Current Situation of Regulations and Premarket Review in Future of Companion Diagnostics in Japan

Daisei Miyamoto
Pharmaceuticals and Medical Devices Agency (PMDA)
Review Director, Office of Medical Devices II
Approval Reviews of IVD Products (Devices and Reagents)

<Disclaimer>

The views and opinions expressed in the following slides are those of the individual presenter and the opinions may be different from the official opinions as PMDA in future.
In vitro diagnostic products are contributing significantly to provide the information for diagnosis, treatment and observation of diseases.

In vitro diagnostic products and systems are consisted by many technologies such as chemical, immunological, biological, electronic and engineering and are improved continuously and speedily.
Organization of PMDA for Review and PMS

- Office of Review Administration
- Office of Standards and Guidelines Development
- Office of International Program
- Office of Review Management
- Office of New Drug I - V
- Office of Cellular and Tissue-based Products
- Office of Vaccines and Blood Products
- Office of OTC/Generic Drugs
- Office of Medical Devices I, II, III
- Office of Conformity Audit
- GLP, GCP, GPSP Inspections

- Office of Safety I, II
- Office of GMP/QMS Inspections
Pharmaceutical Affairs Law (2002)

Article 2 Clause 1
[Drug] subject to the regulation in PAL are defined as the following substances.

ii ） Substances ( other than quasi-drugs ) which are intended for use in the diagnostics, treatment or prevention of diseases in humans or animals, and which are not equipment, dental materials, medical supplies or sanitary materials.

x iii ） Under the PAL, [In vitro diagnostics drugs ( reagents )] are defined the drug which are intended for use in the diagnostics of diseases, and which are not used directly on humans or animals.
Under the PALJ

* \textit{In vitro} diagnostics \textbf{reagents} are categorized in the \textbf{drugs}.
* \textit{In vitro} diagnostics \textbf{equipments} are categorized in the \textbf{medical devices}.

Although IVD reagents are categorized in the drugs, IVD reagents are controlled under the similar rules as the medical devices.

- Risk based classification
- Generic name
- QMS
- Essential principle
General principles for Classification of IVD Reagents

- *In vitro* diagnostic reagents are given generic names and, according to the risks involved, a classification is assigned to all the generic names, which are regulated as required depending on their respective classification.

- Although they are similar to Medical devices from the standpoint of risk-based classification, in case of *In vitro* diagnostic reagents, the focus of the classification is on “diagnostic risk”

- The products are subdivided into those with relatively low diagnostic information risk and others, with those having diagnostic risk classified into two categories.
## Classification of IVD Reagents (2)

<table>
<thead>
<tr>
<th>Risk</th>
<th>Class</th>
<th>Risk Level and Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>Class I</td>
<td>Its diagnostic information risk is relatively low when used in the diagnosis of disease and which its accuracy in terms of the information which they provide is believed to have a relatively weaker impact on life support in comparison with Class III Products. These products contain calibration standards and allow for easy self–checking. However, they do not include OTC products. Example: GOT, GPT, LDH, Estradiol.</td>
</tr>
<tr>
<td></td>
<td>Class II</td>
<td>Its diagnostic information risk is relatively low when used in the diagnosis of disease and which its accuracy in terms of the information which they provide is believed to have a relatively weaker impact on life support in comparison with Class III Products. They include OTC products. Example: Blood Cell Morphology, Autoimmunity.</td>
</tr>
<tr>
<td>Other</td>
<td>Class III</td>
<td>Its diagnostic information risk is relatively high when used in the diagnosis of disease and which its accuracy in terms of the information which they provide is believed to have a relatively strong impact on life support. Example: HIV, HCV, Tumor markers, Microbiology.</td>
</tr>
</tbody>
</table>
Classification and Type of Regulation

<table>
<thead>
<tr>
<th>Classification</th>
<th>Type of Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Self declaration (Market Notification)</td>
</tr>
<tr>
<td>Class II</td>
<td>3rd party Certification (Marketing Certification)</td>
</tr>
<tr>
<td>Class III</td>
<td>MHLW Approval (Marketing Approval)</td>
</tr>
</tbody>
</table>
Category of Approval Applications for IVD Reagents

1. Novel Products
   Products intended to detect or measure novel parameters

2. Products without approval standard
   Products for which approval standards have not been set
   Example: HIV, HCV, HBV, HTLV, Genetic tests

3. Products with approval standard
   Products for which approval standards have been set
   and which meet the approval standards

4. Non-compliance products
   Products for which approval standards, compliance
   certification standards, and standards for waiver of
   approval or certification have set, and which do not meet
   those standards.
Requirements for Approval Application

1. Generic Name (Product Name)
2. Intended of Use
3. Components and Test Principle
4. Main active ingredients
5. Package form
6. Assay procedure or Handling method
7. Manufacturing procedure
8. Storage conditions and Shelf life
9. Manufacturer
   (10. Manufacturer of Drug substances)
11. Remark
## Contents of Approval Application Documents

<table>
<thead>
<tr>
<th>Attached Document (registration data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. History of development and Status of use in foreign countries</td>
</tr>
<tr>
<td>2. Design control</td>
</tr>
<tr>
<td>3. Stability data</td>
</tr>
</tbody>
</table>

| 1. History of development, Status of use in foreign countries and Indication |
| 2. Measurement method, Main ingredients and Similarity to existing products |
| 1. Quality Control |
| 2. Measurement range |
| 3. Calibration and traceability |
| 4. Conformity assessment |
| Storage condition and Shelf life |
## Contents of Approval Application Documents (2)

### 4. Kit Performance

<table>
<thead>
<tr>
<th>Attached Document (registration data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Performance (Recovery test and Dilution test)</td>
</tr>
<tr>
<td>2. Measurement procedure</td>
</tr>
<tr>
<td>3. Specimens (Specificity, Interferences)</td>
</tr>
<tr>
<td>4. Correlation with existing products</td>
</tr>
<tr>
<td>5. Seroconversion data *HIV, HBV, HCV</td>
</tr>
</tbody>
</table>

### 5. Risk analysis

| 1. Risk management (ISO14971) |
| 2. Hazard and Hazardous situation |

### 6. Manufacturing method

| Manufacturing process and Manufacturing site |

### 7. Clinical examination

| Clinical performance study data |
# Contents of Approval Application Documents (3)

3 : Stability  5 : Manufacturing method  7 : Clinical examination

Ο : Mandatory  X : no requirement  △ : upon requirement

<table>
<thead>
<tr>
<th></th>
<th>1 History</th>
<th>2 Design control</th>
<th>3 Kit performance</th>
<th>5 Risk</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novel Products</td>
<td>Ο</td>
<td>Ο</td>
<td>Ο</td>
<td>Ο</td>
<td>Ο</td>
<td>Ο</td>
</tr>
<tr>
<td>Products without approved std.</td>
<td>Ο</td>
<td>Ο</td>
<td>Ο</td>
<td>Ο</td>
<td>Ο</td>
<td>Ο</td>
</tr>
<tr>
<td>Products with approved std.</td>
<td>X</td>
<td>Ο</td>
<td>△</td>
<td>X</td>
<td>△</td>
<td>Ο</td>
</tr>
<tr>
<td>Non-compliance Products</td>
<td>Ο</td>
<td>Ο</td>
<td>Ο</td>
<td>Ο</td>
<td>Ο</td>
<td>Ο</td>
</tr>
</tbody>
</table>
Projects across Multi-Offices in PMDA

- Microdose Trials Project
- Post-approval Manufacturing Changes Project
- In Vitro Companion Diagnostic Devices Project
- Pediatric and Orphan Drugs Project
- Omics Project
- etc

- In Vitro Companion Diagnostic Devices Project Team
  - Discuss the issues and the required guidelines for companion diagnostics

Project members: Offices of Standards and Guidelines Development, New drugs, Medical Devices and Safety
Services of the Office of Medical Devices

Approval Review Services

Scientific reviews (efficacy, safety and quality) of medical devices and IVD reagents for marketing authorization based on the Pharmaceutical Affairs Law of Japan

Consultation and Face-to-face Advice Services

Guidance and Advice for planning and implementation of clinical trials (clinical examination) and approval application documentation
Consultation and Face-to-Face Advice

PMDA recommend manufacturers considering developing the products to request a meeting (Consultation and Face-to-Face Advice) with the relevant IVD reagent review division as early in development as possible.
Upon request, PMDA offers the following face-to-face guidance and advice.

- Clinical Examination Consultations
- Preliminary interview before Approval Application
- Simplified consultations
Clinical Examination Consultations

- discuss with clinical specialists in the target subject areas,
- in accordance with scientific data, based both on feasibility and assessment of ideal products,
- as well as on the consideration of the needs and actual conditions of clinical settings.
- A written record of the discussions is retained along with the materials.

【Contents of Clinical Examination Consultation of IVDs】

Guidance and Advice regarding to

: clinical examination design
: protocols of non-clinical examination
: testing method
: need for clinical examination
【Preliminary interview before Approval Application】
  time : when clinical development is over or nearing completion
  purpose : preparation for filing approval application
  subjects : putting together documentation
              completeness of documentation etc.

【Filing Consultations】
* guidance and advice on the formal completeness of
  materials to be attached when filing approval application
* exclude any counseling involving data assessment
* Example ; A formal check of completeness of application
  materials
Thank you for your Atentions!

Daisei Miyamoto, Ph.D.
Office of Medical Devices II, PMDA

URL: http://www.pmda.go.jp/english/