The 22nd Regular Meeting on Approval Review and Safety Measures for Medical Devices and In Vitro Diagnostics

2024.10.07

Opinions and requests from the in vitro diagnostics industry

1. Requests for revision to the Pharmaceuticals and Medical Devices Act (PMD Act)
   - 1-1 Revision of classification of in vitro diagnostics (separation from pharmaceuticals)
   - 1-2 Revision of manager qualification for businesses (marketing, manufacturing, wholesale sales)

2. Adjustment of review requirements and standards
   - 2-1 Clarification of the purpose of analytical/clinical performance evaluation and agreement and setting of requirements based on them
   - 2-2 Review of the scope of partial/minor changes

3. Optimization of the scope of in vitro diagnostics
   - 3-1 Review of the scope of in vitro diagnostics (revision of Notification No. 662)
   - 3-2 Review of the handling of common reagents

1. Requests for revision to the Pharmaceuticals and Medical Devices Act (PMD Act)

1-1 Revision of classification of in vitro diagnostics (separation from pharmaceuticals)

【Current situation】

- The current Pharmaceuticals and Medical Devices Act covers products classified as "pharmaceuticals," "quasi-drugs," "cosmetics," "medical devices," and

"regenerative medicine products." In vitro diagnostics are classified as "pharmaceuticals," but they have different characteristics from pharmaceuticals.

- ✓ In contrast to pharmaceuticals, which are primarily used directly on humans, in vitro diagnostics have the characteristic of not being used directly on humans.
- ✓ Unlike pharmaceuticals, whose efficacy and safety are determined by the "substance (active ingredient)," the performance (efficacy and safety) of an IVD product is determined throughout the entire testing process, including the skills of clinical laboratory technicians and the usage environment.

- Under current regulations, in vitro diagnostics are not simply regulated as pharmaceuticals; there are some parts that are subject to unique regulations for in vitro diagnostics and other regulations similar to those for "medical devices," and overall they are subject to different regulations than pharmaceuticals.
  - ✓ Regarding manufacturing and quality control, the QMS Ministerial Ordinance, which is the same as for medical devices, applies, and the system is designed differently from pharmaceuticals.
  - ✓ Their position as marketing business has also been separated from the pharmaceutical category and they have been independently designated as in vitro diagnostic marketing business and are listed in the Pharmaceuticals and Medical Devices Act alongside medical devices.

- Unlike the classification used in Japan, in other countries in vitro diagnostics are classified as "medical devices" rather than "pharmaceuticals" and are regulated similarly to medical devices, hence no international harmonization of regulations.

【Subjects】

- Although classified as "pharmaceuticals," in vitro diagnostics have characteristics that differ from pharmaceuticals, and it is necessary to consider regulations that are appropriate to the characteristics of in vitro diagnostics.

【Requests】

Considering the characteristics of in vitro diagnostics and international

harmonization, we would like to see a review of the classification of in vitro diagnostics and make them separation from "pharmaceuticals."

1. Requests for amendments to the Pharmaceuticals and Medical Devices Act (PMD Act)

1-2 Revision of manager qualifications for businesses (marketing, manufacturing, wholesale sales)

【Current situation】

- Since in vitro diagnostics are classified as "pharmaceuticals," the qualifications for each manager (general manager responsible for marketing (MAH general), manufacturing manager, and supervising pharmacist) in each business type (marketing, manufacturing, and wholesale distribution) are stipulated to be a "pharmacist," just like for pharmaceuticals.

【Subjects】

- For quality control and post-marketing safety management of in vitro diagnostics, knowledge of the characteristics of in vitro diagnostics and the entire testing system is more important than pharmacology or pharmacokinetics. In addition, to understand testing systems that use new technologies that have emerged due to recent technological advances, it is becoming necessary to acquire knowledge other than that required to obtain a "pharmacist" license.

- In addition to academic background and qualifications, managers need to have business knowledge, ethics and integrity, communication skills, management skills, and leadership skills, and for this reason, securing and developing managerial personnel has become a challenge for companies (Reference Material 1).

【Requests】

We would like the manager requirements for businesses (marketing, manufacturing, and wholesale sales), which are currently limited to pharmacists, to be revised to take into account the characteristics of in vitro diagnostics.

2. Adjustment of review requirements and standards
2-1 Clarification of the purpose of analytical/clinical performance evaluation and agreement and setting of requirements based on them

【Background】

- The handling of applications for marketing approval in vitro diagnostics is indicated in the notification "Points to Note When Applying for Approval to Manufacture and Market In Vitro Diagnostics" (Notification MHLW PFMC- No. 1121-16 dated November 21, 2014) (hereinafter, "Notice of Points to Note for Applications"). However, there has been an increase in cases where items that were not previously required at the time of approval review are newly required, which is thought to be due to changes in the regulatory environment.

- Since the development of in vitro diagnostic reagents takes anywhere from several years to over a decade, any changes to the review requirements require advance notice and a certain transitional period.

【Subjects】

- There are cases where there is a discrepancy in understanding of the review requirements between the reviewers and the applicants, which means it takes time to respond to the reviewers' sudden requests, and in the worst case scenario, this may result in the application being withdrawn or development having to be restarted.

【Requests】

- We would like to clarify our thoughts on the evaluation samples (definition of clinical samples) for the tests conducted to prepare application documents and ensuring the reliability of the tests (blinding, etc.), which are the main cause of the misunderstanding.

- We would like you to thoroughly discuss the matters necessary for approval review and the areas that need improvement, and then revise the documents, for example by incorporating them in the Notice of Points to Note for Application (including administrative communications, etc.). However, for points that can

be improved in the current notices, we would like to proceed step by step (publicizing them at training sessions, etc.) as necessary, after discussion.

2. Adjustment of review requirements and standards
2-2 Review of the scope of partial/minor changes

【Current situation】

- The scope of partial and minor changes to the marketing approval and certification items for in vitro diagnostics is indicated in the following Notice of Points to note.
  - ✓ "Points to Note when applying for marketing approval In Vitro Diagnostics" (Notification MHLW PFMC- No. 1121-16 dated November 21, 2014), (Partially amended by Notification MHLW PFMC- No. 0120-5 dated January 20, 2015).

【Subjects】

- Nearly 10 years have passed since the issuance of the Notice of Points to Note, and in vitro diagnostics have appeared in response to developments in science and technology and the diversification of the purposes of clinical testing. It is therefore necessary to develop appropriate requirements and standards for the review.

【Requests】

We would like you to review the scope of partial and minor changes to marketing approvals, etc.

3. Optimization of the scope of in vitro diagnostics
3-1 Review of the scope of in vitro diagnostics (revision of Notification No. 662)

【Current situation】

- The current uses of in vitro diagnostic reagents are specified in the Notification No. 662 issued by the Director-General of the Pharmaceutical Affairs Bureau of the Ministry of Health and Welfare on June 29, 1985 (Notification No. 662).

- On the other hand, with the advancement of diagnostic technology, in vitro diagnostics for providing information necessary for medical care/treatment or for prognosis/risk assessment have been developed, and the uses of in vitro diagnostics are becoming more diverse.

- The uses of in vitro diagnostic reagents overseas are clearly stated as "prognosis, prediction, understanding of physiological/pathological conditions, testing at the time of transplantation and deciding on treatment, etc."

【Requests】
In light of the diversification of the purposes of clinical testing, and taking into consideration consistency with overseas regulations, we would like you to review the scope of in vitro diagnostic reagents (revision of Notification No. 662) and set appropriate review requirements in line with the uses and risks.

3. Optimization of the scope of in vitro diagnostics
3-2 Review of the handling of common reagents

【Background & Current situation】
- By combining specimen testing reagents and analytical equipment, and standardizing measurement principles and reaction times across multiple items, automation of specimen testing became possible in the late 1980s.

- One of the regulatory requirements for in vitro diagnostics classified as pharmaceuticals is to specify the components and quantities involved in the reaction. For example, in the case of a measurement system that uses chemiluminescence as its measurement principle, a reagent that stimulates common chemiluminescence to multiple items (common reagent) is included as a component. Therefore, the regulatory procedures for multiple measurement items that use the same analytical equipment must include a description of the common components (Reference 2).

- Since this common reagent is positioned as a component of an in vitro

diagnostic reagents, it is subject to the same regulations as an in vitro diagnostics in terms of labeling, sealing, distribution, etc.

【Requests】

We would like to see it possible for common reagents, which are currently positioned as components of in vitro diagnostic reagents, to be positioned under the regulations as components of analytical equipment used in combination with in vitro diagnostic reagents.

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