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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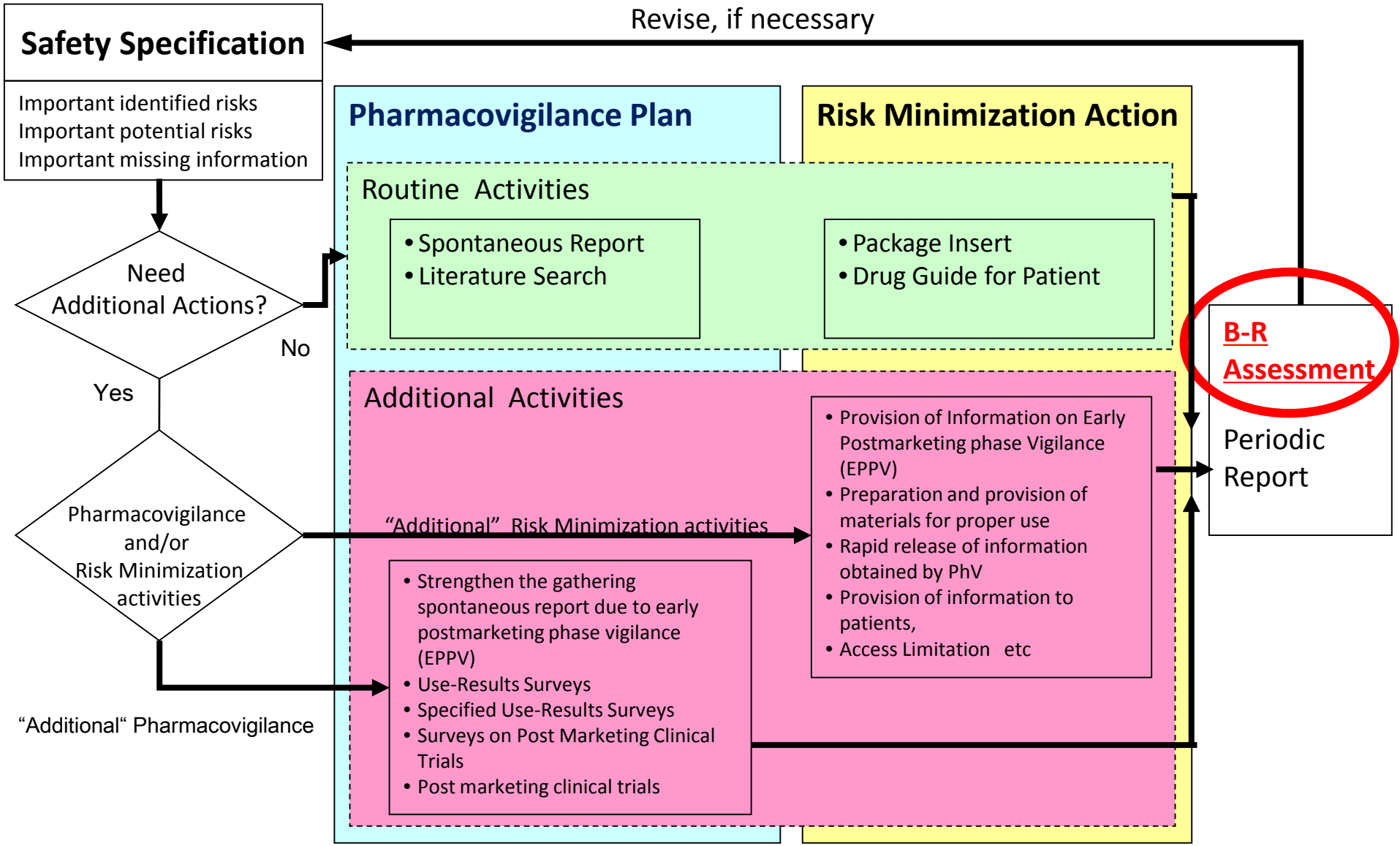
J-RMP Conceptual Diagram

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）: Colleting 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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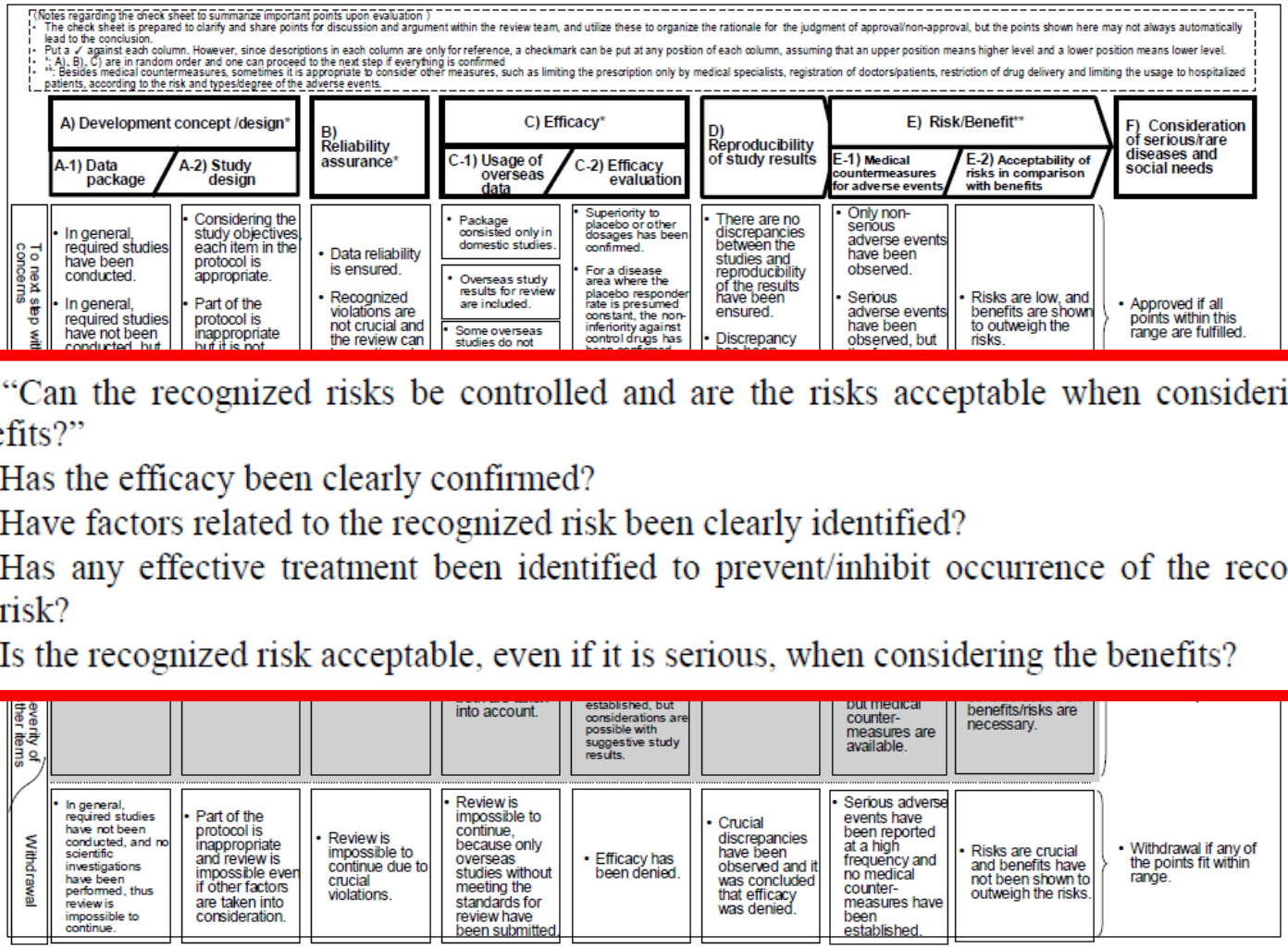
The current B-R assessment in the pre-marketing stage

- 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



(Notes regarding the check sheet to summarize important points upon evaluation)
- The check sheet is prepared to clarify and share points for discussion and argument within the review team, and utilize these to organize the rationale for the judgment of approval/non-approval, but the points shown here may not always automatically lead to the conclusion.
- Put a ✓ against each column. However, since descriptions in each column are only for reference, a checkmark can be put at any position of each column, assuming that an upper position means higher level and a lower position means lower level.
- *: A), B), C) are in random order and one can proceed to the next step if everything is confirmed
- **: Besides medical countermeasures, sometimes it is appropriate to consider other measures, such as limiting the prescription only by medical specialists, registration of doctors/patients, restriction of drug delivery and limiting the usage to hospitalized patients, according to the risk and types/degree of the adverse events.

	A) Development concept /design*		B) Reliability assurance*	C) Efficacy*		D) Reproducibility of study results	E) Risk/Benefit**		F) Consideration of serious/rare diseases and social needs
	A-1) Data package	A-2) Study design		C-1) Usage of overseas data	C-2) Efficacy evaluation		E-1) Medical countermeasures for adverse events	E-2) Acceptability of risks in comparison with benefits	
To next step with concerns	• In general, required studies have been conducted. • In general, required studies have not been conducted, but	• Considering the study objectives, each item in the protocol is appropriate. • Part of the protocol is inappropriate but it is not	• Data reliability is ensured. • Recognized violations are not crucial and the review can	• Package consisted only in domestic studies. • Overseas study results for review are included. • Some overseas studies do not	• Superiority to placebo or other dosages has been confirmed. • For a disease area where the placebo responder rate is presumed constant, the non-inferiority against control drugs has	• There are no discrepancies between the studies and reproducibility of the results have been ensured. • Discrepancy	• Only non-serious adverse events have been observed. • Serious adverse events have been observed, but	• Risks are low, and benefits are shown to outweigh the risks.	• Approved if all points within this range are fulfilled.
Severity of other items				into account.	established, but considerations are possible with suggestive study results.		but medical counter-measures are available.	benefits/risks are necessary.	
Withdrawal	• In general, required studies have not been conducted, and no scientific investigations have been performed, thus review is impossible to continue.	• Part of the protocol is inappropriate and review is impossible even if other factors are taken into consideration.	• Review is impossible to continue due to crucial violations.	• Review is impossible to continue, because only overseas studies without meeting the standards for review have been submitted.	• Efficacy has been denied.	• Crucial discrepancies have been observed and it was concluded that efficacy was denied.	• Serious adverse events have been reported at a high frequency and no medical counter-measures have been established.	• Risks are crucial and benefits have not been shown to outweigh the risks.	• Withdrawal if any of the points fit within range.

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?

http://www.pmda.go.jp/english/service/pdf/review/points.pdf

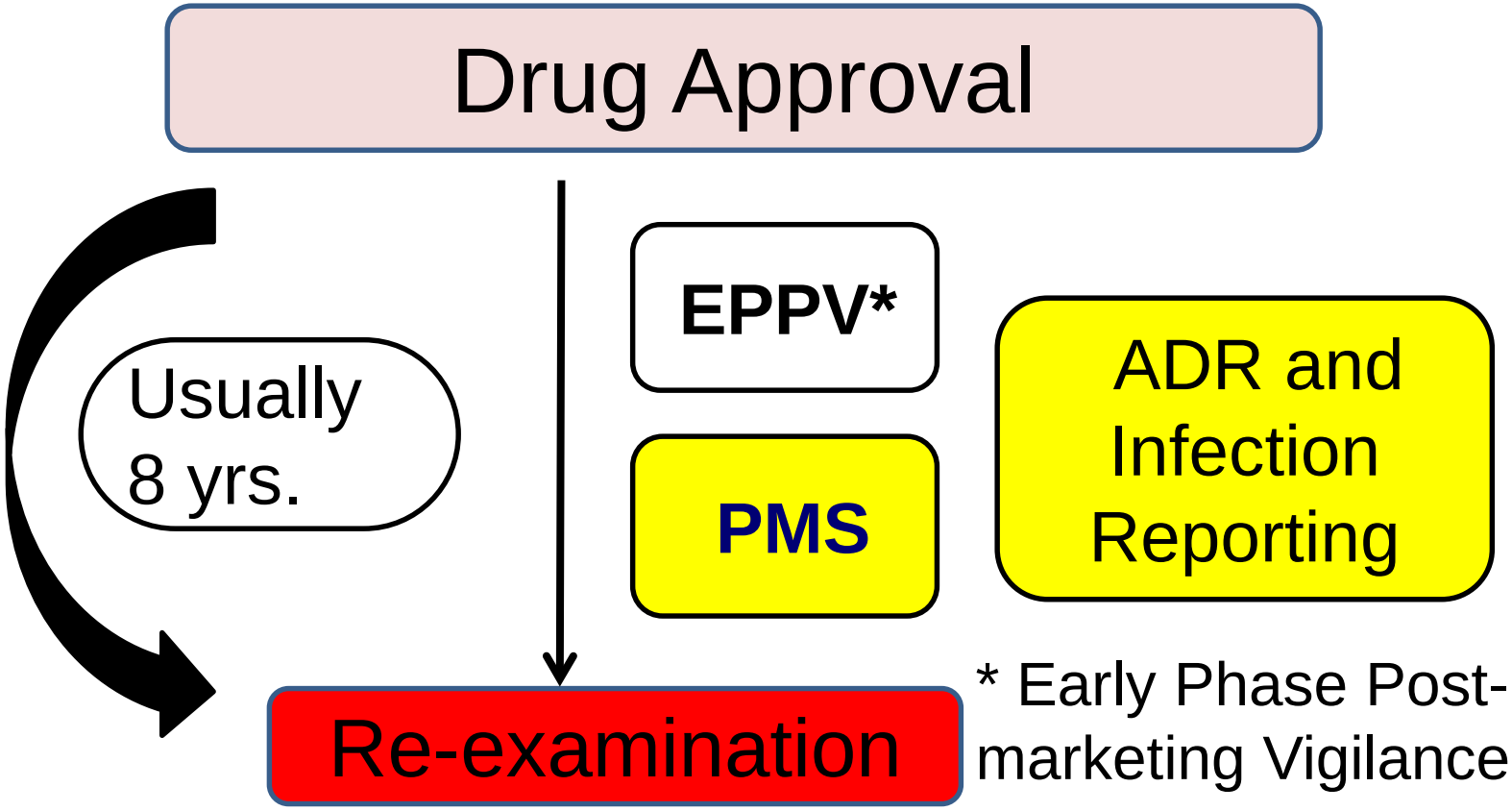
The current B-R assessment in the pre-marketing stage

- 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



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

2002	July	Gefitinib was approved for the indication of locally advanced or recurrent NSCLC
2002	Oct	**Emergency information on the risk of ILD**

- ✓***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*

2010	Sep	Re-examination application and Supplemental NDA
2011	Nov	Re-examination report was published and supplemental approval for the indication of NSCLC with EGFR mutation

Results of clinical trials

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

*：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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	Points to be considered	Result of B-R Assessment
New Drug Review	Published	Review report
Post-marketing Safety Measures	Not published	Evaluation result report
Re-examination	Not published	Re-examination report

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