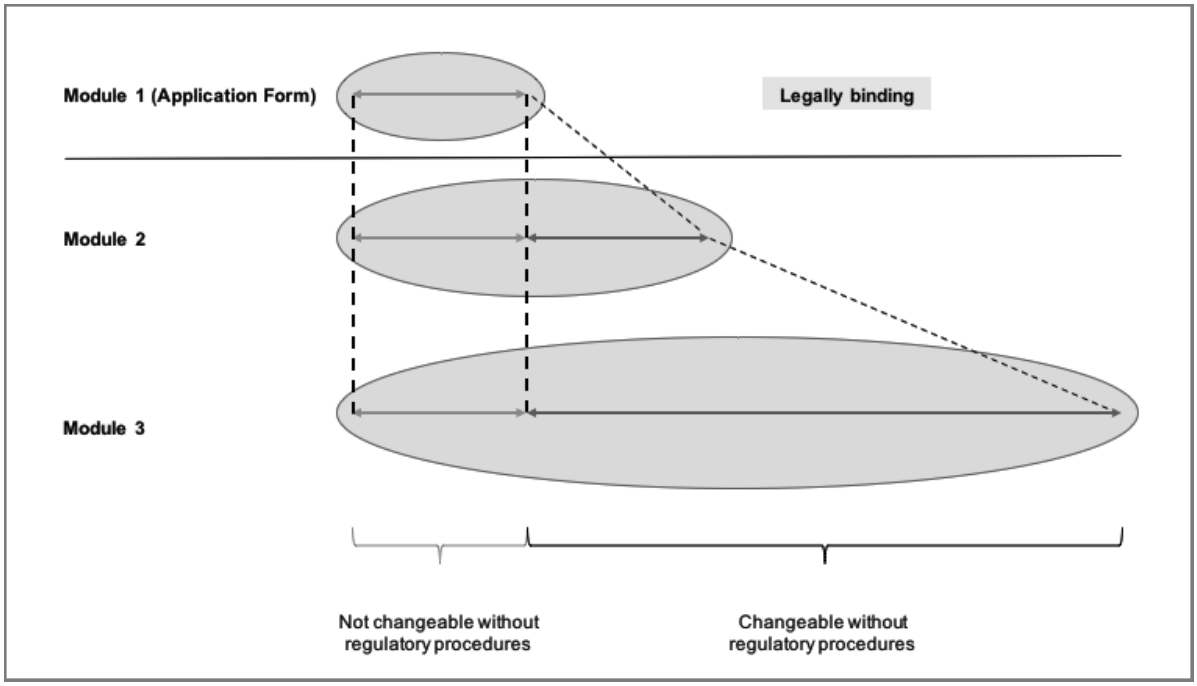

Figure 5: Changeable Content of Modules in Japanese NDA (following Kishioka 2016)

The content, which is provided by the applicant in the J-NDA application form in module 1.2 of the CTD, is handled as “matters subject to approval”.[23, 26] Therefore the content described in that form is legally binding approved matter.[23] Any change to the content of the application form and thus to the approval letter leads to a filing of a change application.[25]

The module 2 of a new drug application, containing the quality overall summary (QoS) in Japanese language, bridges the application form and the module 3. It is one of the key review documents, because first reviewers evaluate module 2 and when they need more detailed information they go into the modules 3 to 5 of the application in the CTD format.[24] (compare Figure 5)

The legally binding approved matters of the Japanese application form are comparable with the established conditions of the US American draft guideline.

3.2.2 Post-Approval Changes according to Japanese Regulations

In Japan, the legal basis for changes in a marketing approval is stipulated in the Pharmaceutical and Medical Device Act. Changes are only approved when the identity of the approved product is not affected and the product remains the same.[27] In case of changes with regard to the active ingredient, its content or dosage form, a new approval application is required. Two reporting categories are existing, minor change notification and partial change approval.[27]

The holder of a marketing authorization is eligible to apply for a partial change of approved items in the approval. Partial change applications (PCA) are described in Article 14, Paragraph 9 of the Pharmaceutical and Medical Device Act (PMDA). The Japanese word for partial change means “change in the currently approved items of the medicinal product”.[27] In other words, an application for a partial change application has to be filed in case the applicant alters the content of the current approval by the change.[23] Also changes requiring adequate change control can be identified as partial changes.[28] This major change needs between 12 and 18 months as a standardized timing for approval.[29]

Changes only requiring minor change notifications (MCN) are stipulated in Article 14 Paragraph 10 of the PMDA.[27] A minor change to an existing approval does not require an application for approval as a partial change does. The manufacturer has to notify the health authority within 30 days after the change has been implemented confirming that the change does not affect the quality of the medicinal product. Related data to the change have to be filed at the manufacturing site. GMP inspectors will confirm the appropriateness of the change procedure later on during a GMP inspection.[23]

Minor changes are others than those specified in the following items in the approval:[27]

- Changes in the manufacturing methods affecting the nature, properties, performance and / or safety of the product [27]

- Deletion of items regarding specifications and test methods as well as regarding changes in the approved specifications [27]
- Change in the methods used for the inactivation or elimination of pathogenic factors [27]
- All other changes affecting the quality, efficacy or safety of the product [27]

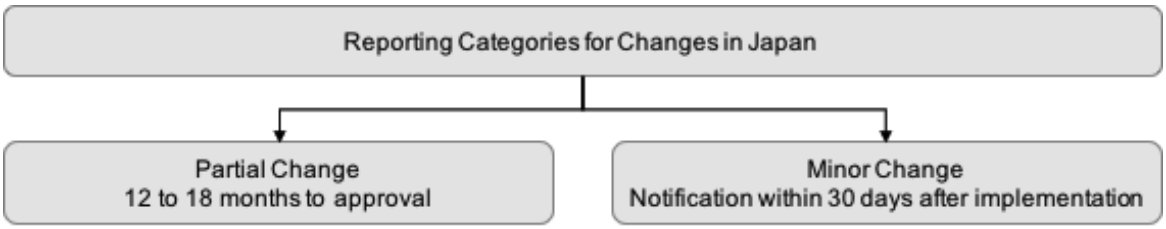

Figure 6: Change Classification in Japan.

In general, the PCA/MCN change classification should be based on CQAs and CPPs which may affect the CQAs, on development data, prior knowledge and the overall control strategy.[26]

Finally, the differences between a partial change application and a minor change notification can be explained as follows: a change in the principle of an unit operation of a critical process or a change in a process control criteria as quality endpoint criteria is filed as a partial change application whereas a process parameter to only control the quality endpoint criteria is filed as a minor change notification.[23]

3.2.3 Application Approval Form as Part of the Japan New Drug Application (J-NDA)

The application form for the marketing approval of drugs in Japan must be submitted in Japanese language.[30] Following content submitted in the application form is legally binding after approval:[23]

- Japanese accepted name (non-proprietary name) [26]
- Brand name[26]
- Composition[26]
- Manufacturing process,[26] process control, control of material and container closure systems[23]
- Specifications and analytical procedures [26]
- Dosage and administration[26]
- Indications[26]
- Storage conditions and shelf-life [26]
- Manufacturing sites information [26]

For the new drug application it is already required to identify the critical and non-critical parameters in the manufacturing process,[25] because the applicant personally distinguishes and establishes in the application form the matters to be addressed in a partial change application and the matters to be addressed in a minor change notification.[28]

From among the standard batch sizes or the process parameters (e.g., temperature, pH, time, etc.) that serve as target values and set values and have a high significance for the quality of drug substance or drug product, have to be enclosed in 《 》. In case these matters would be changed in the future, a partial change approval application (PCA) would be needed.[30] (see 3.2.2 Post-Approval Changes according to Japanese Regulations)

Target values and set values of standard batch sizes or the process parameters having only low significance for the quality of drug substance or drug product,

have to be enclosed in 『』. In case these matters would be changed in the future, a minor change notification (MCN) would be needed.[30] (see 3.2.2 Post-Approval Changes according to Japanese Regulations)

Values other than target values and set values, such as the concentration of reagents, which have only low significance for the quality of the drug substance or the drug product, have to be enclosed in “ ” as minor change notification matter.[30] For other matters, not enclosed in parentheses, partial change applications are needed.[30-31] (see 3.2.2 Post-Approval Changes according to Japanese Regulations)

More detailed information can be found in the guideline for descriptions on application forms for marketing approval of drugs, etc. under the revised pharmaceutical affairs law: PFSB/ELD Notification No.0210001, Feb 10, 2005.

In the manufacturing methods section of the application form the parameters and acceptable ranges of operational conditions around the described target values and set values are listed. In the manufacturing method field of the product application form the essential operating procedures which ensure the consistent quality of the drug product have to be described. Additionally, a list of the acceptable ranges supporting the information in the above-mentioned field should be attached to the CTD section 1.13 of new marketing authorization applications or partial change applications [32] (Changes in the matters in the manufacturing method field need adequate change control and have to be addressed in a partial change application).[28] This list shall allow a faster regulatory review process by making sure that the reviewers comprehend the CTD.[32]

For changes in the application form that are matters to minor change notifications or non-described matters, it is required to submit tabulated information in the CTD section 1.13 [26] (see Table 1) containing control ranges currently used at the manufacturing site, proven acceptable ranges, and justifications for the established values in the application form. If the acceptable ranges have not been explicitly examined, the fact should be also be mentioned.[32]

Table 1: Matters Subject to Minor Change Notification if Changed. Source: PFSB-ELD-20110117

No.	Process	Product application form	Product master formula, etc.	Proven acceptable range	Rationale for establishing values in application form
		Matters subject to a minor change notification if changed	Control range	Edge of failure if it is confirmed	
001	Step	『20°C』	xx°C - xx°C	xx°C - xx°C	

3.3 Quality by Design (QbD) Approach in the ICH Region

The pharmaceutical product quality initiatives "*Pharmaceutical Current Good Manufacturing Practices* (cGMPs) for the 21st Century – A Risk Based Approach" realizes pathways for the regulation of post-approval changes by using more flexibility and risk based standards,[11] such as quality by design. Quality by design is a systemic approach to drug development including the incorporation of prior knowledge, the use of quality risk management and knowledge management,[15] just as established conditions do.[33] The QbD related guidelines are the ICH guidelines Q8 – Q11, but the principles of the quality by design concept are laid down in the annex of the ICH Q8 guideline, showing how concepts can be put into practice.[15] The concepts needed for the quality by design approach were introduced in the international guidelines between 2009 and 2012.[34]

This systematic approach to pharmaceutical development begins with predefined objectives. By defining the quality target product profile (QTTP), the desired product is characterized and the development goals are set. Also critical quality attributes (CQA) of the drug product, the drug substances and the excipients are defined at the beginning of the process, ensuring that the characteristics, which have an impact on the quality, can be analyzed and controlled. Then an appropriate manufacturing process is selected and a control strategy defined.[15]

In an enhanced QbD approach further elements are included into the concept. When a manufacturing process has been selected, critical material attributes (CMA) and critical process parameter (CPP) can be defined [15] that may impact the intermediate CQA of the process steps[35] and their functional relationship is determined.[15]

Additionally, an enhanced approach, an enhanced product and process understanding, combined with a quality risk management system is used for the establishment of an appropriate control strategy which can include design space, as an example.[15]

The quality by design concept introduces the concept of design space as an optional element. A design space is an established range of material attributes and process parameters that demonstrate the achievement of a consistent product quality. The variables and parameters can be identified and selected for inclusion in the design space by using risk assessment and during process development.[15]

As long as the parameters are within the design space, a movement is not considered as a change. Only the movement out of the approved design space is considered to be a change. The movement out of the range would initiate a regulatory change process.[15]

Further information on the quality by design concept can be found in the DGRA Master thesis “Quality by Design in Pharmaceutical Development and Manufacturing” written by N. Sanghavi in 2015.

4 Post-Approval Change Management Protocol (PACMP) in Europe

4.1 Background

The concept of the post-approval change management protocol was introduced the first time in the guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products 2010/C17/01 in the year 2010 (2010/C17/01, now 2013/C 223/01), supporting variation regulation EC 1234/2008.[36],[37]

The protocol describes specific changes that a company would like to implement during a product's lifecycle and how the company would realize and verify these changes.[38]

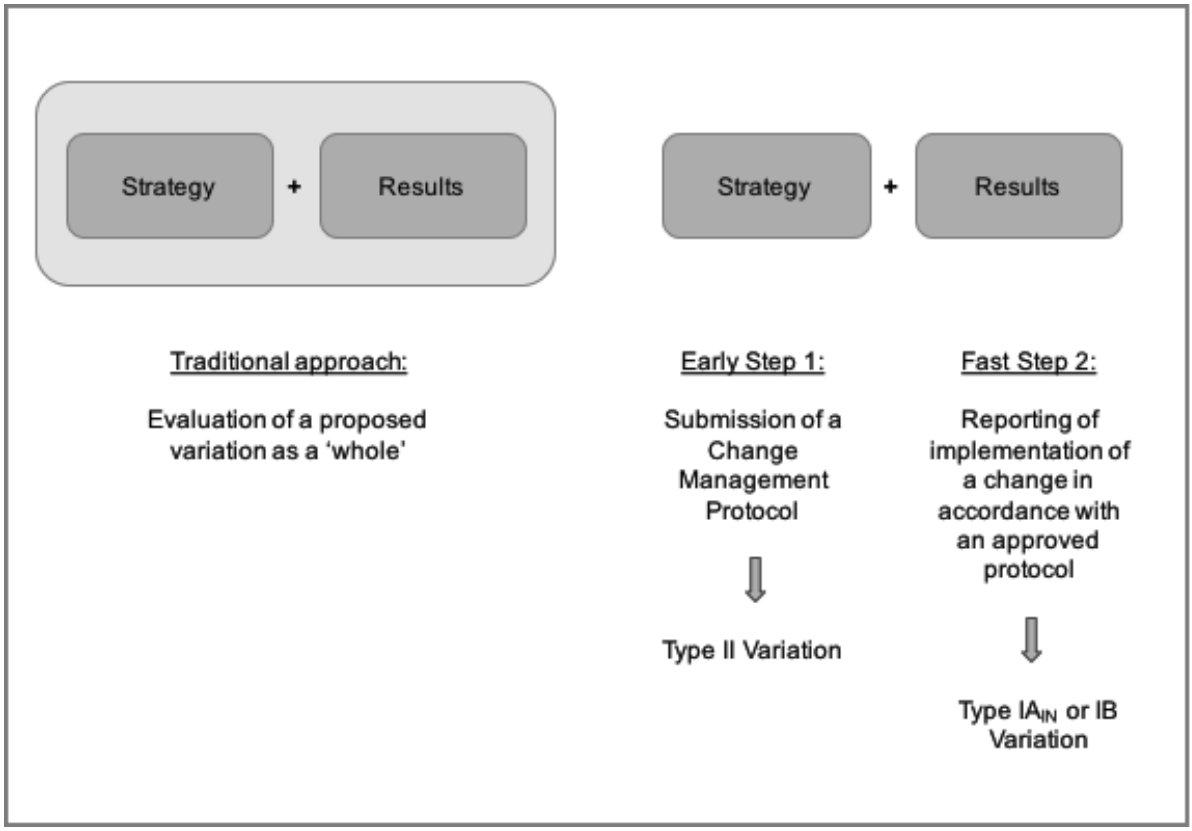

Figure 7: Traditional Variations and Post-Approval Change Management Protocols (following EMA Questions & answers on post-approval change management protocol)

In the traditional approach of change management both, the strategy and the results of a proposed variation are evaluated in one step as a whole. The approach for the post-approval change management protocol is a two-step approach in the assessment of changes. In the first step, the strategy for the change is evaluated. In the later second step, the data, produced based on the agreed strategy from the first step, are evaluated. Under an approved post-approval change management protocol the variations are commonly categorized at least one category lower than they would have been categorized under the traditional approach (see Figure 7).[38]

It is expected that the implementation of a protocol leads to a faster and more assessable implementation of the changes, but the use of a post-approval change management protocol is not mandatory for the pharmaceutical industry.[38]

4.2 Post-Approval Changes according to European Regulations

The European Commission published a guideline on the details of the categories of variations related to the Regulation 1234/2008, as amended. This guideline covers the classification of variations, the procedures as well as the documentation requirements.[36]

The variations are defined and classified in Articles 2 and 3 of the Directive 1234/2008. There are three categorization types of variations, type IA, type IB and type II variations.

Type IA variations are minor variations with “only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned.” Based on Article 8 of the Directive 1234/2008, type IA variations are categorized in two sub-categories: type IA, to be notified to health authorities within 12 months after implementation in so called annual reports. Type IA variations are designated as “do and tell variations”. The sub-category type IA_{IN} variation requires an immediate notification directly after implementation.[39]

Type IB variations are defined in Article 2 of Directive 1234/2008 as variations which are neither minor type IA variations nor major type II variations (nor extensions).[40] Type IB variations are designated as “tell, wait and do variations”.[39] They are minor variations which have to be notified prior to implementation.[39] They are handled in a 30 day procedure. After notification, the marketing notification holder (MAH) must wait 30 days for an opinion of the authority. If no opinion is sent to the MAH within 30 days, the notification may be deemed acceptable and the variation can be implemented.[39]

Type II variations are major variations which could have an impact on the quality, safety, or efficacy of the medicinal product and therefore require approval of the competent authority prior to implementation.[39] Normally type II variations are processed within 60 days, but the time scale might be reduced to 30 days for variations concerning safety issues.[41] The result of the evaluation of type II variations is the preparation of an assessment report. This report is the basis for the final decision or opinion.[39]

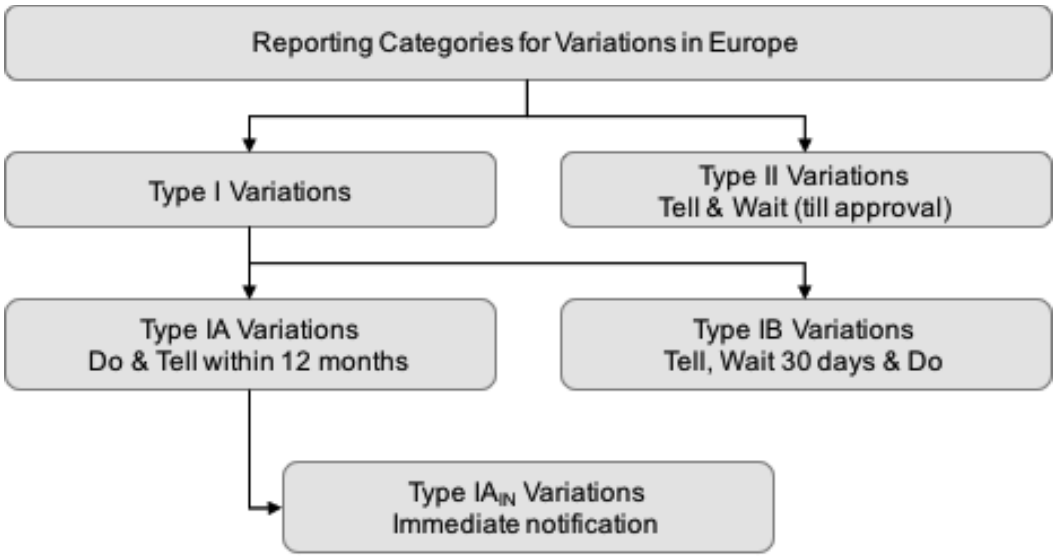

Figure 8: Variation Classification in Europe

A further type of variations has to be considered as extension applications. Such applications will be evaluated with the same procedure as the initial marketing

authorization. The types of application to which it applies are defined in Annex I of the European variation regulation.[39] These include changes to the active substance, a new strength, a new pharmaceutical form or a new route of administration.[40]

4.3 Content and Submission of a Post-Approval Change Management Protocol

The content of the protocol is reliant on the type of the proposed changes. For the purpose of supporting the change proposal, the applicant should submit all relevant information demonstrating adequate knowledge of the change's impact. Adequate scientific knowledge and product and process understanding is demonstrated by the use of an appropriate quality risk management and an effective pharmaceutical quality system. One protocol is specific to one product only, therefore multiple products may not be named in the protocol.[38]

The following content could be contained in the protocol, depending on the type of change:

- Detailed description of the changes and justification for the need for the proposed specific changes within a reasonable timeframe [38]
- Data obtained from development or pilot scale studies supporting the feasibility of the proposed change [38]
- Description of the studies to be performed and the test methods and acceptance criteria and a commitment to update the approved protocol due to relevant changes to the test methods and acceptance criteria or new knowledge or regulatory requirements [38]
- Suitability of the approved control strategy and identification of the impact of the change on the product quality (by risk assessment) [38]

- If applicable, a plan for stability studies should be contained [38]
- Additionally, for small molecule products, a proposal of the reporting category of the change (type IA, IA_{IN} or IB) is needed, whereas changes for biological products shall always be reported as type IB variations.[38]

More than one change can be covered with a single protocol, as long as the simultaneous review of the directly related changes in the same protocol is reasonable.[38]

A post-approval change management protocol may be included in an original marketing authorization application or in an extension application in the section 3.2.R of the module 3. Alternatively, it may be submitted retrospectively as a stand-alone variation (see 4.4 Post-Approval Changes to or under an Approved Post-Approval Change Management Protocol).[38]

When it is submitted as part of the original marketing authorization application (MAA) or an extension application, the evaluation of the proposed protocol will follow the rules of procedure that is applicable to the appropriate marketing authorization application or extension application.[38]

4.4 Post-Approval Changes to or under an Approved Post-Approval Change Management Protocol

The variations classifications guideline (2013/C 223/01) includes specific scopes with regard to a post-approval change management protocol. The introduction of a protocol for the active substance (change no. B.I.e.2) or finished product (change no. B.II.g.2) is classified as a type II variation (see Figure 7). For both changes a detailed description of the proposed change has to be provided as well as the change management protocol related to the active substance or finished product, respectively.[39] The deletion of an approved change management protocol related to the active substance (change no. B.I.e.3) or finished product (change

no. B.II.g.3) does not have any effects on the already approved information in the dossier and is classified as an IA_{IN} procedure type. A justification of the proposed deletion should be provided to the health authority.[39]

There are listed three sub-categories for the implementation of changes foreseen in an approved change management protocol (change no. B.I.e.5 for DS and B.II.g.5 for DP). The implementation of changes not requiring supportive data are classified as type IA_{IN} variations (a), whereas the implementation of changes requiring further supportive data (b) and of changes for a biological/immunological medicinal product (c) are classified as type IB variations.[39]

Changes to an already approved post-approval change management protocol are categorized in change no. B.I.e.4 for DS and B.II.g.4 for DP. For both, drug substance and drug product is made distinction between minor type IB variations (b) and major type II variations (a).[39] Provided that fundamental changes to the content of the protocol are made a new protocol should be submitted, processed as a type II variation.[38]

5 Introduction of the ICH Q12 Guideline

5.1 ICH Q12 - Final Concept Paper

In September 2014, the ICH steering committee endorsed the final concept paper on the ICH Q12 guideline on technical and regulatory considerations for pharmaceutical product lifecycle management [42] to harmonize procedures for managing post-approval manufacturing changes.[43]

Regulatory commitment is interpreted differently in the different regions. The interpretation of how this information relates to the change reporting differs also. The new guideline will clarify regulatory filing requirements during the commercial phase of the product's lifecycle.[42]

The ICH Q12 guideline shall work with the ICH Q8, Q9, Q10 and Q11 guidelines and facilitate the management of post-approval CMC changes in a more predictable and efficient way. In the concept paper is stated that three main issues with regard to change management shall be resolved by the implementation of the ICH Q12 guideline.[42]

The first issue is on the regulatory dossier. A harmonised approach to regulatory commitments shall be investigated and included into the guideline. The purpose of this approach is continual improvement that is enabled by post-approval changes. Additionally, the level of detail and information in the dossier which is necessary for regulatory assessment shall be described for the purpose of creating a more enabling post-approval change management system.[42]

The second issue is on the pharmaceutical quality system aspects of the ICH Q10 guideline. Criteria for a harmonized risk-based change management system shall be established. The guideline should reinforce the need of a knowledge management system maintenance, ensuring continuous product and process information over the entire product lifecycle.[42]

The third issue is on post-approval change management plans and protocols. The concept of a post-approval change management plan shall be introduced. The plan can be used to identify proactively post-approval changes as well as the mechanism to submit and assess these changes. Also criteria for post-approval change management protocols shall be established. The criteria can be adopted by the ICH region. Additionally, enhanced product development and control strategy approaches, such as quality by design, shall be encouraged. These enhanced approaches again can provide opportunities for scientific and risk-based foundations for post-approval change management plans.[42]

With the implementation of the new guideline the representatives of the international council on harmonization intend to bring various benefits for the industry and the regulatory authorities, such as:

- Harmonisation of change management for marketed products [42]
- Facilitation of risk-based regulatory oversight [42]
- Assistance for industry in maintaining the dossier and ensuring conformance by using harmonised approaches and interpretations of expectations [42]
- Highlight the application of the control strategy as a key component of the regulatory commitment in the dossier [42]
- Provision of more regulatory tools for change management, e.g. post-approval change management plans, post-approval change management protocols, comparability protocols and application forms [42]
- Assistance in continual improvement of the manufacturing process and control strategy [42]

5.2 Progress in Drafting the ICH Q12 Guideline

The current working draft of the ICH Q12 guideline contains chapters on categorization of changes, established conditions, post-approval change management protocols, product-specific lifecycle management (PSLCM), pharmaceutical quality system and change management, relationship between assessment and inspection, and approaches to streamline changes to marketed products. Apart from that it includes an introduction, a glossary, references and illustrative examples and case studies. In total, it comprises eleven chapters.[44]

Established conditions will be defined as “legally binding information defined in an approved marketing authorization application. Any change to an established

condition, as defined in an approved application, would initiate a post-approval regulatory submission." [1]

Currently, the draft guidance states, that the greater product and process knowledge, that is gained in an enhanced development approach, can better inform the critical quality attributes and resulting critical process parameter. Then fewer established conditions linked to critical process parameters need to be justified. On the contrary, in a traditional approach the established conditions contain a considerable number of input together with the control of output elements, because in the traditional development approach the relationship between input parameters and critical quality attributes is not well understood.[1]

Initially, the expert working group of the international council on harmonization considered a four tier scheme for post-approval changes. The risk categorization of the changes should be distinguished by those four reporting categories, whereas the first three reporting categories would be subject to reporting established conditions; thus, they would be legally binding.[1] However, in the meantime there was a consensus that there should be only three reporting categories for post-approval changes, prior approval, notification, and do and record procedures:[44]

Prior approval changes are considered to have sufficient risk to product quality and require therefore review and approval before they are implemented.[44]

Certain moderate to low risk changes do not need prior approval but notification. They are communicated as a formal notification to the agencies. The notification takes place, according to regional requirements, either in advance of implementation or within a defined period of time after implementation.[44]

The changes that have the lowest risk are defined as do and record procedure. These changes are managed and documented internally within the pharmaceutical quality system and do not need to be reported to the agencies.[44]

6 Discussion and Conclusion

6.1 Established Conditions

The FDA draft guidance on established conditions states which manufacturing changes do not need to be reported. The guidance has been drafted as it seemed to remain confusion with regard to which changes do not need to be reported to the agency at all.[1] Out of that reason the guidance clarifies which changes are so minor that they can be managed within the internal pharmaceutical quality system of the pharmaceutical companies.[44] But by reading the guidance it seems to be quite superficial. The reason therefore might be that the guidance is fully in support of the Q12 guideline and the FDA may withdraw this guidance if the Q12 will be finalized within the given timelines.[45]

By the application of established conditions the submission of unnecessary supplements shall be reduced and continual process improvement is encouraged. The manufacturer can also be more flexible in the use of risk-based principles for change control. Additionally, transparency is increased, because established conditions provide information to the agencies on the changes manufacturers plan to make in future.[1]

By developing the established conditions table according to the criteria given, the applicant is prompted to plan future changes proactively and to assess their risk already in advance. The regulatory pathway with regard to reporting category of those changes is then already known at time of approval, which should increase the efficiency in implementing the changes. The correct understanding of established condition also provides pathways to better regulate post-approval changes by using more flexibility and risk-based principles.[11]

For the establishment of established conditions a robust pharmaceutical quality system and overall control strategy is essential. Especially for changes in non-established conditions, which are only managed and documented internally by the manufacturer, an effective PQS should be in place. For change management,

which is one of the four key elements of a pharmaceutical quality system, only limited information is provided in the ICH Q10 guideline.[42]

There are also only limited details given in the ICH Q9 guideline on the expectations of knowledge management, one of the PQS enabler.[42] Knowledge that has been gained during the lifecycle of a product could be more effective used when the knowledge management process is defined and described more in detail, so that manufacturer and health authorities can profit from a robust knowledge management.

Established conditions that should be provided in form of a summary in module 2 of the new drug application in the US are captured in the Japanese application form for a new drug application in Japan.

The Japanese application form contains all relevant quality information on specifications and manufacturing of the drug product. For the correct completion of the application form the classification of minor change notifications and partial change applications is necessary.[26] The rationale for the classification is similar to the rationale for proposing established conditions to the FDA. It should be based on critical quality attributes and critical process parameters which may affect the critical attributes. Additionally, a high product and process understanding should have been obtained and an overall control strategy should have been developed in advance. In this way, the applicant already demonstrates the ability to consistently manufacture the product of the intended quality at the time of new drug application.[26]

The criteria for a pass-fail decision in Japan are based on the application form only and are thus specifications of the final drug product and process control parameters.

The content of the approved application form is legally binding, whereas the major contents in the quality overall summary and in module 3 are not legally binding. Only the contents written in the application form are elements of the change control system in Japan. This is a major difference to the submissions in the

European Union and the United States of America, where also the content of the modules 2 and 3 are subject of the approval.

The use of the application form for new drug applications and post-approval changes in Japan is one of the most prominent differences compared to the systems in the other ICH member states. Because of this difference there might be a greater risk to be non-regulatory compliant.[29]

The two post-approval change management systems, approved matters in Japan and established conditions in the US, have similar approaches. Both are binding information regarding the manufacture and control that ensure the quality of a pharmaceutical product. The regulatory commitments are proposed by the applicant and approved by the agencies in both cases. If the marketing authorization holder wants to change an approved item, an approval or a notification is required.

Just as established conditions the content of the Japanese approved form is very flexible, because the classification of the reporting categories depends on the control strategy of the registered product. Furthermore, it has the benefit of transparency. The reporting categories for each element are known with approval. Thereby it is a good tool to share the knowledge about the regulatory process required between the marketing authorization holder, or rather the manufacturer, and the health authority. Additionally, there remains no confusion regarding the appropriate reporting categories for quality changes.[26] The risk-based principles of established conditions and approved matters allow the health authorities to better regulate post-approval changes because they can focus on most important information and changes.[18]

The concept of quality by design, that was introduced between 2009 and 2012 in international guidelines,[34] can be seen as a predecessor of the established conditions concept as it is also a risk-based approach, leading to a reduced number of changes to be filed. Additionally, it is a systemic approach that works around well-defined objectives (critical quality attributes).[46]

Quality by design is recommended as standard control strategy by many organizations because it is nearly impossible to implement an effective quality control by testing a product only after it has been completely manufactured.[46]

By using the quality by design approach, which is based on profound science and quality risk management, product and process understanding and process control are emphasized.[47] In turn, the process understanding is leading to continuous process improvement and it makes it easier to determine the impact of the change on the quality of the drug substance or drug product.[48]

The optional element of the quality by design approach, the concept of design space, is a multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality.[49]

The quality by design paradigm, combined with design space concept, brings more regulatory flexibility. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Process changes within the design space do not require review or approval. Only when the parameters move out of the design space it is considered to be a change and would initialize a regulatory change procedure.[47] Process improvements concerning process consistency and throughput during the product life cycle could take place with less post-approval submissions.[49]

In summary, the regulatory burden of low impact changes is reduced by the application of the above-mentioned approaches.[45]

6.2 Post-Approval Change Management Protocol

With the opportunity of applying a post-approval change management protocol there exists an option for a faster and more predictable implementation of post-approval changes.[37]

Making use of the PACMP could have some advantages. One of them is the predictability when such a protocol is applied. As soon as the protocol, containing the proposed strategy and tests to verify the effect of the change on product quality, is approved,[38] an expedited review of a major change with no requests for further data can be expected.[37] Out of that reason this stepwise approach leads to a faster and more predictable implementation of post-approval changes.[38] And once approved, a specific change can be implemented repeatedly under a single protocol.

Also on a global scale, it might have benefits to apply a post-approval change management protocol. In some emerging market countries, the approval of a change is dependent on an EU-approval. The submission to those countries could be accelerated by the use of post-approval change management protocol.

Before developing a post-approval change management protocol for small molecule products, the following should be taken into consideration: Many variations classified as type II variations for biologicals are only type IB variations for small molecule products. Thus, using the procedure of the post-approval change management protocol is less incentive for small molecules, because the first step of this protocol is a type II variation by default. Therefore, for small molecule products it could be worth to make use of this concept when the protocol is put already in the initial application. In this case, the reporting category will probably be lower.[37] For small molecule products it would also be valuable for more significant changes, which are classified as major type II variations.[39]

In the US is used a similar concept to the PACMP, the comparability protocol (CP), which was introduced in 2003. The requirements of both concepts are very similar in the US and the EU.[38, 50] The main difference is that PACMP have to be product specific whereas one comparability protocol can also be used across multiple products.[38, 50-51]

On the contrary, in Japan there is no similar concept to accept a protocol only on planned changes like the post-approval change management protocol in the EU and the comparability protocol in the US.[31]

In general, this concept of post-approval change management protocol may help the industry to handle changes more efficiently while maintaining regulatory agency oversight.[52]

6.3 ICH Q12 guideline - Harmonization of the Post-Approval Change Management Systems

Under the current systems the management of changes on a global scale is complex, unpredictable and time consuming [1]

That is why there is a wide interest in the development of the ICH Q12 guideline[44] as it could provide necessary tools for advanced planning of changes at the start of the lifecycle management process.[3]

The ICH Q8 to Q11 guidelines use science and risk-based approaches for the change assessment. However, the main focus of the ICH guidelines was on the development side of the process. The ICH Q12 guideline will now fill the gaps for marketed products by addressing post-approval changes.[44]

With the development of the ICH Q12 guideline, the post-approval change management systems with regard to established conditions and post-approval change management protocol, that have previously been discussed in this master

thesis, will be harmonized. It is not yet public known how the systems will be put into practice.

The key element for the ICH Q12 guideline will be the definition of the reporting categories. Only when these have been defined it is possible to go further into detail in this guideline for post-approval change management with regard to established conditions and post-approval change management protocols.

It is necessary to focus on the identification of critical elements to ensure product quality.[18] During the development of the ICH Q12 guideline it is to be clarified how the established conditions will be set from the CTD module 3 and how and where the established conditions will be described in the marketing authorization application.[31] The reporting of the established conditions also needs to be clarified. It has to be decided if it will be handled as in the US and in Japan, that changes on non-established conditions are non-reportable and should be made available upon request or if also non-established conditions are always reportable.

There are still a number of critical issues and gaps to address before the guideline can be approved. For established conditions, there is a need for a decision tree to identify and report established conditions. There is a need to elaborate a performance based approach and there is also a need for illustrative examples. Further gaps are still in the chapter for product-specific lifecycle management strategy. There is also a need to specify how the guidance could be applied for biotech products and vaccines.[44]

But it is a difficult task to circumvent already existing regulations without developing a new formal procedure.[1]

It might also be difficult to harmonize the concept of established conditions. On the one hand, if the established conditions are not defined sufficiently detailed, there might be a scope of interpretation. This would result in different definitions of established conditions, depending on the reviewing authority. At the end, a company might have three different approvals in the ICH region with three different defined established conditions, a parameter that is an established condition in one

approval, might be a non-established condition in another one. The maintenance would then be very complex.

On the other hand, established conditions could rely on trust and experience. The more compliance and experience a company has shown in the past, the more this company might handle changes only under its pharmaceutical quality system.[45]

For the harmonized approach of established conditions it might also be possible that an update of the current national reporting regulations is needed in the ICH countries, such as the European variation classification guideline.[45]

The compatibility of the proposed pathways with the pharmaceutical legislation in the different regions is very important. This might not only be challenging for the establishment of established conditions. In the case of the post-approval change management protocol it is of high importance that the application of this concept is worthwhile. According to the current EU variation classification guideline most changes of small molecule products are type IB variations, thus the initial step 1 of the post-approval change management protocol is higher classified. A downgrade to type IA variations might be a possibility but in most cases not sufficient for the effort. Out of that reason the application of the post-approval change management protocol for small molecule products is only useful for the few higher change types and when it is submitted directly with the initial marketing authorization application.

Another possibility could be that the step 2 of the protocol could be based on a risk assessment. The changes would be handled only under the PQS as do & record changes. On the other hand, a reporting for the second step of the protocol might be useful for receiving a formal acknowledgement of change approval that can be used for submission in other territories if needed. The application of the protocol for small molecule products might also be more attractive to the companies when it can be used across several products.[53]

For Japan, it will also be difficult to implement the concept of the post-approval change management protocol, because they do not have a similar concept to the protocol as the EU and the US already do. Additionally, in Japan exist also less

reporting categories than in the US and the EU. Without changing the current national regulations, it will be hard to incorporate the concept,[53] because by the use of such a protocol, the changes classified as PCA could only be downgraded to MCN in step 2 of the protocol.

7 Outlook

The implementation of the Q12 guideline could allow that more variations could be introduced under the pharmaceutical quality system without the need of regulatory approval or notification. It could turn out to be a shift in paradigm in terms of how post-approval changes are processed in a global level, as some of the non-ICH countries are already beginning to adopt post-approval change management systems that are more in line with those of the EU and the US.[3]

It is expected that the guideline will be released for public comment in the third quarter of the year 2017.[3] Adoption and implementation of the ICH Q12 guidance is then expected in the second quarter of the year 2018.[3]

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9 Annex

9.1 Annex I - Sections of CTD that Typically Contain Established Conditions

Table 2: Sections of CTD that Typically Contain Established Conditions. Source: Draft Guidance Temp 05/22/15

CTD Section	Section Title	Contains Established Conditions	Examples of Established Conditions
3.2.S	DRUG SUBSTANCE		
3.2.S.1	General Information		
3.2.S.1.1	Nomenclature	X	Established Name or Proper Name (for Biologics)
3.2.S.1.2	Structure	X	For a New Chemical Entity: Structure of the drug substance, including stereochemistry, molecular formula, molecular mass For Biotech Products: Schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass
3.2.S.1.3	General Properties		
3.2.S.2	Manufacture		
3.2.S.2.1	Manufacturer(s)	X	Name, address, manufacturing steps and/or type of testing, and responsibility

3.2.S.2.2	Description of Manufacturing Process and Process Controls	X	Sequential procedural narrative, including certain information in the control strategy that assures process performance and drug substance quality, such as: identification of steps, process controls and parameters (with ranges), equipment and operating conditions (including target settings), input materials, and intermediates.
3.2.S.2.3	Control of Materials	X	Material specifications (tests, analytical procedures and acceptance criteria) For Biologicals: Source of materials (e.g. cell and seed source, raw materials) and specification of materials (e.g., tests, analytical procedures and acceptance criteria)
3.2.S.2.4	Controls of Critical Steps and Intermediates	X	Critical process steps: Tests and acceptance criteria that are part of the overall control strategy (including microbial control strategy) Intermediates (e.g., isolated intermediates): Specifications (tests, analytical procedures and acceptance criteria) and hold times
3.2.S.2.5	Process Validation and/or Evaluation		
3.2.S.2.6	Manufacturing Process Development		
3.2.S.3	Characterization		
3.2.S.3.1	Elucidation of Structure and other Characteristics		
3.2.S.3.2	Impurities		
3.2.S.4	Control of Drug Substance		
3.2.S.4.1	Specification	X	Drug substance specifications (tests, analytical procedures and acceptance criteria)

3.2.S.4.2	Analytical Procedures	X	Parameters and criteria for analytical procedures for drug substance specifications that are part of the overall control strategy
3.2.S.4.3	Validation of Analytical Procedures		
3.2.S.4.4	Batch Analyses		
3.2.S.4.5	Justification of Specification		
3.2.S.5	Reference Standards or Materials	X	Qualification protocols for new and existing reference standards or materials
3.2.S.6	Container Closure System	X	Selected container closure system and controls
3.2.S.7	Stability		
3.2.S.7.1	Stability Summary and Conclusions		
3.2.S.7.2	Post-approval Stability Protocol and Stability Commitment	X	Tests, analytical procedures and acceptance criteria; storage conditions; shelf life; post-approval testing protocol; and commitment(s)
3.2.S.7.3	Stability Data		
3.2.P	DRUG PRODUCT		
3.2.P.1	Description and Composition of the Drug Product	X	Description and composition for each strength including list of components, quality standard for the components (e.g., USP or NF), grade, amount of each in the formulation, function of the components in the product Note: This also includes a description of accompanying diluents or devices
3.2.P.2	Pharmaceutical Development		
3.2.P.2.1	Components of the Drug Product		
3.2.P.2.1.1	Drug Substance		
3.2.P.2.1.2	Excipients		
3.2.P.2.2	Drug Product		
3.2.P.2.2.1	Formulation Development		

3.2.P.2.2.2	Overages		
3.2.P.2.2.3	Physicochemical and Biological Properties		
3.2.P.2.3	Manufacturing Process Development		
3.2.P.2.4	Container Closure System		
3.2.P.2.5	Microbiological Attributes		
3.2.P.2.6	Compatibility		
3.2.P.3	Manufacture		
3.2.P.3.1	Manufacturer(s)	X	Name, address, manufacturing stepsa and /or type of testing, and responsibility
3.2.P.3.2	Batch Formula	X	Commercial scale batch formula
3.2.P.3.3	Description of Manufacturing Process and Process Controls	X	Sequential procedural narrative, including certain information in the control strategy that assures process performance and product quality, such as: identification of steps, process controls and parameters (with ranges), equipment and operating conditions (including target settings), input materials For products purporting to be sterile, the control strategy should include details regarding the product or component sterilization methods and/or aseptic manufacturing operations
3.2.P.3.4	Controls of Critical Steps and Intermediates	X	Critical process steps: Tests and acceptance criteria that are part of the overall control strategy (including microbial control strategy) Intermediates (e.g., in-process blend): Specifications (tests, analytical procedures and acceptance criteria)

3.2.P.3.5	Process Validation and/or Evaluation		
3.2.P.4	Control of Excipients		
3.2.P.4.1	Specifications	X	Specifications (tests, analytical procedures and acceptance criteria) for all in-coming materials
3.2.P.4.2	Analytical Procedures	X	Parameters and criteria for analytical procedures for excipient specifications that are part of the overall control strategy
3.2.P.4.3	Validation of Analytical Procedures		
3.2.P.4.4	Justification of Specifications		
3.2.P.4.5	Excipients of Human or Animal Origin	X	List of excipients of human or animal origin, source and associated controls
3.2.P.4.6	Novel Excipients	X	List of novel excipients and associated controls
3.2.P.5	Control of Drug Product		
3.2.P.5.1	Specification(s)	X	Drug product specifications (test, analytical procedure and acceptance criteria)
3.2.P.5.2	Analytical Procedures	X	Parameters and criteria for analytical procedures for drug product specifications that are part of the overall control strategy
3.2.P.5.3	Validation of Analytical Procedures		
3.2.P.5.4	Batch Analyses		
3.2.P.5.5	Characterization of Impurities		
3.2.P.5.6	Justification of Specification(s)		
3.2.P.6	Reference Standards or Materials	X	Qualification protocols for new and existing reference standards or materials

3.2.P.7	Container Closure System	X	Selected container closure system and controls
3.2.P.8	Stability		
3.2.P.8.1	Stability Summary and Conclusion		
3.2.P.8.2	Post-approval Stability Protocol and Stability Commitment	X	Tests, analytical procedures and acceptance criteria; storage conditions; shelf life; post-approval testing protocol; and commitment(s)
3.2.P.8.3	Stability Data		
3.2.A	APPENDICES		
3.2.A.1	Facilities and Equipment	X	List of all facilities, including name, address, manufacturing steps and/or type of testing, and responsibility
3.2.A.2	Adventitious Agents Safety Evaluation		
3.2.A.3	Novel Excipients	X	See 3.2.P.4.6 above
3.2.R	Regional Information		
	Executed Batch Records		
	Method Validation Package		
	Comparability Protocols17	X	Dependent on the proposed change
3.3	Literature References		

Eidesstattliche Erklärung

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

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Unterschrift