Points to Consider: Concurrent Development of Companion Diagnostics and Corresponding New Drugs. What are Issues? Where are We? Where are We Going?

Masaaki Urata
Office of Medical Devices II
In Vitro Companion Diagnostics Devices Project
Pharmaceuticals and Medical Devices Agency (PMDA)
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In Vitro Companion Diagnostic Devices Project in PMDA

We organize the points and issues on companion diagnostics (CoDx) and prepare the necessary guidance.

- Offices of New Drug
- Offices of Medical Devices
- Offices of Safety
- Office of Standards and Guidelines Development
### Activity of In Vitro Companion Diagnostic Devices Project

<table>
<thead>
<tr>
<th>Publication Date</th>
<th>Title</th>
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<tbody>
<tr>
<td>2013. 7 (MHLW)</td>
<td>Notification and Q&amp;A on CoDx management (We cooperated with MHLW for publishing them.)</td>
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<tr>
<td></td>
<td>Guidance to show general principles and technical consideration on the development of CoDx</td>
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PMDA and MHLW cooperation.
Today's Presentation

1. Overseas Regulations on Biomarkers and CoDx
2. Notification and Q&A on CoDx Management (July 1st, 2013)
3. Draft Guidance to Show General Principles and Technical Consideration on the Development of CoDx (Points to Consider)
1. Overseas Regulations on Biomarkers and CoDx

✓ FDA
✓ EMA
Guidances and Papers on Biomarkers and CoDx in FDA (1/2)

<table>
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<tr>
<th>Publication Date</th>
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<tr>
<td>2005. 3</td>
<td>Guidance for Industry: Pharmacogenomic Data Submissions</td>
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<td>2005. 4</td>
<td>Draft preliminary concept paper: Drug-Diagnostic Co-Development Concept Paper</td>
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<td>2008. 4</td>
<td>Guidance for Industry: E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories 【ICH-E15】</td>
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<td>Draft Guidance for Industry and Food and Drug Administration Staff: In Vitro Companion Diagnostic Devices</td>
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## Guidances and Papers on Biomarkers and CoDx in FDA (2/2)

<table>
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<tr>
<th>Publication Date</th>
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<tr>
<td>2011. 8</td>
<td>Guidance for Industry: E16 Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions 【ICH-E16】</td>
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<tr>
<td>2012. 12</td>
<td>Draft Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products</td>
</tr>
<tr>
<td>2013. 1</td>
<td>Guidance for Industry: Clinical Pharmacogenomics: Premarket Evaluation in Early Phase Clinical Studies and Recommendations for Labeling</td>
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</table>
FDA Draft Guidance on CoDx

Draft Guidance for Industry and Food and Drug Administration Staff: In Vitro Companion Diagnostic Devices (2011. 7)

Main Contents:

✓ Definition of CoDx
✓ Review and approval of CoDx and therapeutic products
✓ Labeling
Guidance and Paper on Biomarkers in FDA

Draft Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products (2012. 12)

One of contents:

✓ Clinical studies for biomarker-negative patients


One of contents:

✓ Retrospective analysis of biomarkers
## Guidances and Papers on Biomarkers in EMA (1/2)

<table>
<thead>
<tr>
<th>Publication Date</th>
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<tr>
<td>2002. 11</td>
<td>Position Paper on Terminology in Pharmacogenomics</td>
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<td>2007. 4</td>
<td>Reflection Paper on the Use of Pharmacogenomics in the Pharmacokinetics Evaluation of Medicinal Products</td>
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<tr>
<td>2007. 11</td>
<td>Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling</td>
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<td>ICH E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories 【ICH-E15】</td>
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<td>2008. 4</td>
<td>Draft; Reflection paper on pharmacogenomics in oncology</td>
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## Guidances and Papers on Biomarkers in EMA (2/2)

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<tr>
<td>2010. 6</td>
<td>Draft; Reflection paper on co-development of pharmacogenomic biomarkers and assays in the context of drug development</td>
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<tr>
<td>2010. 9</td>
<td>ICH guideline E16 Genomic biomarkers related to drug response: context, structure and format of qualification submissions 【ICH-E16】</td>
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<td>2011. 6</td>
<td>Draft; Reflection paper on Methodological Issues with Pharmacogenomic Biomarkers in Relation to Clinical Development and Patient Selection</td>
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<tr>
<td>2012. 8</td>
<td>Guideline on the Use of Pharmacogenetic Methodologies in the Pharmacokinetic Evaluation of Medicinal Products</td>
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EMA Reflection Paper on Pharmocogenomic Biomarkers

Draft; Reflection paper on Methodological Issues with Pharmacogenomic Biomarkers in Relation to Clinical Development and Patient Selection (2011. 6)

Some of contents:

✓ Clinical studies for biomarker-negative patients
✓ Retrospective analysis of biomarkers
2. Notification and Q&A on CoDx Management (July 1st, 2013)

- Notification on Approval Application of CoDx and Corresponding Therapeutic Products
- Questions and Answers (Q&A) on CoDx and Corresponding Therapeutic Products
Main Contents of Notification and Q&A on CoDx Management

- Definition of CoDx
- Approval Application and PMDA's Review
Definition of CoDx

- Essential for using the pertinent therapeutic product
- To improve the efficacy or safety of a specific therapeutic product
  1. To identify patients who are expected to respond better
  2. To identify patients who are likely to be at increased risk for adverse reactions
  3. For optimizing the treatment (for example, dose, schedule, discontinuation)
- Except *in vitro* diagnostic devices (IVDs) intended simply for disease diagnosis
In case the CoDx is a first of a kind, application for approval should be made contemporaneously for the CoDx and the corresponding therapeutic product.

The new drug review team and the IVD review team in PMDA coordinate adequately (clinical trial consultation during the development and review).
3. Draft Guidance to Show General Principles and Technical Consideration on the Development of CoDx (Points to Consider)

✓ Objective
✓ Drug Part
✓ IVD Part
Objective of the Guidance

To show **general principles and technical consideration** on the development of CoDx

Smooth and appropriate development and review of CoDx and corresponding drug

It is better to consult PMDA if necessary.
Points to Consider

✔ Drug part of the guidance

1) Clinical studies for biomarker-negative patients
2) Retrospective analysis of biomarkers
3) Validation of CoDx before initiation of confirmatory studies

Today's Topic
Points to Consider

✓ Drug part of the guidance

1) Clinical studies for biomarker-negative patients

an assumption:

a Drug for ○○-positive patients
(for example, Molecular targeted drug)
Points to Consider

One of Viewpoints of Developers or Medical Scientists

Theoretically, in case of molecular targeted drug, biomarker-negative patients do not respond to the drug.

It is useless or ethically problematic to administer the drug to patients diagnosed with biomarker-negative.

On the other hand,

There is a case that biomarker-negative patients respond to the drug (for example, crizotinib).
Crizotinib (1/2)

✓ Approval letter of FDA (post-marketing requirement)

1789-11 (an extract, partial change)

- To assess the adequacy of the current cut-off, conduct a clinical trial to explore response to crizotinib in ALK-negative patients based on current assay cut-off. This should be compared to historic controls and to the response in ALK-positive patients.

- Additional biomarkers should be assessed in ALK-negative patients.
Crizotinib (2/2)

- Presentation of FDA (ASCO, 2012) (an extract, partial change)

<table>
<thead>
<tr>
<th>ALK</th>
<th>Response Rate</th>
<th>N</th>
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<tbody>
<tr>
<td>ALK FISH Positive</td>
<td>50%, 61%</td>
<td>136, 119</td>
</tr>
<tr>
<td>ALK FISH Negative</td>
<td>26%</td>
<td>23</td>
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Efficacy for ALK-negative patients was suggested to some extent.
Rationale for the efficacy in Biomarker-Negative Patients

- **Issue of Pharmacology**: Off-target effect
- **Issue of IVDs**: Detection sensitivity of IVD
- **Issues of Specimens**:
  - Quality of specimens
  - Intra-tumor heterogeneity
Points to Consider

Indeed, a cause of efficacy in biomarker-negative patients may be often unknown in premarketing.

However,

It is useful to investigate whether biomarker-negative patients respond to the specific drug according to circumstances and, if so, to provide such information for an opportunity of investigation to determine the cause.
Points to Consider

To evaluate the following:

- Validity of clinical cut-off value of biomarker
- Benefit-risk balance between biomarker positive and negative patients

**In principle, it is necessary to include both biomarker-positive and biomarker-negative patients in clinical exploratory studies.**
Points to Consider

Examples of Exceptions

✓ Nonclinical or clinical data has showed that it is unlikely that the specific drug is effective for biomarker-negative patients.
✓ The specific drug causes serious side effect.

Practical use of consultation at an early stage is desirable!
Points to Consider

✓ Drug part of the guidance

2) Retrospective analysis of biomarkers
To conduct retrospective analyses of biomarkers with stored specimens of clinical studies conducted previously is useful for improvement of benefit-risk balance of drugs and recommended.

- Such retrospective analyses of biomarkers are, however, exploratory.
- An issue of bias is to be considered.
It is desirable to conduct prospective comparative studies for biomarker-positive patients separately for verification.
Points to Consider

Examples of Exceptions

- Biomarkers related to safety of the specific drug (the biomarker is related to serious side effect.)

- It is difficult to conduct prospective comparative study for a limited number of patients as the result of patient selection with biomarkers.

- Retrospective data might be acceptable from the viewpoint of regulation/science if the following aspects (see next slide) are fulfilled.
Points to Consider

We are considering the following points, referring to "Draft; Reflection paper on Methodological Issues with Pharmacogenomic Biomarkers in Relation to Clinical Development and Patient Selection (EMA, 2011. 6)".

Retrospective data might be acceptable from the viewpoint of regulation/science if the following aspects are fulfilled.

1. Availability of biomarker status information from majority of the subjects (as many as possible) in RCTs
2. Data obtained with the CoDx of which analytical validation has been fully evaluated
3. A predefined hypothesis as well as analysis plan
4. A statistically compelling association having adjusted for multiple testing
5. Replication of results in one or more independent samples.
Points to Consider

✓ IVD part of the guidance
  1) Clinical utility of CoDx
  2) Concordance study
  3) Validation of CoDx

Today's Topic
Points to Consider

In principle (as for concordance study)

- The results of the new IVD should be compared to that of the clinical trial assay (CTA) used in clinical confirmatory study to evaluate equality of performance.

- It is important to conduct the concordance study between the new IVD and the standard test to evaluate analytical performance of the new IVD.
Points to Consider

Examples of points in conducting concordance study

- Basically, it is necessary to use specimens from the patients included in the clinical study of the corresponding drug. It is better to consult PMDA if it is difficult to do so.

- It is important that both positive percentage agreement (PPA) and negative percentage agreement (NPA) are high. It is better to consult PMDA if either PPA or NPA is not high.
To Improve Public Health

Fully Evaluated CoDx

Fully Evaluated Drug
Acknowledgement

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Thank you for your Attention