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Development of a Logic Model for Promoting Incorporation of the Concepts of Impurity-Related ICH Guidelines into Pharmacopoeias Based on Cause and Effect Analysis

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In line with the recent globalization of the drug supply chain and promotion of the use of generic drugs worldwide, quality assurance is required for drugs globally. In particular, controlling impurities is one of the biggest areas of interest regarding pharmaceutical quality, and it is desirable that the latest scientific standards harmonized in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) are not only implemented in approval applications but also incorporated in pharmacopoeias which are public standards to ensure pharmaceutical quality more widely. However, incorporation into a pharmacopoeia takes time because careful consideration is required owing to the characteristics of a pharmacopoeia that is widely used for drugs, including those already on the market. To consider a smooth approach for the incorporation, we retrospectively examined approaches to incorporate the concepts of the ICH Q3C, Q3D, and M7 guidelines covering residual solvents, elemental impurities, and mutagenic impurities which are particularly toxic impurities into the European Pharmacopoeia, United States Pharmacopoeia-National Formulary, and Japanese Pharmacopoeia, with approaches to implement these guidelines into approval processes in Europe, the U.S., and Japan. We also identified barriers and facilitators to this goal via cause and effect analysis. Moreover, we developed a logic model for the smooth incorporation of the concepts of impurity-related ICH guidelines. We expect that our proposed approach will be applied as a framework to smoothly incorporate the results of international harmonization activities for controlling impurities into each pharmacopoeia.

Key words impurity; Japanese Pharmacopoeia; European Pharmacopoeia; United States Pharmacopoeia-National Formulary; International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; cause and effect diagram

Introduction

Securing quality, efficacy, and safety is essential for drugs, and ensuring proper quality is important for ensuring the efficacy and safety of drugs constantly. A pharmacopoeia plays a key role in providing standards for quality assurance. In addition, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines are used for quality assurance. Both pharmacopoeias and the ICH guidelines contribute to quality assurance for drugs.

According to “Good Pharmacopoeial Practices” published by WHO, a pharmacopoeia has a core mission to protect public health by creating and making available public standards to help ensure the quality of drugs, and its standards support regulatory authorities in controlling drug quality and provide tools for both the user and procurer.5) Some 60 pharmacopoeias exist worldwide, such as the European Pharmacopoeia (Ph. Eur.) in Europe, the United States Pharmacopoeia-National Formulary (USP-NF) in the U.S., and the Japanese Pharmacopoeia (JP) in Japan.2,3) A pharmacopoeia is generally composed of general rules, general tests, processes and apparatuses, individual monographs, and general information under general notices applied to the entire pharmacopoeia. A pharmacopoeia is periodically revised to apply appropriate quality control to even already market drugs with the accumulation of new knowledge. The revisions include the incorporation of new sciences and technologies and reflect reviews of existing contents based on the latest concepts.

Although a pharmacopoeia is a tool for ensuring the quality of drugs including already marketed drugs, ICH guidelines have been developed to harmonize the scientific and technical aspects of approval assessments for new drugs as their initial objective since 1990.4) However, as the ICH reflection paper on “Further Opportunities for Harmonization of Standards for Generic Drugs” in 2018 stated that many ICH guidelines are applicable to generic drugs (e.g., ICH Quality Guidelines), the application of ICH quality-related guidelines is currently expected for both new and generic drugs. To date, more than 20 quality related guidelines have been harmonized in the ICH, and the control of impurities is one of the high-interest areas because it affects drug safety.

Impurity-related ICH guidelines include ICH Q3A “Impurities in New Drug Substances”6) and ICH Q3B “Impurities in New Drug Products,”7) which describe general points for control impurities, and ICH Q3C “Impurities: Guideline for Residual Solvents,”8) ICH Q3D “Guideline for Elemental Impurities,”9) and ICH M7 “Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk,”10) which respectively describe the control of residual solvents, elemental impurities, and mutagenic impurities from toxicological viewpoints. These guidelines have been revised for updates.

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Recently, the drug supply chain has been globalized and the use of generic drugs has been promoted to reduce medical expenditures and improve access to drugs. In response to these goals, quality assurance is required for drugs worldwide. Therefore, it is important that the concepts of ICH guidelines are smoothly incorporated into each pharmacopoeia to comprehensively ensure the quality of marketed drugs, including both new and generic drugs. Impurity-related ICH guidelines have been sequentially applied to generic drug applications for approval in countries/regions, and the process of incorporating them into each pharmacopoeia has been initiated.\textsuperscript{11,12} However, because of a pharmacopoeia is widely used for drugs, including for already marketed drugs, but ICH guidelines had basically been developed for new drugs, incorporation of the concepts of ICH guidelines into a pharmacopoeia requires time. For example, the ICH Q3C guideline, which was harmonized in 1997, was incorporated into the JP in 2016.

In such situations, because more smooth incorporation of the concepts of ICH guidelines into a pharmacopoeia will lead to more efficient quality risk management using a pharmacopoeia, we considered a smooth approach for the incorporation. We focused on the incorporation of the concepts of the ICH Q3C, Q3D, and M7 guidelines for residual solvents, elemental impurities, and mutagenic impurities, respectively, which need to be controlled to ensure patient safety, into the Ph. Eur., USP, and JP, which are widely used globally. Although some comparative studies on the contents of the three pharmacopoeias have been reported,\textsuperscript{12,13} no comparative study including their incorporation approaches has been reported. We retrospectively examined the approaches for implementing each guideline into approval applications in Europe, the U.S., and Japan, in addition to the incorporation of each guideline into the three pharmacopoeias. We performed the analysis using a cause and effect diagram to identify barriers to and facilitators of the incorporation. Furthermore, we prospectively considered an approach for the smooth incorporation of impurity-related ICH guidelines into a pharmacopoeia by creating a logic model.

Results and Discussion

Overview of the ICH Q3C, Q3D, and M7 Guidelines and Approaches to Them

(1) Overview of the ICH Q3C, Q3D, and M7 Guidelines and Their Related Information

Table 1 shows an overview of the ICH Q3C, Q3D, and M7 guidelines and their related information.

The ICH Q3C guideline related to residual solvents was first harmonized in 1997, and it currently includes the limits of 60 solvents.\textsuperscript{8} The scope of this guideline covered drug substances, excipients, and drug products, but existing drug products were outside this scope.

The ICH Q3D guideline related to elemental impurities was first harmonized in 2014. It included the limits of 24 individual elemental impurities and described the control of elemental impurities in drug products \textit{via} risk assessment. Although elemental impurities have long been evaluated and controlled using heavy metal and arsenic tests in each pharmacopoeia, recent advances in science and technology have made it possible to analyze trace elements, and they are generally analyzed using methods such as inductively coupled plasma-mass spectrometry. This guideline was not expected to be applied to existing drug products prior to 36 months after publication of the guideline. Regarding quality control focusing on individual elements, the European Medicines Agency (EMA) guideline had already been applied to new drug products since 2008, and for existing drug products a time limit of 5 years was set for implementation by considering the feasibility.\textsuperscript{14} In the U.S. and Japan, there was no domestic guideline prior to ICH.\textsuperscript{15}

In addition, the business plan of the ICH Q3D guideline mentioned financial costs including additional costs for analytical instruments and their maintenance, analyst training, reagents, and reference standards.\textsuperscript{16}

The ICH M7 guideline related to mutagenic impurities was also first harmonized in 2014. Unlike the ICH Q3C and Q3D guidelines, impurities to be controlled are synthetic impurities and the degradation products of individual drugs, but the currently acceptable limits of 14 compounds are listed in this guideline. Because mutagenic impurities can damage DNA at even small amounts and induce cancer, they are analyzed using methods such as GC-MS with high specificity and sensitivity. To evaluate toxicity, quantitative structure–activity relationship systems are used. The scope of this guideline was new drug substances and products, and its application to existing drug products was limited to certain conditions such as changes of drug substance synthesis methods. When its concept paper was endorsed by ICH, the EMA guideline was already implemented in Europe,\textsuperscript{17} and the U.S. Food and Drug Administration (FDA) draft guidance was published in the U.S.,\textsuperscript{18} however, there was no domestic guideline in Japan.\textsuperscript{19}

(2) Approaches to the ICH Q3C Guideline

Table 2 shows standards related to the ICH Q3C guideline and residual solvents in the Ph. Eur., USP, and JP. As shown in Table 2, it was necessary to develop overall rules (hereafter the rules corresponding to the general notices in the USP and JP and general monographs in the Ph. Eur. are called “overall rules”), chapters on analytical procedures and limits, rules on preparation of monographs, and reference standards.

Periods of each stage of publishing in the three pharmacopoeias as well as those from public consultation of the analytical procedures to implementation of the overall rules for the ICH Q3C guideline are summarized in Fig. 1 and 2, respectively. The figures show that the differences in periods for publishing were much larger than those for implementation. From harmonization of the ICH Q3C guideline, implementation of overall rules required 54 months for the Ph. Eur., 132 months for the USP, and 225 months for the JP, as shown in Fig. 1A. As shown in Fig. 1B, the period from harmonization of the ICH Q3C guideline to the first public consultation of overall rules was 11 months for the Ph. Eur. at the shortest and 149 months for the JP at the longest. In Europe, at least as of March 1996, an article in the Pharmeuropa mentioned that the risk of residual solvents does not differ between originator and generic drugs. In addition, a strategy was revealed to set suitable deadlines for application to drugs already listed in the Ph. Eur. with hearing from industry.\textsuperscript{20} In Japan, although the JP draft of overall rules and analytical procedures with limits were published for public consultation in 2009, industry and regulatory bodies commented that it would be difficult to implement them immediately.\textsuperscript{21} Next, the periods from harmonization of the ICH Q3C guideline to the implementation of analytical procedures and public consultation of them are shown in Figs. 1C and 1D. In both cases, the shortest time
among the three pharmacopoeias was for the Ph. Eur. and the longest time was for the JP. In addition, the public consultation was conducted before harmonization of the guideline in Ph. Eur. On the other hand, as shown in Fig. 2, the periods from public consultation of the analytical procedures to implementation of overall rules in the Ph. Eur., USP, and JP were 61, 60, and 76 months, respectively, being similar among the three pharmacopoeias. It was supposed that this period included time required considering the feasibility and preparing for the application of overall rules.

Table 3 shows regulatory documents related to the ICH Q3C guideline and residual solvents published by the EMA, FDA, and Japanese Ministry of Health, Labour and Welfare (MHLW). In Europe, the guideline has been implemented since 1998. In the U.S., the guidance was published in 1997, and a separate guidance in response to incorporation of the ICH Q3C guideline into the USP was published in 2009. The latter guidance described the handling of drugs of each category such as new, generic, OTC, and existing drugs. In Japan, the guideline has been implemented since 2000, being restricted to approval applications for new drugs. Concerning generic drugs, the notifications published in January 2008 and 2016 indicated the necessity of explaining appropriate controls for residual solvents in an approval application document.

Table 3 shows regulatory documents related to the ICH Q3C guideline and residual solvents published by the EMA, FDA, and Japanese Ministry of Health, Labour and Welfare (MHLW). In Europe, the guideline has been implemented since 1998. In the U.S., the guidance was published in 1997, and a separate guidance in response to incorporation of the ICH Q3C guideline into the USP was published in 2009. The latter guidance described the handling of drugs of each category such as new, generic, OTC, and existing drugs. In Japan, the guideline has been implemented since 2000, being restricted to approval applications for new drugs. Concerning generic drugs, the notifications published in January 2008 and 2016 indicated the necessity of explaining appropriate controls for residual solvents in an approval application document.

Although the former notification did not mention the ICH Q3C guideline, another notification published in 2015 related to the JP mentioned this guideline. The timing of implementation of the ICH Q3C guideline for approval applications other than new drug applications was almost the same as that of the overall rules in the USP, and earlier than the timing of their implementation in the Ph. Eur. and JP.
Table 2. Pharmacopoeial Standards Related to the ICH Q3C Guideline and Residual Solvents

|                        | Ph. Eur. | USP | JP |
|------------------------|---------|-----|----|
| Overall rules          | General Monographs | General Notices and Requirements | General Notices |
|                        | 2034 Substances for pharmaceutical use | 5.60.20. Residual Solvents in USP and NF Articles | General Notices 34. |
| Analytical procedures  | General Chapters | General Chapters | General Tests, Processes and Apparatus |
|                        | 2.4.24. Identification and control of residual solvents | 467. Residual Solvents | 2.46 Residual Solvents |
| Limits                 | General Chapters | General Chapters | General Tests, Processes and Apparatus |
|                        | 5.4. Residual solvents | Described in “Technical guide for the elaboration of monographs” | Described in “Guideline for preparation of JP18 draft” |
| Reference standards    | Exist | Exist | Exist |

Ph. Eur., European Pharmacopoeia; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; JP, Japanese Pharmacopoeia; USP, United States Pharmacopoeia.

Fig. 1. Time from Harmonization of the ICH Q3C Guideline to Each Stage in the Ph. Eur., USP, and JP

The baselines of the vertical axis indicate the date of harmonization of the ICH Q3C guideline. Overall rules and analytical procedures in each pharmacopoeia are described in Table 2, but the overall rules in the Ph. Eur. indicate chapter 2034 in Fig. 1A and B. Although some rules and procedures had already been included before the ICH Q3C guideline was harmonized, only the information that was consistent with the guideline are considered in these figures. Ph. Eur., European Pharmacopoeia; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; JP, Japanese Pharmacopoeia; USP, United States Pharmacopoeia.
(3) Approaches to the ICH Q3D Guideline

Table 4 shows standards related to the ICH Q3D guideline and elemental impurities in the Ph. Eur., USP, and JP. As shown in Table 4, it was necessary to develop overall rules, chapters on analytical procedures, and other factors.

Periods of each stage of publishing in the three pharmacopoeias as well as those from public consultation of the analytical procedures to implementation of the overall rules for the ICH Q3D guideline are summarized in Figs. 3 and 4, respectively. As with the case of the ICH Q3C guideline, the figures show that the differences in periods for publishing were much larger than those for implementation. As shown in Fig. 3A, the implementation of overall rules required 38 months for the Ph. Eur. and USP after harmonization of the ICH Q3D guideline. In the JP, implementation is planned from the JP 18th Edition which will be published in April 2021, representing 77 months after harmonization. The period from harmonization of the ICH Q3D guideline to public consultation on the overall rules is presented in Fig. 3B, and the public consultation was conducted approximately 5 years before harmonization in the USP. The periods from harmonization of the ICH Q3D

Table 3. Regulatory Documents Related to the ICH Q3C Guideline and Residual Solvents

| EMA | FDA | MHLW |
|-----|-----|------|
| “ICH Q3C Impurities: Guideline for residual solvents” (implemented in March 1998) | “Guidance for Industry, Q3C Impurities: Residual Solvents” (dated 24 December 1997) | “Guideline for residual solvents” (dated 30 March 1998, implemented in 1st April 2000) |
| “Annexes to CPMP/ICH/283/95 Impurities: Guideline for residual solvents & CVMP/VICH/502/99 Guideline on impurities: residual solvents” (dated 20 February 2013) | “Guidance for Industry, Residual Solvents in Drug Products Marketed in the United States” (dated 24 November 2009) | “Handling of documents to be attached to approval applications for ethical drugs” (dated 9 January 2008) |

EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; MHLW, Ministry of Health, Labour and Welfare.

Table 4. Pharmacopoeial Standards Related to the ICH Q3D Guideline and Elemental Impurities

| | Ph. Eur. | USP | JP |
|---------------|--------|-----|----|
| Overall rules | General Monographs | General Notices and Requirements | General Notices |
| 2034 Substances for pharmaceutical use | 5.60.30. Elemental Impurities in USP Drug Products and Dietary Supplements | Under development |
| 2619 Pharmaceutical preparations | | |
| Analytical procedures | General Chapters | General Chapters | General Tests, Processes, and Apparatus |
| 2.4.20. Determination of elemental impurities | <233> Elemental Impurities—Procedures | 2.66 Elemental Impurities—Procedures |
| Limits | General Chapters | General Chapters | General Information |
| 5.20. Elemental impurities | <232> Elemental Impurities—Limits | Control of Elemental Impurities in Drug Products |
| Rules on preparation of monographs | Deletion of Heavy metal test from monographs (except for veterinary use) | Deletion of Heavy metal test from monographs | — |
| Reference standards | Exist | Not exist | Not exist |

a) The draft was published for public consultation in Nov 2019 for inclusion in 2021. b) This content is scheduled to be combined with chapter 2.66 in 2021. Ph. Eur., European Pharmacopoeia; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; JP, Japanese Pharmacopoeia; USP, United States Pharmacopoeia.
The guideline to the implementation of analytical procedures and public consultation are shown in Figs. 3C and 3D. The public consultation was conducted before harmonization in the Ph. Eur. and USP, whereas it was conducted after harmonization in the JP (Fig. 3D). Although the initial activities of the USP in Fig. 3B and of the Ph. Eur. and USP in Fig. 3D were supposed to control elemental impurities in Europe and the U.S., respectively, regardless of the ICH Q3D guideline, they were not distinguished regarding whether they were for the guideline because their activities finally led to the outcomes shown in Table 4. Comparing Figs. 3C and 3D, the periods from public consultation on the analytical procedures to their implementation in the Ph. Eur., USP, and JP were 24, 71, and 15 months, respectively. In the USP, the timing of implementation of the series of pharmacopoeial rules had been reviewed repeatedly because the discussion in the USP occurred around the same time as that in the ICH.28-29 Meanwhile, as shown in Fig. 4, the periods from public consultation of the analytical procedures to implementation of the overall rules were 81 months for the Ph. Eur. and 96 months for the USP. Concerning the JP, a certain grace period in addition to the 37 months shown in Fig. 4 is planned to be secured.30 As observed for the implementation of the ICH Q3C guideline, this period was supposed to include a certain period required to consider the feasibility and prepare for application of the overall rules. In addition, it was explained that the inclusion of analytical procedures before implementation of the overall rules in the JP was based on a stance of illustrating the concept of controlling elemental impurities in advance.31

Table 5 shows regulatory documents related to the ICH Q3D guideline and elemental impurities published by the three regulatory authorities. In Europe, the draft implementation strategy of the ICH Q3D guideline was published in 2016. In the U.S., the published draft guidance indicated the handling and implementation date of various drug categories in response to the ICH Q3D guideline. Then, implementation expanded to existing drugs in December 2017 in Europe and in January 2018 in the U.S. In Japan, it has been implemented since April 2017, albeit being restricted to approval applications for new drugs and future implementation for existing new drugs was
also mentioned. However, a draft policy regarding how and when to implement the ICH Q3D guideline for generic and existing drugs has not been published. Concerning generic drugs, the notification published in 2016 mentioned metal impurities, but it did not mention the ICH Q3D guideline.

In addition, all three regulatory authorities and pharmacopoeias held various events related to the ICH Q3D guideline. Training and information sessions were mainly held in Japan,32 and workshops were primarily held in Europe and the U.S.33,34

(4) Approaches to the ICH M7 Guideline

Table 6 shows standards related to the ICH M7 guideline and mutagenic impurities in the Ph. Eur., USP, and JP. The Ph. Eur., including overall rules and analytical procedures, but the USP and JP did not include this information. Regarding the USP, the description concerning the ICH M7 guideline was presented in the general chapter draft “1086» Impurities in Drug Substances and Drug Products” at its public consultation in November 2017. Concerning the JP, a general information chapter newly included in June 2019 (Table 6) indicated that the ICH M7 guideline was one guideline to follow when controlling impurities. In addition, a description example to control mutagenic impurities in monographs using the “Manufacture” section was presented in the preparation guideline for JP monograph drafts.35 Although this description has not been used in the JP to date, this method describing the control of mutagenic impurities in the “Manufacture” section is similar to that in the Ph. Eur., which uses the “Production” section to control genotoxic impurities.

We examined the approach for the Ph. Eur., which had already implemented its overall rules. As shown in Fig. 5A, implementation of the overall rules required 34 months from harmonization of the ICH M7 guideline, occurring in April 2017. This was a revision to refer to the ICH M7 guideline instead of the previously referenced EMA guideline. The scope of overall rules was consistent with the ICH M7 guideline, and it did not include the existing drugs basically. In the Ph. Eur., five chapters of analytical procedures for some specific impurities were included in a stepwise manner, and descriptions to control those impurities were introduced in the “Production” section in some monographs (Figs. 5B, 5C).

Next, Table 7 shows regulatory documents related to the ICH M7 guideline and mutagenic impurities published by the three regulatory authorities. In Europe and the U.S., the ICH M7 guideline was published for new drug substances and new drug products in 2015. In the U.S., draft guidance related to generic drugs was published in January 2018 described the evaluation and control of mutagenic impurities. In Japan, it was also published in 2015, although its use was restricted to new drugs substances and new drug products of the approval applications for new drugs. Regarding generic drugs, the notification published in 2016 mentioned mutagenic impurities, but it did not mention the ICH M7 guideline.

Identification of Barriers and Facilitators We identified the components for incorporating concepts of impurity-related ICH guideline into pharmacopoeias under each major category using the following (1) to (5) analysis and illustrated them in the cause and effect diagram as shown in Fig. 6. Figures 7A and 7B present the cause and effect diagrams of barriers and facilitators for the ICH Q3D guideline as examples. Other diagrams for the ICH Q3C and M7 guidelines are presented in Figs. S1A, S1B, S2A, and S2B. As a result, common, or related causes were found in distant branches as summarized in Table 8.

(1) Contents of the ICH Guideline

Comparing Figs. 1A and 3A, approaches to implementing the ICH Q3D guideline in the three pharmacopoeias were shorter than those for the ICH Q3C guideline. In addition, none of the pharmacopoeias has implemented the ICH M7 guideline for existing drugs beyond its scope. In light of the contents of the ICH guidelines (Table 1), only the ICH Q3D guideline described its future application to existing drug products, and only the ICH M7 guideline had a partial list of impurities to be controlled because preparing a list is difficult
as the mutagenic impurities basically differ for individual drugs. Therefore, it was suggested that the handling of existing drugs in the scope of ICH guidelines and the existence of lists of impurities to be controlled affected the time required to incorporate the concepts of the ICH guidelines into a pharmacopoeia.

(2) Analytical Procedures for Impurities
Regarding the analytical procedures for impurities corresponding to the three guidelines (Table 1), they all required advanced analytical instruments with scientific progress. The ICH Q3C and Q3D guidelines mentioned pharmacopoeial procedures. Because pharmacopoeial procedures are expected to be commonly and widely used for monographs, their development takes time, but increasing the versatility by including such procedures in a pharmacopoeia can be a facilitator. From these findings, it was suggested that the novelty and advance-

Table 6. Pharmacopoeial Standards Related to the ICH M7 Guideline and Mutagenic Impurities

|                        | Ph. Eur. | USP | JP |
|------------------------|----------|-----|----|
| Overall rules          | General Monographs | —   | —  |
|                        | 2034 Substances for Pharmaceutical Use | —   | —  |
| Analytical procedures  | General Chapters | —   | —  |
|                        | 2.5.37. Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid | —   | —  |
|                        | 2.5.38. Methyl, ethyl and isopropyl methanesulfonate in active substances | —   | —  |
|                        | 2.5.39. Methanesulfonyl chloride in methanesulfonic acid | —   | —  |
|                        | 2.5.40. Methyl, ethyl and isopropyl toluenesulfonate in active substances | —   | —  |
|                        | 2.5.41. Methyl, ethyl and isopropyl benzenesulfonate in active substances | —   | —  |
| Limits                 | —        | —   | —  |
| Other related chapters | General Chapters | —   | —  |
|                        | «476» Control of Organic Impurities in Drug Substances and Drug Products (draft) | —   | —  |
|                        | «1086» Impurities in Drug Substances and Drug Products (draft) | —   | —  |
| Rules on preparation of monographs | Described in “Technical guide for the elaboration of monographs” | —   | —  |
|                         | Described in “Guideline for preparation of JP18 draft” | —   | —  |
| Reference standards    | Exist    | Not exist | Not exist |

Ph. Eur., European Pharmacopoeia; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; JP, Japanese Pharmacopoeia; USP, United States Pharmacopoeia.

Fig. 5. Time from Harmonization of the ICH M7 Guideline to Implementation of Each Standard in the Ph. Eur.

The baselines of the vertical axis indicate the date of harmonization of the ICH M7 guideline. Overall rules and analytical procedures are described in Table 6. Ph. Eur., European Pharmacopoeia; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.
ment of analytical procedures, and their development in a pharmacopoeia affected the time required for incorporation.

(3) Regulatory Authority’s Management

Regarding the ICH Q3C guideline, we compared the regulatory authority’s management between Europe and Japan because the Ph. Eur. and JP required the least and most time to implement overall rules, respectively (Fig. 1A). It took time to expand the scope to other uses besides approval applications for new drugs in Japan.

Similarly, regarding the ICH Q3D guideline, we compared the regulatory authority’s management between Europe and Japan based on the speed of overall rules implementation (Fig. 3A). In Europe and the U.S., the draft implementation strategy was unveiled, and workshops were held. In Europe, the EMA guideline preceded that of the ICH M7 guideline (Table 1). In addition, as observed for the implementation of the ICH Q3C guideline, it took time to expand the scope beyond approval applications for new drugs in Japan.

Concerning the ICH M7 guideline, we compared the regulatory authority’s management between Europe and the U.S. or Japan because overall rules were implemented only in the Ph. Eur. (Table 6). In Europe, implementation of the EMA guideline preceded that of the ICH M7 guideline (Table 1).

From these findings, we identified that the timing of expansion of the scope beyond approval applications for new drugs, presentation of the draft implementation strategy, completion of workshops, and the existence of preceding guidelines affected the time required for incorporation.

(4) Approach for Incorporation into Pharmacopoeias

Regarding the ICH Q3C guideline, all three pharmacopoeias required a certain period from public consultation of the analytical procedures to overall rules implementation (Fig. 2). Meanwhile, comparing the Ph. Eur. and JP based on the speed of inclusion of the overall rules (Fig. 1A), time was needed from harmonization of the guideline to public consultation of the overall rules and analytical procedures in the JP (Figs. 1B, 1D).

Similarly, regarding the ICH Q3D guideline, some periods were also needed for all three pharmacopoeias from public consultation on the analytical procedures to overall rules implementation (Fig. 4). Meanwhile, comparing the Ph. Eur. or USP and JP based on the speed of inclusion of the overall rules (Fig. 3A), public consultation on the overall rules and analytical procedures was conducted earlier for the Ph. Eur.
and USP (Figs. 3B, 3D). In particular, the first public consultation on the analytical procedures was conducted before harmonization of the guideline for the Ph. Eur. and JP (Fig. 3D). In addition, workshops were held in Europe and the U.S.

Concerning the ICH M7 guideline, overall rules were implemented only in the Ph. Eur. Although the inclusion of analytical procedures and description in the monographs were not originally responses to the ICH M7 guideline, they were included in a stepwise manner (Figs. 5B, 5C).

From these findings, it was identified that the time needed from public consultation on analytical procedures to implementation of the overall rules, the timing of public consultation on the overall rules and analytical procedures, completion of workshops, and the stepwise approach affected the time...
required for incorporation.

(5) Response of Stakeholders

Regarding the ICH Q3C guideline, although the pharmacopoeia, regulatory authority, and industry in Europe had exchanged their opinions before harmonization of the ICH guideline, commonality regarding awareness among those three stakeholders in Japan had not been secured even 12 years after harmonization.

Concerning the ICH Q3D guideline, various activities were held to deepen their understanding regarding the control of elemental impurities, such as workshops in Europe and the U.S. and training and information sessions in Japan, in addition to the development of training materials by ICH (Table 1).

Thus, it was suggested that commonality regarding awareness among stakeholders and efforts to deepen their understanding regarding the control of impurities affected the time required for incorporation.

Based on cause and effect analysis, it was clarified that barriers to incorporate the concepts of the ICH guidelines into a pharmacopoeia were mainly caused by the harmonization process of the ICH guidelines. On the other hand, most facilitators were mainly in the pharmacopoeia development process and were relevant through the three key stakeholders of the pharmacopoeia, regulatory authority, and pharmaceutical industry. Their close collaboration in the exchange of opinions in each country/region from an early stage of discussion in the harmonization process in the ICH was suggested as the most important activity. The barriers and facilitators are summarized in Table 8.

First, because all three pharmacopoeias required a certain period from public consultation of the analytical procedures to overall rules implementation (Figs. 2, 4), consideration of the feasibility and preparation of the application were identified as barriers. This includes the current situation to consider a variety of drug products listed in a pharmacopoeia and preparations for the application and evaluation by the new control of impurities for those drugs. Against these barriers, major three facilitators were identified: securing commonality regarding awareness of the implementation strategy among the three stakeholders, understanding the control of impurities, and early public consultation of pharmacopoeial analytical procedures if the lists of impurities to be controlled exist, such as the ICH Q3C and Q3D guidelines, exist.

Second, expansion of the scope beyond approval applications for new drugs

- The case in which existing drugs are not included in the scope of the ICH guidelines

Required for incorporation, the ICH guidelines

- The case in which existing drugs are not included in the scope of the ICH guidelines

Expansion of the scope beyond approval applications for new drugs

- The case in which existing drugs are not included in the scope of the ICH guidelines

Facilitators

- Holding training and information sessions
- Describing possible applications to existing drugs in the scope of the ICH guidelines
- Stepwise approach

ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Table 8. Summary of Barriers to and Facilitators of the Incorporation of the Concepts of Impurity-Related ICH Guidelines into a Pharmacopoeia

| Barriers                                                                 | Facilitators                                                                 |
|-------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Consideration of the feasibility and preparations of the application    | Securing commonality regarding awareness of the implementation strategy among the pharmacopoeia, regulatory authority, and pharmaceutical industry |
| - Feasibility of pharmaceutical companies applying the concepts of ICH   | - Exchange opinions in each country/region from an early stage of discussion in the ICH |
|   guidelines to a variety of drug products listed in a pharmacopoeia     |                                                                             |
| - Preparation including:                                                |                                                                             |
|   - Securing budgets for introducing equipment and instruments, tests,   |                                                                             |
|     outsourcing of tests, and developing human resources in pharmaceutical companies |
|   - Applying the concepts of ICH guidelines to a variety of drug products listed in a pharmacopoeia in pharmaceutical companies |
|   - Arrangement for assessment systems by the regulatory authority       |                                                                             |
|                                                                           |                                                                             |
| Expansion of the scope beyond approval applications for new drugs        |                                                                             |
| - The case in which existing drugs are not included in the scope of the ICH guidelines |
|                                                                           |                                                                             |
| Difficulty in making the list of impurities to be controlled             |                                                                             |
|                                                                           |                                                                             |
| ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ties, and describing possible applications to existing drugs in the scope of the ICH guidelines.

Third, the difficulty in making the list of impurities to be controlled, such as that in the ICH M7 guideline, could be a barrier because the development of versatile pharmacopeial analytical procedures and evaluation and control of such impurities are more difficult. This would affect the preparations for the application and evaluation by the new control of impurities for a variety of drugs mentioned above. However, stepwise approaches may be facilitators in line with the approach to the mutagenic impurities of the Ph. Eur.

Development of a Logic Model  Figure 8 presents a logic model for smooth incorporation of the concepts of impurity-related ICH guidelines into a pharmacopoeia and for quality assurance with the pharmacopoeia.

First, one long-term outcome is the contribution to public health through the quality assurance of pharmaceuticals using a pharmacopoeia with impurity risk controls. Outcomes toward the long-term outcome consist of incorporation of the concepts of impurity-related ICH guidelines into a pharmacopoeia, approval assessments using the pharmacopoeia, and quality assurance using the pharmacopoeia.

Next, outputs toward these outcomes and activities to achieve the outputs could be categorized into four groups. For all the three stakeholders of the pharmacopoeia, regulatory authority, and pharmaceutical industry, the outputs were securing commonality regarding awareness of the scope of the ICH guideline and the implementation strategy, and understanding regarding the control of impurities. Activities corresponding to these outputs were the exchange of opinions and efforts to deepen the understanding of impurity control. Workshops, training and information sessions would be effective. For the pharmacopoeia, the five outputs were inclusion of the overall rules, inclusion of the analytical procedures, inclusion of limits, revision of monographs, and others. Various activities were conducted to achieve these outputs. In particular, early public consultation of the overall rules would be effective for the exchange of opinions among stakeholders, and early public consultation of analytical procedures is also effective if lists of impurities to be controlled such as residual solvents and elemental impurities exist. For the regulatory authority, the outputs were expansion of the scope beyond approval applications for new drugs such as generic and existing drug applications, and the arrangement of an assessment system. The activities to achieve these outputs were development and preparation. In particular, presentation of the implementation strategy would be effective for the exchange of opinions among stakeholders. For the pharmaceutical industry, the outputs were introduc-
tion of equipment and instruments, development of human resources, and responses to a variety of drug products. Activities to achieve these outputs are securing a budget to support them and consideration of the feasibility and preparation of applications for a variety of drug products. From the experiences of the Ph. Eur., USP, and JP examined in this study, although some activities such as the development of analytical procedures were started before discussion in the ICH, it would be optimal to start collaboration among the three stakeholders at an early stage of discussion in the ICH.

We expect that our proposed approach will contribute to more efficient quality risk management. In this study, we proposed an approach logically based on the historical information of past experience of both pharmacopoeia and pharmaceutical affairs regulation in Europe, the U.S., and Japan by combining the cause and effect diagram used in the manufacturing industry and the logic model used in policy review. The Ph. Eur., USP, and JP are positioned under different laws and administrative systems concerning pharmaceutical affairs in each country/region. These legal and administrative systems define the characteristics and activities of each pharmacopoeia and naturally affect the incorporation of the ICH guidelines. It should be noted that we compared and considered the incorporation approaches from the perspective of the Japanese system. Logic models are continuously reviewed and improved, and it is expected that our proposed approach will be reviewed and improved in the future based on new findings and experiences.

As science advances, the incorporation of concepts globally harmonized at the ICH into pharmacopoeias, which are public quality standards for drugs, have become increasingly important to comprehensively ensure the quality of marketed pharmaceuticals regardless of whether they are new, generic, or existing drugs. Recently, the drug supply chain has been globalized in Japan, and the Japanese Society of Generic and Biosimilar Medicines issued their statement on the necessity of finding approaches to widely apply the concepts of the ICH M7 guideline to not only new drugs but also existing and generic drugs in response to the contamination of valsartan products by N-nitrosodimethylamine in 2018. Because the risk of impurity-related toxicity in patients does not differ among new, generic, or existing drugs, it is desirable to widely apply the ICH M7 guideline. Although this would not be simple because of the need for new evaluations such as toxicology assessments, it is expected that discussion concerning the implementation strategy will progress among the pharmacopoeia, regulatory authority, and pharmaceutical industry. In addition, the need for pharmacopoeial analytical procedures would be one of the themes to be discussed given that the Ph. Eur., but not the USP and JP, has already included some of these procedures. This is because it is necessary to remember that the development of different procedures in each pharmacopoeia will burden pharmaceutical companies because analytical procedures for each individual mutagenic impurity need to be developed, unlike the case of residual solvents and elemental impurities. Toward a common long-term outcome, each stakeholder’s role in controlling the risk of impurities is expected to be discussed.

We expect that our proposed approach will be applied for responses to not only revisions of these three guidelines but also new impurity-related ICH topics such as “Assessment and Control of Extractables and Leachables for Pharmaceuticals and Biologics,” which became a topic in the ICH in 2019. We also expect our approach will be applied globally in other countries/regions. With the globalization of the drug supply chain, it is more desirable that the timing of incorporation of the concepts of ICH guidelines into each pharmacopoeia would be as similar as possible to reduce the burden caused by different test requirements in each country/region. Then, it would be useful to exchange information concerning implementation strategies for approval assessment and pharmacopoeia through various international harmonization and collaboration frameworks such as the ICH, Pharmacopoeia Discussion Group, International Pharmaceutical Regulators Programme, and International Meeting of World Pharmacopoeias. We hope that our study will promote further collaboration among stakeholders, and fulfill the mission of pharmacopoeia to ensure patient and public health through quality assurance.

Conclusion

In this study, we retrospectively examined approaches to incorporating the concepts of ICH guidelines for residual solvents, elemental impurities, and mutagenic impurities into the Ph. Eur., USP, and JP using various implementation approaches for drug approval applications in Europe, the U.S., and Japan. Moreover, we identified barriers and facilitators via cause and effect analysis and considered an approach for smooth incorporation of the concepts of impurity-related ICH guidelines into pharmacopoeias by creating a logic model. This study identified that close collaboration among the pharmacopoeia, regulatory authority, and pharmaceutical industry was most important for this purpose. In particular, because a certain period was needed to consider the feasibility and prepare for the application, the exchange of opinions about implementation strategies among the three stakeholders from an early stage of discussion in the ICH would promote incorporation, and lead to more efficient quality risk management.

Our proposed approach is expected to be widely applied for smooth incorporation of the concepts of impurity-related ICH guidelines into pharmacopoeias for the quality assurance of pharmaceuticals for public health.

Experimental

Overview of the ICH Q3C, Q3D, and M7 Guidelines and Approaches to Them

First, we summarized the ICH Q3C, Q3D, and M7 guidelines and their related information using ICH public documents.

Second, we examined standards related to the ICH Q3C, Q3D, and M7 guidelines and the implementation timing of rules and chapters in the Ph. Eur., USP, and JP, which were issued by the end of June 2019. We focused on public consultation to hear opinions from stakeholders and searched each public consultation medium of the three pharmacopoeias issued by November 2019, namely Pharmedusa Online, Pharmacopoeial Forum Online, and the Pharmaceuticals and Medical Devices Agency (PMDA) website for public consultation timing of rules and chapters, respectively. We also examined the websites of the issuing organizations, namely the European Directorate for the Quality of Medicines & HealthCare, Unit-
ed States Pharmacopeial Convention, and Japanese MHLW to examine the circumstances leading to their inclusion.

Third, we examined public documents from the EMA, U.S. FDA, and MHLW to obtain information on approval applications in Europe, the U.S., and Japan.

Identification of Barriers and Facilitators We created cause and effect diagrams to identify barriers to and facilitators of incorporating the concepts of impurity-related ICH guidelines into a pharmacopoeia. The cause and effect diagram is also called a fish bone diagram or Ishikawa diagram. This technique is commonly used to find the causes of an effect for quality risk management in the manufacturing industry, and it has also been applied to social science research. For the quality problems in the manufacturing industry, 4M (Material, Machine, Method, and Man) or 5M (Material, Machine, Method, Man, and Measurement) are often used as the major categories of causes. We used 5M from the viewpoint of creating a pharmacopoeia as follows: contents of the ICH guideline for Material, analytical procedures for impurities for Machine, approach for incorporation into a pharmacopoeia for Method, response of stakeholders for Man, and regulatory authority’s management for Measurement. Then, we identified components under each heading of the major categories of causes by analyzing the results of “Overview of the ICH Q3C, Q3D, and M7 Guidelines and Approaches to Them.” Individual cases were added as branches. After drawing the diagrams, we summarized the identified barriers and facilitators.

Development of a Logic Model We considered an approach for the smooth incorporation of the concepts of impurity-related ICH guidelines into a pharmacopoeia and for quality assurance with the pharmacopoeia by creating a logic model. A logic model is a graphic depiction that systematically illustrates strategies for achieving the purpose of a policy. This technique is also used in social science research. Under the long-term outcome, we set outcomes for each resource, namely the pharmacopoeia, regulatory authority, and pharmaceutical industry. We also set outputs corresponding to the outcomes and activities to achieve the outputs, based on the results in “Overview of the ICH Q3C, Q3D, and M7 Guidelines and Approaches to Them” and facilitators identified in “Identification of Barriers and Facilitators.”

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Conflict of Interest Maki Matsuhama and Rieko Saito are staff members at the PMDA, but the views expressed in this manuscript are those of authors and do not necessarily reflect the views of the PMDA and the Japanese Pharmacopoeia.

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