PMDA Perspectives on Companion Diagnostics Development in Japan

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Presentation Topics

- CDx Regulation in Japan
- CDx Development and Evaluation
- Current Challenges and Future Perspectives
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- CDx Regulation in Japan
- CDx Development and Evaluation
- Current Challenges and Future Perspectives
# Notification and Administrative Notice

<table>
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<tr>
<th>Issue date</th>
<th>Title</th>
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<tr>
<td>July 1, 2013</td>
<td>Notification on Marketing Authorization Application of In Vitro</td>
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<td>Companion Diagnostics and Corresponding Therapeutic products</td>
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<td></td>
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<td>Therapeutic products</td>
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<tr>
<td>Dec 26, 2013</td>
<td>Technical Guidance on Development of In Vitro Companion Diagnostics</td>
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<td>and Relevant Drugs</td>
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<td>Feb 29, 2014</td>
<td>Points to consider on Marketing Authorization Application Form of</td>
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<td>Companion Diagnostics</td>
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<td>Companion Diagnostics</td>
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<td>June-July 2018</td>
<td>Questions and Answers on Application Dossier of Companion Diagnostics</td>
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<td>(in preparation)</td>
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**Notification and Administrative Notice**

- **2013.7.1 Notification**
  - Definition of CDx
    - A companion diagnostic is an in vitro diagnostic reagent or device essential for the safe and effective use of a corresponding therapeutic product
  - Contemporaneous MAA of CDx and therapeutic product

- **2013.12.24 Administrative Notice**
  - Technical Guidance
    - Points to consider for CDx development
    - Evaluation of analytical and clinical performance

- **2014.2.19 2014.3.28 Notification**
  - Description of Application Form

- **2018 July? Administrative Notice**
  - What should be described in application dossier
    - Encourage sharing of the necessary data or information between drug and CDx sponsor
### CDx Approved in Japan

<table>
<thead>
<tr>
<th>CDx Trade Name</th>
<th>Corresponding drug</th>
<th>Biomarker</th>
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</thead>
<tbody>
<tr>
<td>POTELIGEO TEST IHC/POTELIGEO TEST FCM</td>
<td>mogamulizumab</td>
<td>CCR4 protein</td>
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<tr>
<td>Cobas BRAF V600 mutation test</td>
<td>vemurafenib</td>
<td>BRAF mutation</td>
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<tr>
<td>Histofine ALK iAEP kit</td>
<td>alectinib</td>
<td>ALK protein</td>
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<tr>
<td>Vysis ALK Break Apart FISH probe kit</td>
<td>crizotinib and alectinib</td>
<td>ALK fusion</td>
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<tr>
<td>THxID BRAF kit</td>
<td>dabrafenib/trametinib</td>
<td>BRAF mutation</td>
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<tr>
<td>Cobas EGFR mutation test v2.0</td>
<td>osimertinib</td>
<td>EGFR mutation</td>
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<tr>
<td>OncoGuide AmoyDx ROS1 Gene Fusions Detection Kit</td>
<td>crizotinib</td>
<td>ROS1 fusion (RNA)</td>
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<td>PD-L1 IHC 22C3 pharmDx [Dako]</td>
<td>pembrolizumab</td>
<td>PD-L1 protein</td>
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<tr>
<td>Ventana OptiView ALK (D5F3)</td>
<td>crizotinib and ceritinib</td>
<td>ALK protein</td>
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<td>MEBGEN RASKET-B kit</td>
<td>cetuximab and panitumumab</td>
<td>KRAS and NRAS mutation</td>
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<tr>
<td>BRACAnalysis CDx</td>
<td>olaparib</td>
<td>BRCA1 and BRCA2 mutation</td>
</tr>
<tr>
<td>Oncomine Dx Target test</td>
<td>dabrafenib/trametinib</td>
<td>BRAF mutation</td>
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as of June 26, 2018
Approval of BRACAnalysis CDx™

- Approved in March 2018 as **medical device software**
- Intended use: aid in identifying breast cancer patients eligible for treatment with Lynparza (olaparib)
- Conditions of approval
  - Submission of annual report on the evaluation of the robustness of the variant classification process, classification changes and newly identified variants.
  - Assurance of cyber security and patient privacy
Analysis of BRCA1/2 gene

- Sanger sequencing
- Multiplex PCR

DNA isolation

Variant call

Variants classification

Analysis results

MD software

Eligibility for Olaparib

BRACAnalysis CDx™ approved as MD software

Physician in Japan

Shipment

Myriad Genetic Laboratories in US

Input: variant data

Output: Eligibility for Olaparib

Conditions to ensure the quality of variant data

Order variant classification

Announce of the completion of variant identification

Reporting

DB

BRACAnalysis CDx™ approved as MD software
Presentation Topics

- Regulation of CDx in Japan
- CDx Development and Evaluation
- Current Challenges and Future Perspectives
CDx Development

- Early stages of the therapeutic product (TP) development
  - Rationale for therapy targeted to a biomarker positive or negative population
  - Determination of the clinical cutoff

- Prior to Major Efficacy Trial
  - Analytical validation studies should be completed.
  - Variables that affect the test result should be specified and controlled.

- Later Stages of the TP development
  - Evaluation of clinical performance of the candidate CDx
  - Confirmation of the cut-off value
Evaluation of CDx

Basic Principles:
- CDx should provide accurate and reproducible results.
- CDx should be able to identify a population expected to benefit from the therapeutic product.

Analytical Performance
- Accuracy
- Precision (repeatability and reproducibility)
- Specificity
- Detection Limit
- Interfering substances
- Cross-contamination
- Robustness

Clinical Performance
What to be described in application dossier

New Administrative Notice expected to be issued in July

- Rationale for clinical cut-off based on exploratory trial data in which both biomarker positive and negative patient were enrolled
- Description of CTA methods used to establish clinical cut-off based on exploratory trial
- Rationale of the clinical cut-off for patient enrollment in major efficacy trial, taking into consideration of the impact of the difference between CTA and the candidate CDx (basically based on concordance study)
Data to be provided for Marketing Authorization Application (MAA) of CDx

- Kit design
- Performance Evaluation
  - Rationale of CDx development
  - Establishment of clinical cut-off

Evaluation of clinical performance & cut-off value

- Test methods
- Sample prep.
- Pre-analytical variables
- Test results
- Efficacy data of BM-positive and negative population

To be described in application dossier

Coordinated MAA of CDx and TP

- Test methods
- Sample prep.
- Pre-analytical variables
- Test results
- Summary of major efficacy trial

Application for NHI coverage

Application for NHI price listing
Regulatory Framework of DNA Sequencing-based Dx System

Class III IVD reagent
- Nucleic acid extraction
- Reagents for library construction

Class I MD
- DNA sequencer

Class III MD
- Software
- Database

Reagents for sequencing sample prep.

DNA sequencing-based Dx system (Combination MD: Class III)
Evaluation of NGS-based CDx

- Basic principles are the same as conventional CDx.
  - CDx should provide accurate and reproducible results.
  - CDx should be able to identify a population expected to benefit from the therapeutic.

- Validation approach considering the characteristic feature of NGS-based system could be possible.
Evaluation of NGS-based CDx

- In principle, clinical specimen should be used to evaluate analytical performance.
- For rare variants, use of contrived sample could be acceptable if the scientific rationale is provided.
- It is acceptable to evaluate analytical performance for the representative subset of variants if scientific rationale is provided.
  - the representative subset of variants should cover the range of variants to be detected by the system.
  - Variant type (SNV, indels, CNV, fusion), genome context, length should be considered.
Follow-on CDx

- Comparability of clinical performance of follow-on CDx to the original CDx could be demonstrated by analytical concordance study.

- Reference in concordance study should be the originator product of which clinical performance is demonstrated based on clinical trial data of the corresponding TP.
  - Approved follow-on CDx should not be a reference in concordance study.

<Possible Issues>
- Acceptability of the reference CDx approved outside of Japan (e.g. US-approved but not Japan-approved CDx)
Presentation Topics

- Regulation of CDx in Japan
- CDx Development and Evaluation
- Current Challenges and Future Perspectives
Challenges in CDx evaluation

- Pan-cancer claim
  - Availability of specimens
  - How to provide evidence to support test performance for all tumor types

- CDx development in rare disease
  - How to ensure analytical and clinical performance with limited specimens
  - How to conduct bridging study
Challenges after implementation of oncology panel into clinical settings

- Possibility to identify patients eligible for TP using oncology panel in medical facilities
  - Use of panel result is expected by physicians considering early patient access to TP and the limitation of clinical specimen
  - Measures to ensure the safety and efficacy of the corresponding TP are necessary.

- Possibility to establish standards for comparability evaluation
  - Comparability of genetic tests, especially for NGS-based tests
Cancer Genome Consortium for Medicine in Japan

11 core medical facilities for cancer genome profiling for medicine

Approx. 100 associate medical facilities

Genome profiling using oncology panel

Annotation of variants using DB

Evaluation of variant annotation and reporting of the possible best treatment by expert panel
Implementation of Oncology Panel in Japanese Clinical Setting

**DNA sequencing**
- Oncology Panel
- DNA sequencer

**Variant call**
- GeneX: c.2611C>T
- GeneY: c.1652A>G
- GeneZ: ...........

**Annotation**
- Pathogenic or Actionable/VUS
- Internal or external Databases

**Software**

**Reporting**
- Pathogenic Variant
- GeneA SNV
- GeneB CNV
- ...

**Internal or external Databases**

**Clinical Specimen**

**Approved as IVD Medical Device**

Discussion on possible treatment for Japanese patient based on the report and related info.

Suggestion of possible best treatment by Expert Panel
Role of approved CDx

- Originally approved CDx serves as standard Dx system to ensure the safety and efficacy of TP.

Clinical Trial

Lab test1
Lab test2
Lab test3
Lab test4

Clinical performance evaluated by concordance study

Post approval of the drug

Originally approved CDx
Reimbursement
After implementation of oncology panel,

The requirement for the diagnostic system to ensure the safety and efficacy of the corresponding therapeutic product will NOT change.

Enrollment of patients based on biomarker A status.

Oncology panel serves as standard Dx system for biomarker A.

Clinical performance evaluated by concordance study.
Further more..

Is it possible to ensure the clinical efficacy and safety of therapeutic product by the establishment of comparability standards?
New administrative notice will be issued soon to clarify the scientific data and justification to be provided in application dossier.

PMDA expects the new administrative notice will be used as a tool to facilitate the communication and data sharing between drug and CDx sponsors.

Along with for the implementation of oncology panel into medical setting in near future, how to evaluate the comparability of NGS-based tests for CDx use is under discussion.
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