The Future Direction of Japan Regarding Benefit-risk Balance Assessment

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Agenda

1. The study group of J-RMP including investigation of benefit-risk assessment

2. The current benefit-risk assessment in Japan

3. Challenges for the future

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Safety Specification

- Important identified risks
- Important potential risks
- Important missing information

Need Additional Actions?

Yes

Pharmacovigilance and/or Risk Minimization activities

“Additional” Pharmacovigilance

No

Pharmacovigilance Plan

Routine Activities

- Spontaneous Report
- Literature Search

Additional Activities

“Additional” Risk Minimization activities

- Strengthen the gathering spontaneous report due to early postmarketing phase vigilance (EPPV)
- Use-Results Surveys
- Specified Use-Results Surveys
- Surveys on Post Marketing Clinical Trials
- Post marketing clinical trials

Risk Minimization Action

- Package Insert
- Drug Guide for Patient

- Provision of Information on Early Postmarketing phase Vigilance (EPPV)
- Preparation and provision of materials for proper use
- Rapid release of information obtained by PhV
- Provision of information to patients,
- Access Limitation etc

Periodic Report

B-R Assessment

Revise, if necessary

http://www.pmda.go.jp/english/service/rmp.html
Study Group on J-RMP

- Established in 2012 to investigate measures to effectively implement J-RMP, supported by MHLW research fund
- Consist of researchers from academia, regulatory bodies, and industry
- Research projects include:
  - Studying the methodologies of benefit-risk evaluation, especially in the post-marketing stage
- In 2015, the study group will suggest future directions about what should be done in order to improve B-R assessment.
Study Group on J-RMP

- Literature search (2012): Collecting information on the followings: Methodology, Actual cases of B-R assessment, B-R assessment in EMA or FDA etc
- Studying the practical situation on B-R assessment in Japan (2013): Survey on evaluation result reports in the post-marketing stage etc
- Meeting: EMA (Jan, 2013), FDA (Jan, 2014), CIRS workshop (Jun, 2014) etc
- Drafting a framework (2014: under consideration)
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The current B-R assessment in the pre-marketing stage

- PMDA published “Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drug” in 2008
  - Check-list approach
  - Summary of the points that need to be considered during the actual evaluation process of drugs after a new drug application has been submitted, covering all new drugs which are reviewed by teams at the PMDA
Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drug

9) For “Can the recognized risks be controlled and are the risks acceptable when considering the benefits?”
   - Has the efficacy been clearly confirmed?
   - Have factors related to the recognized risk been clearly identified?
   - Has any effective treatment been identified to prevent/inhibit occurrence of the recognized risk?
   - Is the recognized risk acceptable, even if it is serious, when considering the benefits?
The current B-R assessment in the pre-marketing stage

- It is possible to regard the consideration points as a “framework.”
- The regulatory decision on each consideration point are described in the review report.

There are no standardized visualization tools which have achieved international consensus at the present stage.
B-R assessment in the post-marketing stage

Re-examination reports are posted on the PMDA website

Drug Approval

Usually 8 yrs.

EPPV*

PMS

ADR and Infection Reporting

* Early Phase Post-marketing Vigilance

Re-examination

11th Annual Meeting DIA JAPAN 2014 | November 16-18 | Tokyo Big Sight | Ariake
The current B-R assessment in the post-marketing stage

Data attached for re-examination applications are

- spontaneous reports (serious adverse reaction / infection)
- research reports
- reports of concrete measures taken in overseas
- use-results surveys reports
- specified use-results surveys reports
- post-marketing clinical trial reports

In addition, when regulatory actions are taken in the post-marketing setting and/or important issues regarding efficacy or safety occurs,

- PMDA publishes an evaluation result report, which has become available on MHLW or PMDA website recently
# B-R assessment of Gefitinib in the post-marketing stage

<table>
<thead>
<tr>
<th>Year</th>
<th>Month</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>July</td>
<td>Gefitinib was approved for the indication of locally advanced or recurrent NSCLC</td>
</tr>
<tr>
<td>2002</td>
<td>Oct</td>
<td><strong>Emergency information on the risk of ILD</strong></td>
</tr>
<tr>
<td>2010</td>
<td>Sep</td>
<td>Re-examination application and Supplemental NDA</td>
</tr>
<tr>
<td>2011</td>
<td>Nov</td>
<td>Re-examination report was published and supplemental approval for the indication of NSCLC with EGFR mutation</td>
</tr>
</tbody>
</table>

- **Drug use Surveillance** conducted by MAH in Japan
- **Nested-case-control study** conducted by MAH in Japan
- **Randomized controlled clinical trials** conducted by MAH in East Asia (IPASS study) etc.
- **Two Randomized controlled clinical trials** conducted by research groups in Japan
# Results of clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Line</th>
<th>Purpose</th>
<th>Primary endpoint</th>
<th>Control arm</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS</td>
<td>First</td>
<td>Non-inferiority (limit: 1.20)</td>
<td>PFS</td>
<td>Carboplatin/paclitaxel</td>
<td>0.74 (0.65, 0.85)</td>
</tr>
<tr>
<td>V-15-32</td>
<td>Second</td>
<td>Non-inferiority (limit: 1.25)</td>
<td>OS</td>
<td>Docetaxel</td>
<td>1.12 (0.89, 1.40)</td>
</tr>
<tr>
<td>INTEREST</td>
<td>Second</td>
<td>Non-inferiority (limit: 1.154)</td>
<td>OS</td>
<td>Docetaxel</td>
<td>1.04 (0.93, 1.15)</td>
</tr>
<tr>
<td>WJTOG 3405*</td>
<td>First</td>
<td>superiority</td>
<td>PFS</td>
<td>Cisplatin/docetaxel</td>
<td>0.49 (0.34, 0.71)</td>
</tr>
<tr>
<td>NEJ002*</td>
<td>First</td>
<td>superiority</td>
<td>PFS</td>
<td>Carboplatin/paclitaxel</td>
<td>0.30 (0.22, 0.41)</td>
</tr>
</tbody>
</table>

*: Patients with EGFR-mutation
In our opinion

- Gefitinib might be one of rare and ideal cases that we could evaluate B-R balance by using the results of randomized controlled clinical trials in the post-marketing stage.

- On the other hand, in most of cases, information on benefit is not simultaneously available while the information on risk is accumulated in the activity of PhV in the post-marketing stage.

- Furthermore, contrary to the clinical trial data in the pre-marketing stage, the data collected in the post-marketing stage include any evidences at all levels.
Issues on B-R assessment in the post-marketing stage

Regarding B-R assessment in the post-marketing stage, 
– How do we collect information about efficacy?
– How do we describe and visualize the result of B-R assessment in the “real world” medical setting?
– What are the points that need to be considered during the actual B-R assessment?
– Who assess B-R balance?
– How do we utilize the result of BR assessment?

We are now analyzing prior regulatory decisions and gaining experiences about J-RMP review process.
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<table>
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<tr>
<th>Points to be considered</th>
<th>Result of B-R Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Drug Review</td>
<td>Published Review report</td>
</tr>
<tr>
<td>Post-marketing Safety Measures</td>
<td>Not published Evaluation result report</td>
</tr>
<tr>
<td>Re-examination</td>
<td>Not published Re-examination report</td>
</tr>
</tbody>
</table>
Discussion about B-R framework in the study group

- At first, we checked to see if we could utilize the “PTC” as B-R framework in the post-marketing stage.
- Reviewed some past drug regulatory decisions (e.g. evaluation results report, re-examination report, Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter)).
- As a result, “PTC” is not enough for B-R assessment in the post-marketing stage
- Explored the essentials of review points to be taken into account in B-R assessment in the post-marketing stage
Drafting B-R framework (under consideration): Essentials of review points in the post-marketing stage

- **Benefit:**
  - evidence (prolongation of PFS in 1st line etc.), data-source (RCT etc.), special considerations (which data is clinically important? etc.).

- **Risk:**
  - evidence, data-source, risk minimization plan, special considerations

- **Characteristics of patients**
  - number of patients, seriousness, special population etc.

- **Current treatment option:**
  - currently available treatment/prevention etc.

- **Convenience:** patients-friendliness etc.

- **Uncertainty:**
  - patient population without enough information, relationship between the study treatment and current treatment, inconsistency between studies etc.

- **Final assessment of B-R**
Conclusions of the study group (1)

- B-R framework in the pre-marketing stage in Japan
  - Considering developing PTC for future versions may be needed

- B-R framework in the post-marketing stage in Japan
  - More appropriate decision-making is expected by standardized procedure of B-R assessment using a framework
  - In light of the character of new information obtained in the post-marketing stage, it is reasonable to begin with qualitative framework because it is simple, flexible and easy to use approach.
  
  - For regulators and MAH, need to discuss B-R framework, to gain experiences about B-R assessment.
Conclusion of the study group (2)

Framework

- Framework provide a course in the B-R assessment
- Several B-R frameworks are proposed and fundamental thinking method is similar
- It is non-essential question: Which one is better, “qualitative” or “quantitative “?
- However, we think that it might be difficult to interpret the result of quantitative B-R assessment because the weighting of benefits and risks is conducted under the quantitative methodology (MCDA etc.).
- Concerning quantitative methodology, we would like to pay attention to quantitative framework development.
Conclusion of the study group (3)

- Visualization of B-R
  - Effects table (EMA)
  - FDA’s B-R framework (FDA)
  - Currently in Japan, the result of B-R assessment is described in review reports etc.
  - As a communication tool, an optimal way depends on how/whom you communicate with.
  - There are no standardized visualization tools which have achieved international consensus at the present stage. We need to think together!
Thank you