Application of Pharmacogenomics to Drug Development in Japan

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Clinical Pharmacology
Pfizer Japan
Agenda

- Pharmacogenomics and Clinical development
- Pharmacogenomics Considerations
- Infrastructure for Pharmacogenomics
Millions compound screening

Pre clinical evaluation (Pharmacology, Safety)

Clinical Pharmacology, Safety

1-2 products

Discovery  Exploratory Development  Full Development

Phase I  Phase II  Phase III  Phase IV

0  5  10  15

Years

11-15 years

Idea

Drug

Patent life : 20 years
The figure shows the number of submissions of new molecular entities (NMEs) — drugs with a novel chemical structure — and the number of biologics license application (BLA) submissions to FDA over a 10-year period. Similar trends have been observed at regulatory agencies worldwide.
Future Drug Development

Source: Pharma 2010 -Threshold of Innovation-, IBM

![Graph showing trends in drug development over time from 1980 to 2020]

- **Conventional Drug** vs. **High value-added adjunctive agent**
- **Target-oriented therapeutic solution** vs. **Gene therapy**

- **Generic” targeting** → **“Novel” targeting**
- **Mega screening** → **Biological screening**
- **Drug for all patients** → **Drug for selected patients**
- **Mega trials** → **Specific trials with small number of patients**
- **High attrition** → **Low attrition**
Creating opportunities to increase the value of the drugs we develop using genetics

- Obtain greater understanding of disease
  - Predict disease severity, onset, progression
  - Identify genetic subtypes of disease
  - Aid in discovery of new drug targets

- Distinguish subgroups of patients who respond differently to drug treatment

- Aid interpretation of clinical study results
Potential Impact on Clinical Trials

<table>
<thead>
<tr>
<th>(Millions)</th>
<th>Potential to reduce cost by 25%-45%</th>
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<tbody>
<tr>
<td>$225-250</td>
<td></td>
</tr>
<tr>
<td>$25-30</td>
<td></td>
</tr>
<tr>
<td>$30-35</td>
<td></td>
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<tr>
<td>$5-10</td>
<td></td>
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<tr>
<td>$10-15</td>
<td></td>
</tr>
<tr>
<td>$5-10</td>
<td></td>
</tr>
<tr>
<td>$145-185</td>
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Typical clinical trial costs from IND submission to NDA approval

- Reduce by 20% number of compounds in Phases 2 and 3, with early screening
- Reduce by 50% average number of patients in Phase 2 with preselection
- Reduce by 10% average number of patients in Phase 3 with preselection
- Reduce by 20% average length of Phase 3 trials with preselection
- Additional costs of PGx testing
- New clinical trials costs for an approved drug using PGx

Source: Advance Tech Monitor 2000
## Top 20 Pharma Engagement in USA

<table>
<thead>
<tr>
<th>Phase</th>
<th>Engagement</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA Banking</td>
<td>90%</td>
</tr>
<tr>
<td>Phase I Inclusion /Exclusion</td>
<td>70%</td>
</tr>
<tr>
<td>Phase II</td>
<td>30%</td>
</tr>
<tr>
<td>Phase III</td>
<td>10%</td>
</tr>
<tr>
<td>Phase IV</td>
<td>&lt; 5%</td>
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</table>
Pharmacogenomics Considerations
Polymorphism in key metabolic enzymes?

- Influence on key pathways of drug metabolism?
  an active metabolite levels?
  important drug interactions?

- Are genetic differences in transporter proteins likely to influence bioavailability or clearance?

- Would genotyping in clinical trials (for analysis or screening purposes) reduce variability or enable better interpretation of efficacy and safety?
**Phase I**

- CYP1A1/2
- CYP1B1
- CYP2A6
- CYP2B6
- CYP2C8
- CYP3A4/5/7
- CYP2D6
- CYP2E1
- esterases
- epoxide hydrolase (NQO1)
- DPD
- ADH
- ALDH
- others

**Phase II**

- UGTs
- STs
- GST-M
- GST-T
- GST-P
- GST-A
- NAT1
- NAT2
- TPMT
- COMT
- HMT
- others
Racial Differences in Phenotype and Genotype

<table>
<thead>
<tr>
<th>Racial Group</th>
<th>Phenotype (PM)</th>
<th>Genotype (Alleles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasians</td>
<td>2 [5%]</td>
<td>*2A *2B(2-5%)</td>
</tr>
<tr>
<td>Asians</td>
<td>13 [23%]</td>
<td>*2A *2B(20-30%) *3</td>
</tr>
</tbody>
</table>

Antifungal approved April 2005
**Study**

No. of Pts : 100 (age: 58.5±13.4)
Administration: multiple dose for around 1 month
  oral: 200 or 300mg bid
  iv: 3mg/kg or 4mg/kg , bid

PG and PK Screen (NONMEM)

<table>
<thead>
<tr>
<th>Period</th>
<th>plasma sampling (hr) from previous dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-dosing</td>
</tr>
<tr>
<td>1st week</td>
<td>●</td>
</tr>
<tr>
<td>&gt; 2nd week</td>
<td>○</td>
</tr>
</tbody>
</table>

Genotypes of 2C19 in patients

<table>
<thead>
<tr>
<th>N</th>
<th>Homo EM</th>
<th>Hetero EM (HEM)</th>
<th>PM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*1/*1</td>
<td>*1/*2</td>
<td>*1/*3</td>
</tr>
<tr>
<td>Total: 84</td>
<td>28</td>
<td>26</td>
<td>14</td>
</tr>
<tr>
<td>(%)</td>
<td>32.6</td>
<td>46.5</td>
<td>20.9</td>
</tr>
</tbody>
</table>
Simulated plasma concentration in an averaged Japanese patient (age: 60-year-old, body weight: 52 kg, Albumin: 35 g/L)

**Oral:** 300 mg q 12h on Day one followed by 150 mg or 200 mg q 12h for a further 13 days

**IV:** 6 mg/kg q 12h on Day one followed by 3 mg/kg or 4 mg/kg q 12h for a further 13 days
Do “disease genes” influence clinical trial design?

- Is there the potential for using genotyping to select subpopulations with more uniform disease characteristics?
- Can genotyping be used to identify “at risk” populations (prevention strategy)?
- Can genotyping be used to help identify subjects at risk for adverse events (safety strategy)?
Does genetic variability have implications for clinical trial design?

- Can genotyping for analysis purposes (PK/PD analyses, response differences) aid in interpretation of study results?
- Can genotyping at screening offer the potential for crisper results and/or smaller sample size in proof of concept studies?
- Predefined Hypotheses
- Findings during Trial of Drug X
- Future issues around Drug X (later trials, postmarketing)
- Hypotheses regarding related drugs
- Questions regarding disease (ID subpopulations, new drug targets)
- Portfolio-wide issues, e.g., QT prolongation
- Analyses triggered by competitors or Regulatory Agencies
Do genetic differences relating to drug response or disease severity have market implications?

- Diagnostic test requirement for safety or efficacy?
- Differentiation from other products?
- Market for patients with high response rate?
- Market for patients with otherwise very unfavorable prognosis?
- Elimination of subpopulation with serious AEs
- Influence on price?
ADHD (Attention Deficit/Hyperactive Disorder)

- Reuptake inhibitor of ADHD approved in FDA Jan 2003
- 2D6 is major metabolic enzyme affecting CL and AUC
- 2D6 genotyping was conducted in the BD study
  
  EMs: 3017 pts, PMs: 237 pts (7.3%)

<table>
<thead>
<tr>
<th></th>
<th>EM</th>
<th>PM</th>
</tr>
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<tbody>
<tr>
<td>AUC (µg.hr/mL)</td>
<td>2.6</td>
<td>18.6</td>
</tr>
<tr>
<td>CL (L/hr/kg)</td>
<td>0.35</td>
<td>0.03</td>
</tr>
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</table>

- Patient discontinuation by AEs and/or efficacy

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>EM</th>
<th>PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>5.8 %</td>
<td>8.9%</td>
<td></td>
</tr>
<tr>
<td>Lack of Efficacy</td>
<td>26.0 %</td>
<td>17.3%</td>
<td></td>
</tr>
</tbody>
</table>
Information of CYP2D6 EM/PM in several sections

- **Human PK**
  A fraction of population are PM’s resulting in ….

- **Drug-Drug Interactions**
  Inhibitors of 2D6 in EM’s increase exposure …similar to PM’s

- **AEs**
  The following ADR’s were either twice as frequent or statistically significantly more frequent in PM’s to EM’s

- **Laboratory test**
  Lab. tests are available to identify 2D6 PM’s…. ☒ Not official test
Infrastructure for advanced PG application
<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
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<tbody>
<tr>
<td>Aug. 1998</td>
<td>Implementation of Japanese version of ICH E 5 guideline</td>
</tr>
<tr>
<td>April 2001</td>
<td>Implementation of Ethical Guideline by three ministries</td>
</tr>
<tr>
<td>Mar. 2004</td>
<td>Start the WG for PG independent guidance at JPMA</td>
</tr>
<tr>
<td>June 2004</td>
<td>MHLW : Open VGDS draft to public</td>
</tr>
<tr>
<td>Dec. 2004</td>
<td><strong>Amendment of Ethical Guideline</strong> by three ministries</td>
</tr>
<tr>
<td></td>
<td>FDA PG related guidelines became effect officially- Analytical method, PG data submission</td>
</tr>
<tr>
<td></td>
<td>Start the request for VGDS by MHLW (Deadline end of Sep. 2005)</td>
</tr>
<tr>
<td>July 2005</td>
<td><strong>Review of PG independent guidance</strong> to get public comments</td>
</tr>
</tbody>
</table>
Guidance of Information submission for developing PGx clinical trial guidelines

March 18, 2005

- The guidance was issued.
- Manufactures are recommended voluntarily to submit.
- Submission period: 30 September 2005
- This VGDS would be used for the new guidance/guideline development.
- Information submitted must be disclosed
Guidance for Industry Pharmacogenomics Data Submission

**Nov. 3, 2003**  1st Draft
- To facilitate scientific progress in the field of Pharmacogenomics
- To facilitate the use of pharmacogenomic data in drug development
- To ask VGDS (Voluntary Genomic Data Submission) which is not subject to regulatory decision making

**March 22, 2005**  Final Version

**VGDS (Voluntary Genomic Data Submission)**
- Establish criteria for submission of data
- Definitions of biomarkers
New PGx guideline is needed?

- Interpretation of the essentials of ethical guideline when it is applied to clinical trials included PGx
- Basic concepts for protocol and ICD preparation
- Standardized procedures of samples & data handling with care of patient’s privacy & confidentiality
- Sample banking

Now, final draft prepared is under reviewing publicly

Dialogue between industry and regulatory agencies

Penetration into each clinical study site
Ethical guidelines by three ministries

The guideline do not be applied to the registration oriented clinical studies and PMS under the Pharmaceutical Affairs Law.

But,
- Clinical sites and CROs request to follow this ethical guideline.
- PGx study is being conducted with many different interpretation of this guideline at industries, clinical sites, CROs, etc.
Definition of Sample category for PG

Category A:
- PG analysis as a part of clinical trial
- PG result must be included to CSR.
  PG sample will be handled with subject ID,
  so it means that PG samples will be de-identified.

Category B:
- PG analysis related clinical trial and test drug
- PG sample will be **coded** by the discarding
  of the cording list of S-ID and PG-ID

Category C:
- PG analysis for exploratory disease research and
  genomic drug discovery outside the clinical trial limit
- PG samples will be **anonymized** and be banked routinely with PG code
Personal Information in Japanese Law

Any information to be able to identify a specific individual (Personal Information)
- Name
- Date of birth
- Other descriptions regarding specific individual
- Visual information specified

Clinical information in CRF (Subject ID)

List for identification of name and ID was discarded

Act concerning Protection of Personal Information

Chapter 1 Article 2
“Personal information” means the information about a living individual, which contains the name, the date of birth and/or any other descriptions by which a specific individual can be identified (including information that can be easily collated with other information) so that a specific individual can be identified.

K. Sekiguchi, J-Pfizer, BioJapan. Sep. 9, 2005
Can New guidance solute many issues to conduct PGx study in Japan?

Issues

1. Ethical issues
   - Enough information to IRB and subjects
   - Prior informed consent to subjects with sufficient explanation
   - Appropriate handling samples and disposal
   - Appropriate anonymization procedure

2. Sample Banking
   - Sufficient description in an informed consent form
   - Classification of PG research for future investigation?
     Trial/Drug-related gene or not
     Target or random screening for discovery
Category A:
Protocol + PG appendix + ICD for CT + IC for CT

Category B/C:
Protocol + PG supplement + ICD for CT + PG ICD + IC for CT
+ PG IC

ICD: document for explanation
IC: Informed consent form
Informed Consent Considerations

Blood Sample DNA Extraction → Informed Consent → Options

Genetic Testing (Coded)
- Time Limit
- Clinical Purpose (Defined Research)
- Withdrawal & Sample Destruction

Understanding Patient Response

Genetic Research (Anonymized)
- No Time Limit
- Research Purpose

New Disease Genes & New Drug Targets

Source: Presentation materials, Gentris, 2005

K. Sekiguchi, J-Pfizer, BioJapan. Sep. 9, 2005
**Disposition of Samples**

**Due to withdrawal**

**Category A**: Dispose

**Category B, C**: Dispose PG sample only when a withdrawal is accepted before a discard of cord list

**After the completion of clinical trial**

**Category A**: Dispose after the fixed storage period

PG samples will be disposed from the patients who does agree to de-identification only and/or not agree to random drug research

**Category B, C**: Not dispose and bank for random drug research
Anonymization process

- Collect samples from relevant clinical trials voluntary, and avoid retrospective collection
- Obtain EC/regulatory approvals and specific informed consent with widest possible remit for use
Aims:

- collect samples from relevant clinical trials
- obtain widest possible remit for use for PG
- avoid retrospective collection - incomplete, inefficient
- centralized company resource

Principles:

- regulatory and IRB/EC approval
- full description during informed consent process (separate ICD for banking)
- participation in sample banking is optional for subjects
- additional data protection (anonymization)
## Flow of Returning Genetic Results

**De-identified PGx data/Interpretations**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Clinical Investigator</th>
<th>Central Lab.</th>
<th>Pfizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>PG sample labeled SID</td>
<td>DNA analysis</td>
<td>Results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discard</td>
<td>Sealed letter</td>
</tr>
</tbody>
</table>

### Study process

- **Blood**: PG sample labeled SID
- **Central Lab.**: DNA analysis
- **Pfizer**: Results, Sealed letter

### Returning Process

- **Request**: Translation from Name to SID, Prepare Request form with SID
- **Sealed letter**: Translation from SID to Name, Hand the sealed letter to subject

Can ask the explanation of results, if needed

*In clinical study, clinical investigator is keeping the list of subject ID - subject name*
Why Pharmacogenomics?

Why now?

- Genetic polymorphisms impact safety & efficacy of most drugs
- Every drug in development today will be marketed in a genetically informed environment
- Patients & regulatory groups will demand responsible use of this genetic information
- New FDA Guidance on Pharmacogenomics now makes it mandatory in the USA
Pharmacogenomics: systemic genomic analysis in populations of treated subjects to identify variants that predict drug response including the occurrence of adverse reactions.
Thank you!