Regulator’s Perspective on Precision Medicine

Kaori Shinagawa, MD, PhD
Senior Scientist for Clinical Medicine
Pharmaceuticals and Medical Devices Agency
Visiting Lecturer, Keio University School of Medicine
Disclosure

I have no potential conflicts of interest to report.

Disclaimer

The views and opinions expressed in this presentation are those of the speaker and not necessarily those of PMDA.
Overview

- Japanese position for Precision Medicine
- PMDA strategy and initiatives to promote the development of Personalized and Precision Medicine
  - PMDA The Scientific Board
  - Regulatory issues related to Pharmacogenomics/Biomarkers
  - Regulatory issues related to Companion Diagnostics
- Examples of Precision Medicine in Cardiology
- Comments on Precision Medicine in Cardiology
Personalized and Precision Medicine (PPM)

**Precision medicine**
An evolving strategy for disease prevention and tailored treatment that incorporates individual genetic, environmental, and experiential variability

**Possible advantage of Precision medicine**
- Identifying patients most likely to benefit and those most likely to experience adverse reactions in response to a drug
- Increasing the treatment effect
- Contributing to the reduction of the medical cost
- Increasing the success rate in developing innovative new drugs
The strategies proclaim promotion of R&D by leading-edge technologies, including

1. promotion of the simultaneous development of molecular-targeted drugs and \textit{in vitro} diagnostics (companion diagnostics) for predicting the efficacy of drugs and their adverse reactions,

2. promotion of research related to the methods for evaluating the companion diagnostics in coordination with drug review

3. reinforcement of research on the development and evaluation methods to promote the practical application of personalized medicine.

Japanese government supports the development of PPM Healthcare Policy Strategy (The Cabinet of Japan, June 14, 2013)
2.1. Personalized medicine in cancer therapy

- An all-inclusive approach encompassing epigenomic analysis and other omics analyses are expected to be accelerated, resulting in diversification of cancer drugs.
- Another recent movement is to achieve personalized medicine based on multi-level omics analysis by combining proteome, metabolome, transcriptome, epigenome analyses, etc.
- Development of companion diagnostics is a critically important factor in increasing the success rate of tests in drug development.
Approved drugs with Pharmacogenomics (PGx) information on their labels in Japan

- The number represents approved PGx information on drug label under the section dosage/administration or indication/usage.

![Graph showing the number of approved drugs with PGx information on their labels in Japan over fiscal years from 2002-03 to 2014-15.](image)

Ootsubo Y et al, Pharmacogenomics, 2013 (Updated until FY2015)
UGT1A1 allele and irinotecan-induced neutropenia

Irinotecan Label ('08/6)

[Important Precautions]

• UGT1A1 alleles (*6 and *28) have been reported to be associated with a risk of irinotecan-induced SAE (neutropenia)
• Data from prospective study shows the higher frequency of neutropenia in the Japanese subjects homozygous for *6 or *28 or double heterozygous (*6/*28)

[Clinical Studies]

<table>
<thead>
<tr>
<th>UGT1A1 allele</th>
<th>Gr. 3 &amp;4 neutropenia</th>
<th>Gr. 3 &amp;4 thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>UGT*6/00/28</td>
<td>14.3% (3/21)</td>
<td>14.3% (3/21)</td>
</tr>
<tr>
<td>UGT*6/00/28</td>
<td>24.1% (7/29)</td>
<td>6.9% (2/29)</td>
</tr>
<tr>
<td>UGT*6/00/28</td>
<td>80.0% (4/5)</td>
<td>20.0% (1/5)</td>
</tr>
</tbody>
</table>

Biomarker information in the drug label
PMDA perspective on PGx guided drug development

- Drug development using PGx/Biomarkers (BM)

Pre clinical
- Synthesis, Preparation, Pharmacology, Toxicology

Clinical
- IND
- Phase I
- Phase II
- Phase III
- NDA

Post Market
- Phase IV

- Predicting toxicity
- Research/Select Candidates of BM, Mechanism
- Dose adjustment
- Trial enrichment
- Exploratory analysis for Inclusion/exclusion criteria
- BM for efficacy/safety monitoring
PGx/BM qualification by regulatory authorities

- PMDA scientific consultation regarding PGx/BM qualification
  - Provide an official consultation report to the applicant
- Focus on PGx/BM qualification for clinical or nonclinical context of use but not individual drug/diagnostic development
- Qualification: A graded, fit-for-purpose evidentiary process linking a biomarker with biological and clinical end points
  - Required by the PMDA, FDA and the EMA for a biomarker to be used as an end point in clinical trials that are intended to support the regulatory approval of a drug

Diagram:
- FDA
- Joint meeting (J-VXDS)
- EMA
- Confidential Agreement
- BM qualification meeting (VXDS)
- PMDA
- Consultation on PGx/BM qualification
- Private sector
Definition of Companion Diagnostics (CDx) in Japan

A companion diagnostic is an in vitro diagnostic reagent or device essential for the safe and effective use of a corresponding therapeutic product to:

- identify patients who are most likely to respond to the therapeutic product
- identify patients who are likely to be at increased risk for adverse reactions by the treatment of the therapeutic product
- optimize the dosage and administration or discontinuation of the therapeutic product

An in vitro diagnostic reagent or device used for diagnosis, but not a determining factor of the use of a therapeutic product, is **NOT** considered companion diagnostic.
<table>
<thead>
<tr>
<th>CDx Trade Name</th>
<th>Drug Trade Name (INN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POTELIGEO TEST IHC</td>
<td>POTELIGEO (Mogamulizumab)</td>
</tr>
<tr>
<td>POTELIGEO TEST FCM</td>
<td></td>
</tr>
<tr>
<td>Cobas BRAF V600 mutation test</td>
<td>Zelboraf (vemurafenib)</td>
</tr>
<tr>
<td>Histofine ALK iAEP kit</td>
<td>ALECENSA (alectinib)</td>
</tr>
<tr>
<td>Vysis ALK Break Apart FISH probe kit</td>
<td>Xalkori(crizotinib) ALECENSA (alectinib)</td>
</tr>
<tr>
<td>THxID BRAF kit</td>
<td>Tafinlar (dabrafenib) Mekinist (trametinib)</td>
</tr>
<tr>
<td>Cobas EGFR mutation test v2.0</td>
<td>TAGRISSO(osimertinib)</td>
</tr>
<tr>
<td>OncoGuide AmoyDx ROS1 Gene Fusions Detection Kit</td>
<td>Xalkori (crizotinib)</td>
</tr>
<tr>
<td>PD-L1 IHC 22C3 pharmDx [Dako]</td>
<td>KEYTRUDA (pembrolizumab)</td>
</tr>
</tbody>
</table>
Dose selection of Rivaroxaban in Japanese patients based on PK/PD modeling

Example of Precision Medicine in Cardiology

Dose selection of Rivaroxaban in Japanese patients based on PK/PD modeling

https://www.xarelto.jp/ja/home/index.php

Predicted value from PK/PD modeling

<table>
<thead>
<tr>
<th>Simulation value</th>
<th>Cmax (μg/L)</th>
<th>AUC0-24 (μg·h/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian 20mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japanese 15mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japanese 20mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Simulation value

Caucasian

20mg

Japanese

15mg

20mg

Simulation value

Caucasian

20mg

Japanese

15mg

20mg
The impact of CYP2C9 and VKORC1 genetic polymorphism on maintenance dose of warfarin

<table>
<thead>
<tr>
<th>Gene Polymorphism</th>
<th>Warfarin sensitivity</th>
<th>Warfarin maintenance dose</th>
<th>Frequency in Japanese</th>
<th>Frequency in Caucasian</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKORC1 H1, H2</td>
<td>high</td>
<td>low</td>
<td>89%</td>
<td>14~37%</td>
</tr>
<tr>
<td>CYP2C9 variant</td>
<td>high</td>
<td>low</td>
<td>&lt;5%</td>
<td>1~20%</td>
</tr>
</tbody>
</table>

Genotypes of VKORC1 1173 C>T variant

![Box plot showing warfarin dose differences across genotypes](chart.png)

**Caucasian**  **Japanese**


Prediction of Efficacy of Tolvaptan by Urine osmolality (U-OSM)

New Criteria

(1) U-OSM > 352 (mOsm/L)
(2) % decrease of U-OSM > 26 (%)

\[ tP < 0.001, \text{ OR 39.3} \]

Example of Precision Medicine in Cardiology

Disease-specific Induced pluripotent stem cells (iPSC)

- iPSC retains the whole genome information
- Disease-specific iPSC lines from patients with diseases is a promising approach
  - for studying disease mechanisms
  - for drug screening

Hypertrophic Cardiomyopathy- iPSC-Cardiomyocytes

Myofibrillar disarray was prominently suppressed by ET$_{A}$-blocker

Yuasa S, et al. The Japanese Society for Regenerative Medicine meeting, Luncheon Seminar  2016.3.17
• The development of targeted therapies and personalized medicine approaches in cardiovascular disease has been challenging
  ✓ Most cardiovascular therapies treat acquired syndromes, such as acute coronary syndrome (ACS) and congestive heart failure (CHF), which develop over many decades and represent the end result of several pathophysiological mechanisms.
  ✓ Classification of cardiovascular diseases is based on the observed clinical phenotype (e.g., ACS, CHF) rather than on the underlying mechanism driving the disease
• New insights into how cardiovascular diseases develop and the identification of causative factors at the individual patient level, may lead to greater clinical implementation of personalized medicine for common cardiovascular diseases.
Big data comes from clinical databases

- Big data analysis must be held to the same standards as traditional research methods and reproducibility across different sources has been a common concern.

- The fundamental pitfalls of observational data analysis should be taken into account; selection bias, information bias, confounding, other errors, etc.

- The risks of such pitfalls demand strict scientific testing and innovative methods for peer review of big data analytic models.
Limiting the patient population based on precision phenotyping and ‘omics’ analyses

- Is the selected patient population clinically reasonable?
- Were criteria for patient selection well defined?
- How will it change the patient’s health outcome?
- No efficacy for test (biomarker) negative patients?

- Therefore, there should be at least some data on the tests (biomarkers) negative population.

- To obtain regulatory acceptance, there is a need to establish firm evidence that interventions, which are based on precision phenotyping and ‘omics’ analyses improve health outcomes through prospective randomized clinical trials for common diseases in cardiology area.
Conclusions

• PMDA supports drug development related to precision medicine and believes that it will contribute in bringing improved medicines to patients in most need

• Cardiology is one of the area of interest for precision medicine

• We need more experience from using new interventions based on precision phenotyping and ‘omics’ analyses

• Early consultation with PMDA is encouraged for drug development programs based on these approaches