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CHANGE MANAGEMENT SYSTEMS IN THE ICH REGION LIKE JAPAN AFTER APPROVAL WITH AN EMPHASIS ON "ESTABLISHED CONDITIONS

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Abstarct: Global post-approval change management is difficult, uncertain, and time-consuming. There are many systems in place even within the ICH region. Different national protocols for managing post-approval modifications have been established in the US, Japan, and Europe. To make it clear which CMC changes require FDA reporting, the FDA published the guidance on established conditions in 2015. While some CMC modifications can only be made in accordance with the pharmaceutical quality system (PQS) and its enablers, as outlined in the industry Q10 guidance, established conditions are defined as the product description, manufacturing process, facilities and equipment, and components of the control strategy. Since Japan's Pharmaceutical Affairs Law was updated in 2005, the PMDA has had a comparable mechanism. Since the 2005 revision of Japan's Pharmaceutical Affairs Law, which improved post-marketing measures, the PMDA has already had a system akin to this. In contrast to the US and EU, Japan includes a synopsis of the key components of the application in module 1 of the NDA. The information contained in the synopsis is authorized and legally binding. The post-approval change management protocol, on the other hand, is a two-step method for evaluating changes that was developed by the EU in 2010. The classification of changes may be less than it would have been under the conventional method if a post-approval change management strategy had been used. A harmonization of post-approval modifications for marketed drugs within the ICH regions is currently being worked on by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. The ICH Q12 guideline is not yet accessible to the general public. The ICH Q12 guideline's current working draft includes chapters on post-approval change management procedures, established conditions, and change classification, among other topics. A paradigm shift in how post-approval adjustments are processed globally could occur if the guidelines are implemented.

Key Words: Post Approval changes with ICH regions, Pharmaceutical quality system (PQS), ICH Q12 guideline, Established Conditions.

I. INTRODUCTION

Global post-approval change management is currently difficult, uncertain, and time-consuming [1]. Even within the ICH region, there are disparate systems in place, and the classification of the reporting categories varies across nations. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has three founding members: the United States, Japan, and Europe. Each of these countries has set up a risk-based post-approval modification management system.

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

The industry and authorities have adopted the ICH idea as a way to standardize drug regulatory criteria. The three regions that the ICH founders are focusing on are Japan, the US, and Europe (the so-called TRIADE). The Health Authorities and Associations in each region serve as representatives.[2] South Korea, Brazil, Switzerland, and

Canada are additional members.[3] In order to ensure that safe, high-quality, and effective medications are produced and registered, the ICH seeks to increase global uniformity in drug registration. In order to accomplish this, industry and regulatory professionals collaborated to create the ICH guidelines.[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]

Guidelines have been harmonized thus far on four primary topics: multidisciplinary (M-guidelines), safety (S-guidelines), quality (Q-guidelines), and efficacy (E-guidelines). The quality rules govern the themes of Chemistry, Manufacturing, and Control (CMC) for pharmaceuticals. Among the things that have been harmonized are risk management, stability studies, and impurity threshold definition.[6]

Established conditions

This guideline establishes a harmonised approach to defining which elements in an application are considered necessary to assure product quality and therefore would require a regulatory submission if changed post-approval. These elements are being defined in this guideline as “Established Conditions for Manufacturing and Control” (referred to as ECs throughout this guideline).

ECs in a Regulatory Dossier

The scientific risk-based methods that can be applied to the definition of ECs and their reporting categories are covered in this chapter. The scientific risk-based methods discussed in this chapter may be taken into consideration, or regional legal frameworks, enhanced by regulation and advice, may define ECs and their reporting categories.

ECs and supporting documentation are included in every regulatory dossier. Supporting information is sent to regulators to share development and production information at a suitable level of detail, but it is not regarded as an EC. Finding the components of CMC that are ECs and those that are supporting information is based on knowledge acquired throughout the product lifecycle, including pharmaceutical development and the characterization of chemical and biological drug substances and drug products. An MAH should clearly identify the elements of CMC which they consider to be an EC and those which they consider to be supportive information. The rationales for the ECs are provided in the appropriate CTD modules.

Similarly, the rationales for the associated reporting categories for changes to the ECs should be provided

in the appropriate CTD modules. The regulator assesses the ECs with respect to established scientific guidelines.

II. METHODOLOGY

Approved Matters as Established Conditions in Japan

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]

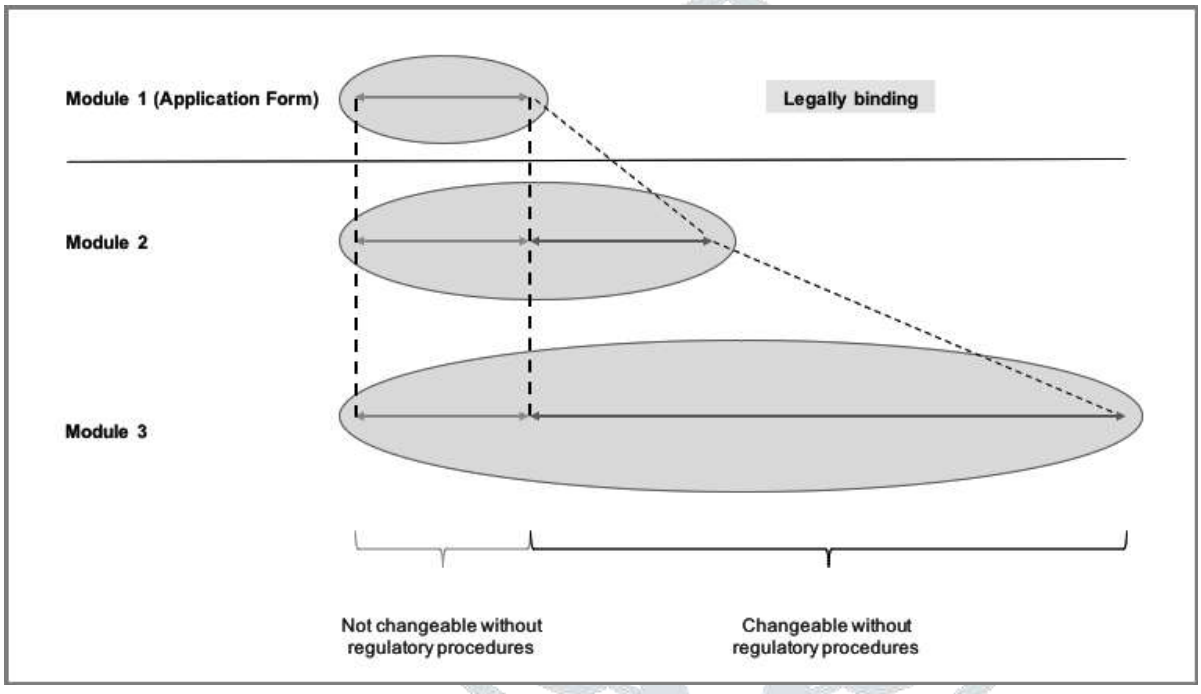

Figure 1: Changeable Content of Modules in Japanese NDA (following Kishioka 2016)

The applicant-provided content in module 1.2 of the CTD's J-NDA application form is treated as "matters subject to approval."[23, 26] As a result, the information presented in that format is an authorized and legally binding matter.[23] A change application is filed whenever there is a modification to the application form's content and, consequently, to the approval letter.[25]

A new drug application's module 2 connects the application form and module 3 by providing the quality overall summary (QoS) in Japanese. It is one of the most important review documents since the first reviewers assess module 2, and they go on to modules 3 through 5 of the application in the CTD format when they require more specific information.[24] .

Post-Approval Changes according to Japanese Regulations

The Pharmaceutical and Medical Device Act in Japan specifies the legal foundation for modifications to a marketing approval. Only when the certified product's identification is unaffected and stays the same are changes permitted.[27] A new approval application is needed if the active substance, its composition, or the dosage form change. There are now two reporting categories: partial change approval and minor change notice.[27] A marketing permission holder may request a partial modification of the permitted goods in the approval. The Pharmaceutical and Medical Device Act's (PMDA) Article 14, Paragraph 9 describes partial change applications (PCA). "Change in the currently approved items of the medicinal product" is the Japanese term for a partial change.[27] To put it another way, if the applicant changes the content of the current approval, a partial

modification application must be submitted.[23] Partial modifications can also be defined as those that need proper change control.[28] The typical approval period for this significant modification is 12 to 18 months.[29]

According to PMDA Article 14 Paragraph 10, changes that only call for minor change notifications (MCN) are permitted.[27] While a partial change necessitates an application for permission, a small modification to an existing approval does not. Within 30 days following the change's implementation, the maker must inform the health authority, attesting that the modification has no effect on the medication's quality. At the manufacturing site, relevant data pertaining to the change must be filed. Later on in a GMP inspection, GMP inspectors will verify that the change technique is adequate.[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

- 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]

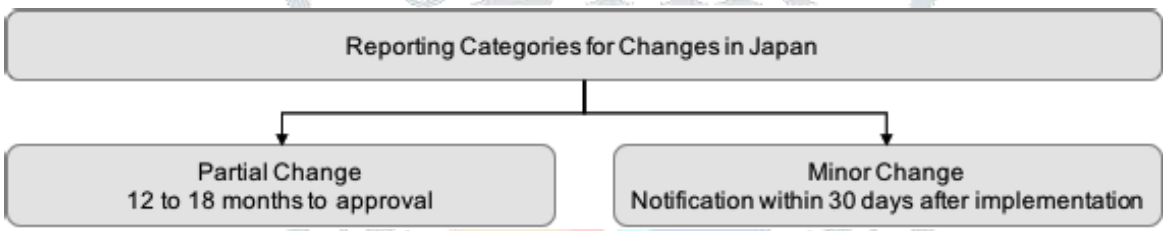

Figure 2: Change Classification in Japan.

- CQAs and CPPs should generally be the basis for the PCA/MCN change classification, as they may have an impact on the CQAs, development data, prior knowledge, and the overall control approach.[26]

Lastly, the following explains the distinctions between a minor change notification and a partial change application: While a process parameter that just controls the quality endpoint criteria is filed as a minor change notice, a change in the principle of a critical process's unit operation or a change in a process control criterion as a quality endpoint criterion is filed as a partial change application.[23]

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]

Because the applicant personally separates and specifies 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, it is already necessary to identify the critical and non-critical parameters in the manufacturing process for the new drug application [25].[28]

It is necessary to include the standard batch sizes or process parameters (such as temperature, pH, duration, etc.) that have a high significance for the quality of the drug substance or drug product and act as target and set values. Any future changes to these issues would require a partial change approval application (PCA).[30] (Refer to 3.2.2, Japanese Regulations on Post-Approval Changes.) It is necessary to include target values and set values of standard batch sizes or process parameters that have little bearing on the quality of the drug substance or drug product. A minor change notification (MCN) would be required if these issues were to change in the future.[30] (Refer to 3.2.2, Japanese Regulations on Post-Approval Changes.)

As a minor change notification matter, values other than target and set values, including reagent concentrations, which have little bearing on the quality of the drug substance or drug product, must be enclosed in "".[30]

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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	

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]

Predetermined goals are the first step in this methodical approach to pharmaceutical development. The quality target product profile (QTTP) is used to define the development goals and characterize the desired product. Additionally, the drug product's critical quality attributes (CQA), drug substances, and excipients are specified at the start of the process to allow for the analysis and control of the qualities that affect the product. After that, a control plan is established and a suitable production method is chosen.[15]

An improved QbD technique incorporates additional components into the idea. Following the selection of a manufacturing process, the functional relationship between critical material attributes (CMA) and critical process parameters (CPP) can be established [15], which may have an effect on the intermediate CQA of the process steps [35].[15]

The development of a suitable control plan, which may incorporate design space, for instance, also involves an improved methodology, a better understanding of the product and process, and a quality risk management system.[15]

Design space is presented as an optional component in the quality by design idea.

III. RESULTS AND DISCUSSIONS

Which manufacturing changes are exempt from reporting requirements are specified in the FDA draft guidance on established conditions. The guidance was created because it appeared that there was still uncertainty about which adjustments did not require any reporting to the agency.[1] For this reason, the guidelines make it clear which changes are so small that they can be handled by the pharmaceutical companies' own pharmaceutical quality system.[44] However, after reviewing the guidelines, it appears to be quite superficial. Therefore, the explanation could be that the FDA may withdraw this guidance if the Q12 is finalized within the specified timeframes, even though the guidance completely supports the Q12 guideline.[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]

All pertinent quality information about the drug product's specs and manufacture is included in the Japanese application form. Classifying minor change notices and partial change applications is essential for the

proper completion of the application form.[26] The classification's justification is comparable to that of the FDA's proposed established conditions. Critical quality attributes and critical process factors that could influence the critical attributes should serve as its foundation. Furthermore, a comprehensive control strategy should have been created beforehand, along with a high level of product and process awareness. In this sense, at the time of the new medication application, the applicant already shows that they can reliably produce the product of the desired quality.[26]

IV SUMMARY

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

V. CONCLUSION

A standardized, risk-based, and scientific framework for handling post-approval CMC modifications throughout the product lifecycle is offered by the ICH Q12 guideline. A key regulatory instrument in this framework is Established Conditions, which specify the precise manufacturing and control components required to guarantee product quality and, as a result, necessitate regulatory notification if altered. Change management systems based on ECs allow for risk-based categorization of changes, balancing the degree of regulatory oversight with the potential impact on product quality. Across ICH regions, ECs provide clarity and predictability by clearly defining which parameters are regulatory commitments and which can be adjusted under the company's Pharmaceutical Quality System (PQS) without prior approval.

In addition to ECs, the Product Lifecycle Management (PLCM) document and Post Approval Change Management Protocols (PACMPs) offer a predetermined, structured process for effectively executing specific changes.

The pace of implementation varies:

- The wide use of ECs is made possible by the US framework's strong alignment with Q12.
- Some legislative amendments are still pending, and the EU has only largely adopted EC notions.

o Although full integration is still under progress, Japan has progressed adoption in response to PMD Act amendments2.

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