Regulatory Perspective on Co-development of Drugs and Companion Diagnostics in Japan, US and EU

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Agenda

• Principal regulatory guidance related to CoDx (Companion Diagnostics) in Japan, the US and the EU

• Definition of CoDx

• Biomarker-negative patients in clinical trials

• Retrospective analyses on biomarkers
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## Principal regulatory guidance in Japan

<table>
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<tr>
<th>Publication Date</th>
<th>Title</th>
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<tr>
<td>July, 2013</td>
<td>Notification on Approval Application for <em>In Vitro</em> Companion Diagnostics and Corresponding Therapeutic Products</td>
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<td>July, 2013</td>
<td>Questions and answers (Q&amp;A) on CoDx and corresponding therapeutic products</td>
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<tr>
<td>Dec., 2013</td>
<td>Technical Guidance on Development of <em>In Vitro</em> Companion Diagnostics and Corresponding Therapeutic Products</td>
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<td>Dec., 2013</td>
<td>Questions and Answers (Q&amp;A) on “Technical Guidance on Development of <em>In Vitro</em> Companion Diagnostics and Corresponding Therapeutic Products”</td>
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## Principal regulatory guidance in the US

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<tr>
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<tbody>
<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Draft Guidance for Industry and Food and Drug Administration Staff: In Vitro Companion Diagnostic Devices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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<tr>
<td>Dec., 2012</td>
<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Draft Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products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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<tr>
<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>June, 2011</td>
<td>Draft; Reflection paper on Methodological Issues with Pharmacogenomic Biomarkers in Relation to Clinical Development and Patient Selection</td>
</tr>
<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 related to CoDx (Companion Diagnostics) in Japan, the US and the EU

• Definition of CoDx

• Biomarker-negative patients in clinical trials

• Retrospective analyses on biomarkers
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 a particular therapeutic result of product
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product
- Monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness
FDA does not include in this definition clinical laboratory tests intended to provide information that is useful to the physician regarding the use of a therapeutic product, but that are not a determining factor in the safe and effective use of the product.

- Examples of such tests are commonly used and well understood biochemical assays (e.g., serum creatinine or transaminases) used to monitor organ function.

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Definition of CoDx in the US

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

• Note, however, that circumstances may occur when use of such tests, in the context of the therapeutic product, rises to an IVD companion diagnostic device level and approval or clearance for such use will be necessary.

• Note also that a novel IVD device providing information that is useful in, but not a determining factor for the safe and effective use of a therapeutic product, would not be considered an IVD companion diagnostic device.
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.
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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.

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<th>FISH</th>
<th>Response Rate (investigator assessments)</th>
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<tr>
<td>ALK-Positive</td>
<td>50%(67/135), 61%(71/116)</td>
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<tr>
<td>ALK-Negative</td>
<td>26%(5/19)</td>
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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.
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),

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Biomarker-negative patients in Japan

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

- 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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American Society of Clinical Oncology Provisional Clinical Opinion: Testing for KRAS Gene Mutations in Patients With Metastatic Colorectal Carcinoma to Predict Response to Anti–Epidermal Growth Factor Receptor Monoclonal Antibody Therapy

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

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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.

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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.

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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.
Conclusions

• The regulatory technical guidance on development of CoDx was released in December, 2013 in Japan. The English version of this guidance as well as the notification is available in the following website.
  
  http://www.pmda.go.jp/english/service/in_vitro_e.html

• PMDA’s view on CoDx and selection of patients based on biomarker status is harmonized with the draft concept papers in the US and the EU.

• PMDA believes that the Japanese new technical guidance contributes to global development of CoDx and personalized medicine.
Acknowledgment

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Thank you

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