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Review

Insights into post-marketing clinical validation of companion diagnostics with reference to the FDA, EMA, PMDA, and MFDS

Su Lim Kang,[1] Ji Yean Kwon,[1,2] and Sung Min Kim[1,2]

[1]Department of Medical Device and Healthcare, Dongguk University-Seoul (04620) 26, Pil-dong 3-ga, Jung-gu, Seoul, Republic of Korea; [2]Department of Regulatory Science for Bio-health Medical Device, Dongguk University-Seoul (04620) 26, Pil-dong 3-ga, Jung-gu, Seoul, Republic of Korea

Companion diagnostics are increasing clinical demand globally, regulatory frameworks for clinical validation are strengthening. Post-marketing verification is an important aspect of providing high-quality, personalized treatment to patients because it can ensure long-term safety and effectiveness, while also generating effective risk management and performance evidence. Certain compliance issues related to the requirements for post-marketing clinical trials can potentially impact manufacturers, so it is essential to have a clear understanding of the regulatory process. In this study, we perform an institutional comparison as well as a case analysis by country (U.S. Food & Drug Administration, European Medicines Agency, Pharmaceuticals and Medical Devices Agency, and Ministry of Food and Drug Safety) on the post-marketing safety and effectiveness of companion diagnostics. We collected guidelines and guidance documents published by each regulatory agency and Post-marketing research case analysis examined the data collection items as well as the materials or templates required to be submitted. The results indicate that there are institutional differences in the post-marketing surveillance activities carried out by different regulatory authorities, and the data required may vary accordingly. The findings of this study are expected to provide new insights that can support manufacturers and developers of companion diagnostics in securing evidence regarding post-marketing safety and effectiveness.

INTRODUCTION

The goal of modern medicine is to improve the quality of life of patients by treating and preventing diseases as effectively as possible through rapid and accurate diagnosis as well as lowering management costs, and it is changing to more targeted treatment and personalized treatment. Companion diagnostics (CDx) means a device that is essential for the safe and effective use of a corresponding medicinal product according to EU IVDR, and CDx select patients with a positive benefit-risk profile.[1,2] CDx have become essential for targeted treatment following the paradigm shift in precision medicine, as shown in Table 1, and there is increasing clinical demand for CDx.

Recent years have seen strengthened regulations and guidelines for CDx, beginning with those announced by the U.S. Food & Drug Administration (FDA) in 2014, which was followed by the In Vitro Diagnostic Regulation (IVDR) in Europe.[3] In particular, the implementation of the IVDR has established strict requirements for thorough review by the notified body along with technical documentation and clinical evidence, and a significant level of clinical evidence is required not only in pre-marketing clinical trials but also in post-marketing.[4] Previous studies have shown that both the FDA and the European Medicines Agency (EMA) have requested post-marketing clinical trials in cases where there is missing or insufficient information on biomarker-negative patients.[5,6] The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan and the Ministry of Food and Drug Safety (MFDS) in Korea have also been requesting evidence for post-marketing performance data through post-marketing surveillance (PMS_ activities in recent years.

Post-marketing management of CDx is important because it can be difficult to maintain consistent device performance due to the complex development process involved.[7] This post-marketing validation is important for providing quality, personalized care to patients because it can track long-term safety and efficacy, while also generating effective risk management and performance evidence.[8] In particular, it is essential to have a clear understanding of the regulatory process, because compliance issues related to these requirements for post-marketing clinical trials can have potentially serious consequences for manufacturers.[9] One previous study notes that, although it is important to discuss relevant issues involved in the evaluation of laboratory-based CDx, it is also important to demonstrate the ability to ensure consistent safety and post-marketing efficacy after approval.[10] Likewise, there have been various studies describing the overall system for the post-marketing clinical regulation of CDx.[4,8,11,12] However, there has been no study focusing on this area as an independent topic that derived implications through the institutional analysis and application of case analysis using procedures to ensure post-marketing safety and effectiveness of CDx.

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Correspondence: Sung Min Kim, Department of Medical Device and Healthcare, Dongguk University-Seoul (04620) 26, Pil-dong 3-ga, Jung-gu, Seoul, Republic of Korea.
E-mail: smkim@dongguk.edu

Table 1. Application of CDx for targeted therapy

Product Name	Manufacturer	Disease	Diagnosis principle	Therapeutic products
Abbott RealTime IDH1	Abbott Molecular, Inc.	acute myeloid leukemia	PCR	Tibsovo (ivosidenib)
OncoGuide NCC Oncopanel System	Sysmex	solid tumor	NGS	Lytgobi (Futibainib)
PD-L1 IHC 22C3 pharmDx, GE006	Agilent Technologies	non-small cell lung cancer	IHC	Keytruda (Pembrolizumab)
PDGFRB FISH Assay	ARUP Laboratories, Inc.	myelodysplastic syndrome/ myeloproliferative disease	FISH	Gleevec (imatinib mesylate)

In this study, institutional comparison and case analysis were performed by country (FDA, EMA, PMDA, and MFDS) to collect legal requirements on the post-marketing safety and effectiveness of CDx.

DATA EXTRACTION

Regulatory framework by regulatory authorities

To investigate and analyze the specific clinical regulatory requirements set by each regulatory agency, we collected the guidelines and guidance documents published by each regulatory agency: FDA, Procedures for Handling Post-Approval Studies (PASs) Imposed by Premarket Approval Application Order; EMA, Regulation (EU) 2017/746 of the European parliament and of the council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing directive 98/79/EC and commission decision 2010/227/EU; Chambers and partners. Healthcare: Medical Devices 2023; MFDS, 2021 medical device re-evaluation explanatory material. We extracted the systems for activities performed to ensure post-marketing safety and effectiveness, after which we conducted a comparative analysis of the different systems maintained by different regulatory authorities. The comparative analysis largely consisted of analyzing the purpose of the system, data requirements, and collection methods.

Case study

To investigate and analyze post-marketing research cases, we first investigated data collection items. If a relevant research database was available, research data were extracted. In terms of the transparency of information disclosure, information that could not be found in the database was sourced from papers conducted in the relevant country or recommended materials (including clinical trial information and reporting templates) from a working group composed of various stakeholders. We also examined the data and forms that must be submitted in addition to post-marketing studies, and—where possible—applied the collected data to the templates and presented them as the basis for regulatory requirements. During the data extraction process, the scope of post-marketing clinical trials was extracted from activities to ensure the post-marketing safety, efficacy, or performance of the device, and other content was excluded.

Regulatory framework

United States (FDA)

The United States has established the legal authority for PASs, a post-marketing study, under Title 21 part 822 of the Code of Federal Regulations (CFR) and section 522 of the Food, Drug, and Cosmetics Act.[11] PASs are generally intended to collect specific data to address questions about the post-marketing performance or experience of an approved medical device, and its primary purpose is to evaluate the safety and effectiveness of the device. PASs may be required as a condition of approval by a PMA under 21 CFR 814.82(a)(2) to demonstrate reasonable and continuous performance of the safety and effectiveness of an approved device. Specifically, the FDA deems it acceptable to collect certain data (study design, objectives, population, and endpoints to be collected, the length of follow-up and frequency of assessments, and procedures for a determination of adverse events) in a post-market setting rather than a premarket setting in certain circumstances when there is uncertainty about the specific benefits or risks of the device. Two reports (an intermediate report and a final report) must be submitted after conducting the study (Table S1).[13]

Europe (EMA)

Manufacturers must establish a post-market surveillance (PMS) system for each device, which must be an integral part of the quality management system, based on Article 78 of the EU-IVDR. The process for verifying the overall post-marketing safety and performance of the IVD is shown in Figure S1. Therefore, a PMS appropriate for the device type must be planned, established, documented, implemented, maintained, and updated in proportion to the risk level (Table S2).[14] CDx are classified as Class C based on the risk level of *in vitro* diagnostic medical devices, and requires PMS, post-market performance follow-up (PMPF), and periodic safety update reporting (PSUR). Also, manufacturers shall make PSURs available to the notified body involved in the conformity assessment and, upon request, to competent authorities. PMS is an activity wherein information related to product quality, usability, safety, and performance is collected, analyzed, managed, and reported for the purpose of identifying corrective or preventive actions in the post-marketing phase life cycle of the device. The PSUR should summarize the results and conclusions of the analysis of PMS data collected as a result of the PMS plan referred to in Article 79 of the IVDR, together with the rationale and explanation for the preventive and corrective actions taken. In particular, it should state the following over the life cycle of the device: the conclusions of the benefit-risk determination, the main results of the PMPF, and estimates of the number of sales of the device and the size and other characteristics of the population using the device, and, where feasible, the frequency of use of the device. The PMPF aims to ensure safety, performance, and scientific validity over the expected life of the device, ensure the acceptability of the benefit-risk ratio, detect new risks based on factual evidence, and detect various risks

Table 2. Types of CDx-related post-marketing systems by regulatory authorities

	United States	EU	Japan	Korea
Regulatory authorities	FDA	EMA	PMDA	MFDS
Regulation	CFR Title 21 part 814.82	IVDR	Act on Pharmaceuticals and Medical Devices	In Vitro Diagnostic Medical Devices Act
Systems related to post-marketing clinical trials	PAS	PMS PMPF (+PSUR)	PMS re-evaluation	re-evaluation renewal
Database	PAS database	EUDAMED (European database for medical devices)	PMDA database	medical device integrated information system

through a set plan (Figure S2). For Class C, the PSUR must be prepared periodically and be included in the technical documentation, and it must be updated periodically according to the risk-based classification of the device.[15]

Japan (PMDA)

Japan's (PMDA) PMS is conducted in accordance with Ordinance No. 38 ("Good Post-marketing Study Practice," 2005) of its Ministry of Health, Labor and Welfare (MHLW), and is designed to monitor the quality, effectiveness, and safety of medical devices, either for manufacturers and distributors of medical devices or those who have received permission for imported medical devices. It is defined as an investigation or test conducted for the purpose of collecting, detecting, confirming, or verifying information, and it is performed using the procedures shown in Figure S3. There are three methods for capturing PMS activities (use history investigation, post-marketing database research, and post-marketing clinical trials). The re-evaluation system involves conducting PMS for certain medical products to collect information on the efficacy and safety of the product obtained in an actual clinical environment, it evaluates the results of use of MHLW-designated devices in Japan based on investigation reports submitted by suppliers.[16]

Korea (MFDS)

Korea's (MFDS) re-evaluation system is implemented for medical devices that are recognized as requiring re-examination in terms of their safety and effectiveness at the latest scientific level among all medical devices that have been approved, certified, or notified based on the MFDS Notice No. 2024-6 ("Regulations on Re-evaluation of Medical Device"). The subject of the re-examination is a medical device that has been approved, certified, or notified pursuant to Article 2 of the MFDS Notice No. 2024-6, and for which the Commissioner of the MFDS determines that a re-examination of safety and efficacy is necessary due to problems that have occurred or are likely to occur due to post-marketing information. It comprehensively evaluates safety and effectiveness by considering the risks and benefits of using the medical device (Figure S4). The data that must be submitted in this process include application forms, adverse event analysis reports, and safety information. In particular, safety information is an activity that collects new data or information related to the safety and effectiveness of approved devices.[17] Table S3 lists the types of reports that should be submitted. The renewal system refers to a renewal every 5 years to facilitate efficient management that involves periodically reviewing safety and effectiveness as well as organizing products that are not manufactured (imported) after receiving permission, certification, or notification based on the MFDS Notice No. 2023-68 ("Regulations on renewal of medical device manufacturing license"). This is done 180 days before the expiration of the validity period to continue manufacturing and importing it even after the validity period expires, during which time the submitted data is reviewed, and the validity period of the permission (certification/notification) is renewed by issuing a new permit (certificate). Table S4 lists the types of reports that should be submitted.

Institutional comparison

In the United States, Japan, and Korea, PMS activities are conducted for products where regulatory authorities recognize the need after the launch of a CDx, but in Europe, PMS activities must be conducted for all CDx (Table 2).

There are differences in the systems for ensuring the post-marketing safety and effectiveness of CDx by regulatory authorities. The FDA assesses safety and effectiveness by collecting the post-marketing performance of devices approved through PAS, and it requires data to be collected in the post-marketing environment rather than pre-marketing when there is uncertainty about specific benefits or risks. In particular, in the case of CDx, after marketing, it is necessary to include patient results with negative biomarkers, and interim and final reports must be submitted. EMA contains PMPF or PSUR activities within one system called the PMS. The PMS collects safety and performance-related information in the post-marketing stage, and a PMPF plan must be established. In particular, an analysis to ensure the acceptability of the benefit-risk ratio should be included. PMDA encourages the collection of actual clinical data by verifying the quality, safety, and effectiveness of devices through PMS activities. Re-evaluation is conducted on devices designated by MHLW, and it is also recommended that data collected from actual clinical practice, such as patient drug response, be used. MFDS requests data that meet the latest scientific standards for devices that have been deemed to require re-examination. The recently introduced renewal system is for the periodic review and management of safety and effectiveness every 5 years, and safety and efficacy verification data and action

Table 3. Details of post-marketing systems by regulatory authorities

FDA	PAS	Purpose	Collect specific data to address questions about post-marketing performance or experience with a device and to assess the safety and effectiveness of the device
		Data	Study design, objectives, population and evaluation variables, follow-up period, and evaluation frequency
		Method	Submission of an interim report (registration status report, PAS progress report recommended) and a final report (completeness, compliance with protocol methodology, description of performance and safety/efficacy evaluation results)
EMA	PMS	Purpose	Collect, analyze, manage, and report information related to quality, usability, safety, and performance for the purpose of identifying corrective and preventive actions during the post-marketing phase of the device life cycle
		Data	Information on serious incidents, data on non-serious or undesirable side effects, follow-up information, relevant experts and literature, information provided by users/distributors/importers, and public information on similar devices
		Method	PMS plan is required to be written in technical document
	PMPF	Purpose	Ensure safety, performance, and scientific validity over the expected life of the device, ensure acceptability of the benefit-risk ratio, and detect new risks based on factual evidence
		Data	Specific methods and procedures of the PMPF to be applied, such as post-marketing clinical performance studies, rationale for the appropriateness of the methods and procedures, risk management, specific objectives to be addressed by the PMPF, evaluation of performance data related to equivalent or similar devices and state-of-the-art technology, relevant CS and standards/guidelines, and study schedule
		Method	Verify the safety and performance of the device over its expected life cycle, Identify previously unknown risks or performance limitations and contraindications, Identify and analyze emergent risks based on factual evidence, Ensure continued acceptability of clinical evidence and benefit-risk ratios, Identify potential misuse of the devices
PMDA	PMS	Purpose	Manufacturers and distributors of devices or those who have received permission for imported medical devices. Collect, detect, confirm, and verify information on the quality, effectiveness, and safety of devices
		Data	Purpose, outline description of the medical information database used in the survey, number of subjects, scope of subjects, survey method, survey period, survey items, and analysis items and methods
		Method	Preparation of operating procedure manual for PMS
	Re-evaluation	Purpose	For certain medical products, verification of product efficacy and safety obtained in real clinical settings
		Data	Gather information on the efficacy and safety of products obtained in real-world clinical settings
		Method	Evaluation of results of use of devices designated by the MHLW in Japan based on investigation reports submitted by companies
MFDS	Re-evaluation	Purpose	Verification of safety and effectiveness at the latest scientific level for devices recognized as requiring reexamination among approved devices
		Data	Clinical performance according to product characteristics when it is difficult to measure clinical sensitivity, clinical specificity, and clinical sensitivity/clinical specificity
		Method	Submission of re-evaluation application, clinical performance test data, technical document review data, and supporting data
	Renewal	Purpose	Once approved, certified, or notified, it is updated every five years for efficient management by periodically reviewing safety and effectiveness and organizing products that are not manufactured (imported)
		Data	Original permit (certificate), safety and effectiveness maintenance verification data (review data for reflection of latest standards, performance and safety confirmation data), production (import) performance data, and safety information and action data
		Method	If you wish to continue manufacturing or importing even after the expiration date, apply 180 days before the expiration date, review the submitted data, and renew the validity period of the permit (certification/report) by issuing a new permit (certificate)

data must be submitted 180 days before expiration. The comparison table is presented in Table 3.

Case study

United States (FDA)

The recommended elements that should be written in the protocol of a PAS study are as listed in Table S5: background, purpose, objectives, study design, study population, enrollment and recruitment plan, statistically sound sample size, and primary/secondary endpoints (including side effects and complications), procedures used to determine side effects and complications, follow-up period, description of follow-up assessments, description of data collection procedures, data analysis and statistical plan, interim data release plan, data collection forms, informed consent, institutional review board approval documentation, and timeline (Table S6). Table S7 shows one example of a study collected from the FDA's PAS database. The PAS case used

the MK-3475 MSI-H FMI F1CDx Post Approval Analysis study, and observed the extended objective response rate for 26 weeks in a total of 41 subjects.

Europe (EMA)

Data that should be included in the PMS include information on serious incidents (PSUR); data on non-serious or undesirable side effects; follow-up information; relevant experts or literature consulted; information provided by users, distributors, and importers; and information about similar devices (customer complaints and warranty claims, user feedback, social media and gray literature information searches, regulatory agency databases, maintenance or service reports, self-feedback reports, and failure analysis). The PMPF example in Table S8 presents data extracted from FoundationOne CDx Technical information. Since the PMPF case could not confirm the specific details, an example was created using clinical trial information. The data in the PSUR should include the conclusion of the risk benefit analysis, key findings, and device sales, scale, and frequency of use. The template of a PSUR is presented in Table S9.

Japan (PMDA)

There are three types of survey methods for PMS activities (usage performance survey, post-marketing database survey, and post-marketing clinical trial), but in general, it is necessary to include the purpose of the survey, number of subjects, scope of subjects, survey method, survey period, survey items, analysis items, methods, and any other pertinent information. As PMDA's PMS case could not be confirmed with publicly available information, the PMS plan of other *in vitro* diagnostic devices was analyzed, and Table S10 was prepared by referring to the template recommended by PMDA. The PMS case was clinical validation of F1CDx as a companion diagnosis to identify patients with recurrent or metastatic adenoid cystic carcinoma for treatment with immunosuppressants. The contents were prepared while referring to clinical trials conducted in Japan.[18]

Korea (MFDS)

Among the data that must be submitted during re-evaluation, the relevant safety information consists of four types of data, and it can be demonstrated using templates. The case for re-evaluation was created as an example in a published pamphlet using actual recall data or papers.[19–23] Information on domestic and foreign academic papers comprises newly confirmed facts published in papers (Table S11), clinical trial data information comprises facts that have been newly confirmed through clinical trial data, and are prepared by referring to the approved clinical trial protocol (Table S12). Information on product manuals from foreign manufacturers refers to the renewal of precautions for use and how to use in the manual (Table S13), and for information announced by domestic and foreign government agencies, newly confirmed facts are recorded in precautions for use and how to use after determining which type of information the collected information is (Table S14).

For renewal *in vitro* diagnostic reagents (including CDx), data on storage method, period of use or expiration date, data on analytical performance tests, data on quality control tests, reference materials, and sample storage must be submitted. Table S15 presents the data that must be submitted for *in vitro* diagnostic reagents.

CONCLUSION

Precision medicine is gradually expanding, accelerating improved sensitivity and accurate treatment targeting through the analysis of personal health information through molecular diagnosis.[24] In particular, as it became known that a patient's prognosis can vary depending on the presence or absence of genetic mutations, CDx emerged along with the concept of targeted treatment that has a therapeutic effect only on specific patients.[2] For CDx, deriving reliable accuracy and precision of diagnostic results based on high-quality sensitivity and specificity is of utmost importance in making treatment decisions.[25] CDx has experienced technological, medical innovation, and regulatory changes over the past decade.[26] As regulatory requirements have strengthened, many new guidelines have been reviewed by country.[4,5,27,28]

A properly set up post-marketing strategy can get a product to market quickly and seamlessly, leading to early adoption of the product and increased uptake by doctors and patients. Post-marketing validation is critical to providing high-quality, personalized care to patients because it can generate effective risk management and performance evidence while tracking long-term safety and efficacy.[8] In particular, post-marketing management of CDx is important because complex development processes can make it difficult to maintain consistent device performance.[7] Compliance-related issues can have serious consequences for manufacturers because they must have the ability to generate customized, post-market real-world data in a timely manner that meets regulatory requirements and expectations.[8,9] Therefore, a deeper understanding of the complex and rapidly changing regulatory framework is needed.[29] This study has performed a cross-agency comparison and case analysis by country (FDA, EMA, PMDA, and MFDS) with the aim of securing clinical evidence regarding the post-marketing safety and effectiveness of CDx.

There are no specific requirements for PMS for CDx, as PMS activities are conducted by risk class in all four countries. Therefore, general IVD requirements should be followed. PMS activities require data to ensure safety and effectiveness during the expected life cycle or post-marketing of the device and are conducted with the common goal of investigating previously unidentified risks or experiences. However, it has been confirmed that there are institutional differences in PMS activities determined by each regulatory authority, and the data or data required may vary accordingly. The FDA requires the collection of post-marketing data in certain situations where there is uncertainty about the specific benefits or risks of a device. The EMA requires that the safety and performance of devices be verified throughout their life cycle, or that previously unidentified risks be identified and analyzed. PMDA is required to collect information on the quality, effectiveness, and safety of the device through three types of investigations and prepare operating procedure manuals and plans accordingly, requiring as much actual clinical field data

as possible. The MFDS requires that the safety and effectiveness of certain licensed devices be evaluated to ensure they meet current scientific standards and that their performance be updated. The data or evaluation items required may also vary depending on these regulatory systems.

Identifying country-specific regulatory requirements and conducting case studies has the potential to provide evidence to support effective practical application. These studies are expected to help CDx manufacturers and developers secure evidence on post-marketing safety and effectiveness, and to be useful as evidence to help establish systematic regulatory strategies and implement efficient practices. However, data on the EU's post-marketing analysis cannot be used because the database EUDAMED is still not fully functioning and cannot be found in the database due to transparency issues with information disclosure.[30] Therefore, it is judged that there will be a need to supplement the current research through case studies using actual data in the future. In particular, new study designs and data considerations may need to be applied according to regulators and other stakeholder. Research to generate real-world data, such as post-marketing clinical trials, is a valuable activity because it can optimize the quantity and quality of samples, enroll diverse patients, and supplement clinical evidence that was lacking during the initial introduction of the product.[31]

In the United States, EU, Japan, Korea, and other countries where CDx regulations have been implemented, they are considered an important progress point in ensuring patient safety and improving treatment.[26] As such, the strengthening of regulatory requirements will lead to institutional differences across countries. Therefore, it is expected that we will see many efforts to realize international harmonization of regulatory systems in the future. In particular, the International Medical Device Regulatory Forum has developed harmonized guidelines to support the establishment of a successful global regulatory strategy for CDx[32,33] and is expected to develop into a more internationally harmonized regulatory environment in the future.

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AUTHOR CONTRIBUTIONS

Conceptualization, investigation: S.L.K.; Data collection, extraction & analysis: S.L.K. and J.Y.K.; Writing – original draft, review & editing: S.L.K. and J.Y.K.; Visualization: J.Y.K.; Supervision, project administration, S.M.K.

DECLARATION OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

SUPPLEMENTAL INFORMATION

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