Regulatory Perspective and Challenges Regarding Companion Diagnostics in Japan

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Agenda

- Definition of CoDx
- Biomarker-negative patients in clinical trials
- Retrospective analyses on biomarkers
- Information on CoDx in drug labels
- Regulatory challenges
Companion diagnostics WG

Companion diagnostics (CoDx) working group in PMDA

One of the projects across multi-offices in PMDA

Founded in April, 2012

HP: http://www.pmda.go.jp/rs-std-jp/standards-development/cross-sectional-project/0013.html

Principal regulatory guidance in the US

<table>
<thead>
<tr>
<th>Publication Date</th>
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<tr>
<td>April, 2005</td>
<td>Draft preliminary concept paper: Drug-Diagnostic Co-Development Concept Paper</td>
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<tr>
<td>July, 2011</td>
<td>Draft Guidance for Industry and Food and Drug Administration Staff: In Vitro Companion Diagnostic Devices</td>
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<td>Draft Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products</td>
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<tr>
<td>Jan., 2013</td>
<td>Guidance for Industry: Clinical Pharmacogenomics: Premarket Evaluation in Early Phase Clinical Studies and Recommendations for Labeling</td>
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## Principal regulatory guidance in the EU

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<td>June, 2010</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>Aug., 2012</td>
<td>Guideline on the Use of Pharmacogenetic Methodologies in the Pharmacokinetic Evaluation of Medicinal Products</td>
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## Principal regulatory guidance in Japan

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<td>Notification on Approval Application for In Vitro Companion Diagnostics and Corresponding Therapeutic Products</td>
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Definition of CoDx in the US

FDA: Guidance for Industry and Food and Drug Administration Staff - In Vitro Companion Diagnostic Devices

An IVD companion diagnostic device could be essential for the safe and effective use of a corresponding therapeutic product to:

► Identify patients who are most likely to benefit from the therapeutic product

► Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product

► Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness

► Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population

FDA does not include in this definition in vitro diagnostic tests that are not essential to the safe and effective use of a therapeutic product. Uses of diagnostic devices that are suggested but not required in therapeutic product labeling are not considered “essential”.

► Examples of such clinical laboratory tests are commonly used and well understood biochemical assays (e.g., serum creatinine or transaminases) that are used to monitor organ function, but are not essential for the safe and effective use of a therapeutic product.
Definition of CoDx in Japan

PMDA: Notification on Approval Application for *In Vitro* Companion Diagnostics and Corresponding Therapeutic Products

A CoDx is essential for using the pertinent therapeutic product, and corresponds to either of the following (except *in vitro* diagnostic agents or medical devices intended simply for disease diagnosis, etc.):

- that is used to identify patients who are expected to respond better to a specific therapeutic product.
- that is used to identify patients who are likely to be at high risk of developing adverse events associated with a particular therapeutic product
- that is necessary for optimizing the treatment including dose, schedule, and discontinuation of a particular therapeutic product

Q: What examples are there of “*in vitro* diagnostic agents or medical devices intended simply for disease diagnosis” described in Section 1 of this Notification?

A: Examples may include *in vitro* diagnostics that are used for *biochemical assays* related to organ functions such as serum creatinine, transaminases, and blood glucose level, *hematological assays* such as prothrombin time kit, *bacterial or viral identification and susceptibility tests* for infections, as well as *tests used to identify the disease*, check the treatment effect, assist in follow-up observation, or evaluate the severity in routine clinical practice.

However, diagnostics of these types may also be judged as CoDx depending on the clinical necessity, etc.
Agenda

- Definition of CoDx
- Biomarker-negative patients in clinical trials
- Retrospective analyses on biomarkers
- Information on CoDx in drug labels
- Regulatory challenges

Biomarker-negative patients in clinical trials

Rationale for efficacy in biomarker-negative patients

- Difficulty in establishment of cut-off value (or poor performance) of diagnostics, especially IHC tests
  - Ex.) Cetuximab/Panitumumab for EGFR-negative patients
- Poor quality of biospecimens
- Off-target effects of molecular targeted drugs
  - Ex.) Crizotinib for ALK-negative patients (ROS-positive)
- Intra-tumor heterogeneity

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Biomarker-negative patients in the US

FDA: Guidance for Industry : Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products Draft Guidance

- It is generally desirable to have some data in the non-enrichment population to determine whether they respond less well, or indeed do not respond at all.

- These data also can provide an assessment of safety in the non-selected population.

- The data need not be obtained in the controlled trials supporting effectiveness but could be obtained in earlier studies.

A number of considerations would support collection of less information on the non-enrichment-factor population.

- A clear pathophysiologic basis for concluding that the non-enriched population will not respond

- Early clinical studies that show very marked difference in response between the enrichment and non-enrichment populations
Biomarker-negative patients in the EU

EMA: Reflection Paper on Methodological Issues Associated with Pharmacogenomic Biomarkers in Relation to Clinical Development and Patient Selection

The regulatory acceptability of excluding biomarker-negative patients from trials will depend on the strength of evidence (plausibility, scientific rationale and clinical data) provided for the lack of effect in these patients.

Biomarker-negative patients in Japan

PMDA: Technical Guidance on Development of In Vitro Companion Diagnostics and Corresponding Therapeutic Products

It is important to establish a development strategy for a therapeutic product which reflects the necessity of analyzing biomarker-negative patients from early development phase.

In clinical trials in early development phase, such as exploratory dose-response studies, both biomarker-positive and negative patients should be included in principle.
Biomarker-negative patients in Japan

PMDA: Technical Guidance on Development of In Vitro Companion Diagnostics and Corresponding Therapeutic Products

This does not apply to cases where there is good reason not to include biomarker-negative patients in clinical trials, such as cases:

- where it is extremely unlikely that the therapeutic product will show efficacy in biomarker-negative patients from non-clinical or clinical trial data (including retrospective analysis results),

- or where the therapeutic product is highly toxic, strongly suggesting a safety concern that treating a wider range of patients with it would expose them to unreasonable risk.

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Retrospective analyses in the US

FDA: Draft Preliminary Concept Paper - Not for Implementation: Drug-Diagnostic Co-Development Concept Paper

Although prospective data are preferred, in cases where the analyte is stable and where collection bias (including spectrum bias, verification bias, and sampling bias) can be carefully characterized and addressed, prospectively designed retrospective clinical utility studies may be possible.

Retrospective analyses in the EU

EMA: Reflection Paper on Methodological Issues Associated with Pharmacogenomic Biomarkers in Relation to Clinical Development and Patient Selection

Retrospective validation or acceptance of retrospective data in the regulatory/scientific context might be possible if the following aspects are fulfilled:

- data from conducted RCTs (randomized controlled trials)
- availability of marker status information from majority of the subjects in those RCTs

(continued on next slide)
Retrospective analyses in the EU

EMA: Reflection Paper on Methodological Issues Associated with Pharmacogenomic Biomarkers in Relation to Clinical Development and Patient Selection

- A predefined hypothesis as well as analysis plan
- A statistically compelling association having adjusted for multiple testing
- Replication of the results in one or more independent samples

Retrospective analyses in Japan

PMDA: Technical Guidance on Development of In Vitro Companion Diagnostics and Corresponding Therapeutic Products

It is necessary, in principle, to conduct prospective randomized controlled trials. On the other hand, examples of cases where it is difficult to conduct prospective randomized controlled trials include the following three cases:

- Cases where it is difficult to verify its qualification by prospective randomized controlled trials from an ethical point of view, such as cases where it has been suggested that the safety biomarker is associated with extremely serious adverse events.

(continued on next slide)
Retrospective analyses in Japan

PMDA: Technical Guidance on Development of In Vitro Companion Diagnostics and Corresponding Therapeutic Products

- Cases where it is difficult or inappropriate to verify its qualification by prospective randomized controlled trials, such as cases where restricting patient population to be treated based on the status of the efficacy biomarker would make it extremely difficult to conduct a randomized controlled trial from the viewpoint of sample size.

- Cases where evaluation of the biomarker based mainly on the results of the retrospective analyses is acceptable even after considering potential biases arising from the retrospective analyses. (Next Slide)

Evaluation of the biomarker based mainly on the results of the retrospective analyses is acceptable if the retrospective analyses meet all of the following conditions:

- The retrospective analysis derives from randomized controlled trials which were appropriately planned and conducted and in which data were obtained, in principle, from all registered subjects wherever possible.

- The retrospective analysis uses measurement methods which have undergone certain analytical test validation. (continued on next slide)
Retrospective analyses in Japan

PMDA: Technical Guidance on Development of In Vitro Companion Diagnostics and Corresponding Therapeutic Products

- An appropriate hypothesis and statistical analysis on the biomarker had been defined before analyzing data.
- Statistically appropriate analysis in terms of multiplicity adjustment, etc., has been planned and conducted.
- Consistent analytical results have been obtained from results of two or more independent clinical trials each of which meets all of the above four conditions.

Retrospective analyses

Examples: Labeling of Cetuximab/Panitumumab for patients with colorectal cancer

<table>
<thead>
<tr>
<th>Cetuximab</th>
<th>KRAS</th>
<th>RAS</th>
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<tr>
<td>Japan</td>
<td>Precautions for Indications (not CoDx)</td>
<td>Limitation of Use (not CoDx)</td>
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<tr>
<td>US</td>
<td>Indications (CoDx)</td>
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<td>EU</td>
<td>Indications and Contraindications</td>
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<th>Panitumumab</th>
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<td>Japan</td>
<td>Indications (before CoDx regulation)</td>
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Information on CoDx

FDA-approved companion diagnostics and corresponding drugs

HP: http://www.fda.gov/CompanionDiagnostics

- Tarceva (erlotinib)
  - NDA: 021743
  - PMA: P120019
  - Device Manufacturer: Roche Molecular Systems, Inc.
  - Intended Use (IU)/Indications for Use (IFU):
    The cobas® EGFR Mutation Test is a real-time PCR test for the qualitative detection of exon 19 deletions and exon 21 (L858R) substitution mutations of the epidermal growth factor receptor (EGFR) gene in DNA derived from formalin-fixed paraffin-embedded (FFPE) human non-small cell lung cancer (NSCLC) tumor tissue. The test is intended to be used as an aid in selecting patients with metastatic NSCLC for whom Tarceva® (erlotinib), an EGFR tyrosine kinase inhibitor (TKI), is indicated.
Information on CoDx in drug labels in the US

Erlotinib prescribing information in the US

1 INDICATIONS AND USAGE

1.1 Non-Small Cell Lung Cancer (NSCLC)

TARCEVA is indicated for:

- The first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test [see Clinical Studies (14.1)].

2.1 Patient Selection

Select patients for the first-line treatment of metastatic NSCLC with TARCEVA based on the presence of EGFR exon 19 deletions or exons 21 (L858R) substitution mutations in tumor specimens [see Clinical Studies (14.1)]. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

14 CLINICAL STUDIES

14.1 Non-Small Cell Lung Cancer (NSCLC) – First-Line Treatment of Patients with EGFR Mutations

The safety and efficacy of TARCEVA as monotherapy for the first-line treatment of patients with metastatic NSCLC containing EGFR exon 19 deletions or exon 21 (L858R) substitution mutations was demonstrated in a randomized, open-label, clinical trial conducted in Europe (Study 4). One hundred seventy-four (174) White patients were randomized 1:1 to receive erlotinib 150 mg once daily until disease progression (n=86) or four cycles of a standard platinum-based doublet chemotherapy (n=88); standard chemotherapy regimens were cisplatin plus gemcitabine, cisplatin plus docetaxel, carboplatin plus gemcitabine, and carboplatin plus docetaxel. The main efficacy outcome measure was progression-free survival (PFS) as assessed by the investigator. Randomization was stratified by EGFR mutation (exon 19 deletion or exon 21 (L858R) substitution) and ECOG PS (0 vs. 1 vs. 2). EGFR mutation status for screening and enrollment of patients was determined by a clinical trials assay (CTA). Tumor samples from 134 patients (69 patients from the erlotinib arm and 65 patients from the chemotherapy arm) were tested retrospectively by the FDA-approved companion diagnostic, the cobas EGFR Mutation Test.

Information on CoDx in drug labels in Japan

Ex.) Alectinib (ALK inhibitor) / Vysis ALK Break Apart FISH Probe Kit and Histofine ALK iAEP Kit (IHC)

Vemurafenib (BRAF inhibitor) / cobas BRAF V600 Mutation Detection Kit

- "Use approved in vitro diagnostics" is stated in “Precautions for Indications and Usage” section or “Precautions for Dosage and Administration” section in principle.

- The following information on in vitro diagnostics is described in “Clinical Studies” section in principle.

  - Trade name of CoDx
  - Whether this CoDx was used in clinical trials or it was demonstrated that this CoDx is concordant with tests used in clinical trials
  - What are used in clinical trials as tests for biomarker-based patient selection

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### Multiplex diagnostics

Cases where multiplex diagnostics such as next generation sequencing (NGS) are used in clinical trials

1. Multiplex diagnostics for measurement of one biomarker are necessary because there are many mutation sites in the biomarker.

2. "Pattern X determined by multiplex diagnostics" is defined as reasonable target population of a drug such as molecular targeted therapy for an activated signal pathway.

3. Measurement of many biomarkers is necessary because there are many biomarkers with corresponding molecular targeted therapy such as EGFR and ALK etc. in lung cancer (umbrella trial in master protocol).
Clinical use of NGS in the US

In English
Posted: 06/16/2014

NCI Press Release
Lung-MAP Launches: First Precision Medicine Trial From National Clinical Trials Network

A unique public-private collaboration among the National Cancer Institute (NCI), part of the National Institutes of Health, SWOG Cancer Research, Friends of Cancer Research, the Foundation for the National Institutes of Health (FNIH), five pharmaceutical companies (Amgen, Genentech, Pfizer, AstraZeneca, and AstraZeneca's global biologics R&D arm, MedImmune), and Foundation Medicine today announced the initiation of the Lung Cancer Master Protocol (Lung-MAP) trial.
Clinical use of NGS in the EU

PMDA Workshop

PMDA Workshop on CoDx was held on Sep. 1st, 2014.

More than 400 participants from academia, industries and regulators.

This workshop concluded that stakeholders must cooperate to deal with the following issues.

- What type/amount of clinical data are necessary for approval of follow-on CoDx
- How to regulate multiplex diagnostics such as NGS
Main discussion points regarding NGS

Regarding review of marketing authorization applications

- Is each component of NGS in vitro diagnostic or medical device?
- How to evaluate analytical performance of NGS
- How to define “patients with X mutation as detected by approved NGS” as indication of corresponding drug (clinical performance of NGS as CoDx)
- How to ensure quality of clinical database
- How to deal with update of clinical database after marketing authorization of NGS (and corresponding drug)
Conclusions

- The notification and Q&A mainly on definition of CoDx were released in July, 2013 in Japan. The regulatory technical guidance on development of CoDx was released in December, 2013 in Japan.

- Japanese regulatory view on CoDx and selection of patients based on biomarker status is harmonized with the draft concept papers in the US and the EU.

- Clinical use of NGS is inevitable. Japanese original regulatory framework will be necessary for dealing with challenges related to NGS.

Acknowledgment

- Current and former members of companion diagnostics working group of PMDA

  http://www.pmda.go.jp/rs-std-jp/standards-development/cross-sectional-project/0013.html

- Our paper regarding PMDA’s view on CoDx will be published soon.

Ask