Extrapolation of the non – Japanese TQT data to Japanese NDAs

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Outline

- Current status of ICH E14 in Japan
- Points to be considered for use of foreign TQT in Japanese NDA
- Dosage used in foreign TQT studies
- Future directions

Current status of ICH E14 in Japan

- May 13th, 2005 ICH E14 Step 4 signed off
- Oct 23rd, 2009 ICH E14 and Q&A notification in Japan
- Oct 23rd, 2009~ Oct 31st, 2010 grace period before the E14 guideline takes effect
- Nov 1st, 2010 ~ the E14 guideline applied to new drugs seeking approval

Clinical trial consultations including E14 related matters

	During grace period 10/23/09~10/31/10	Implementation of the guideline 11/1/10~7/31/11
Clinical trial consultations	348	306
Including matters directly related to E14 guideline	13	12
PMDA comments on E14 guideline (ex. Clinical data package)	31	38

Implementation of the E14 guideline in Japan

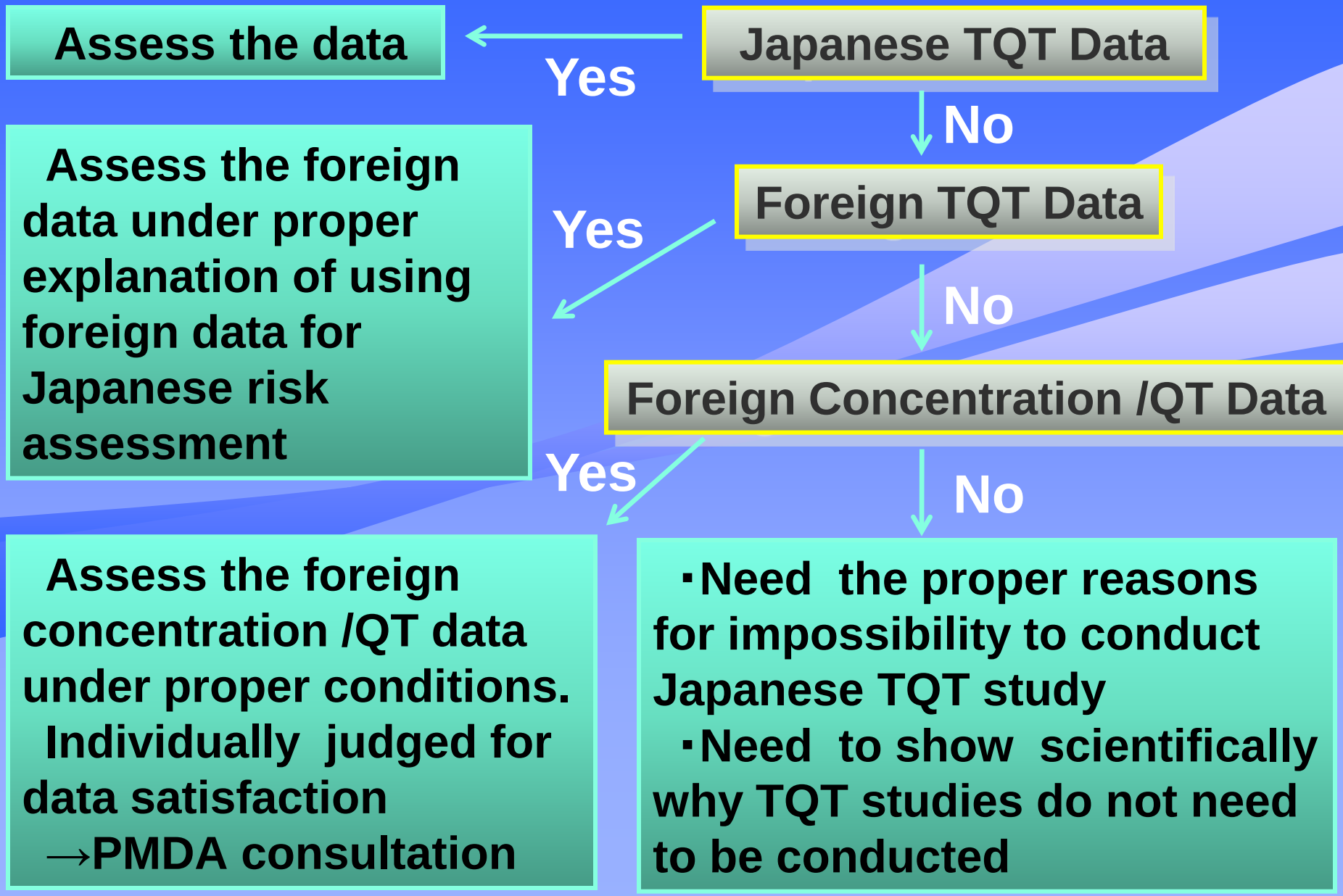
- Factors that could reduce the need for TQT
  - inability to conduct the study with healthy volunteers or patients
  - how the drug is used (ex. Administered under continuous monitoring)
  - nonclinical data

- The need for TQT will be assessed individually, depending on drug property and related information.
- PMDA consultation is recommended.

Possible cases regarding TQT data for Japanese NDA

- **Japanese TQT study**
  - **clinical development is limited to Japan**
  - **clinical development in Japan is ahead of other regions**
  - **clinical development is ongoing simultaneously in several regions including Japan**
- **Foreign TQT study only**

Use of foreign TQT data in Japan



Extrapolation of foreign TQT studies in Japanese NDA

- The availability of foreign data used to assess the delay of cardiac repolarization should be assessed individually.
- When foreign TQT data is used in Japanese NDAs, a proper explanation of why foreign TQT data is being used for Japanese risk assessment is always necessary.
- The reason foreign TQT data is available for Japanese QT prolongation risk assessments should be included in CTD2.7.2.

Points to be considered for use of foreign TQT in Japanese NDA, and necessity of additional data for Japanese risk assessment

- QT prolongation risk when drugs with similar mechanisms are used
- Characteristics of the drug
  ex. Oncology drug
- Characteristics of patients
  ex. elderly, structural heart disease

Points to be considered for use of foreign TQT in Japanese NDA (continued)

- **Situation in foreign countries:**
  period and frequency of post approval use reports of adverse cardiovascular events
  ex. Sudden cardiac death, TdP

- **Results of foreign TQT studies**
  positive, negative

- **Dosage used in TQT studies**
  dosage range higher than the therapeutic dose

Points to be considered for use of foreign TQT in Japanese NDA (continued)

- Foreign data during clinical development, apart from TQT studies:
  ECG data, adverse cardiovascular events

- Comparison of Japanese and foreign data
  - Evaluation of ethnic factors according to ICH E5 guideline
    Intrinsic factors, extrinsic factors
  - Putative therapeutic dose
    Same? Different?
  - Comparison of PK/PD profiles

Points to be considered for use of foreign TQT in Japanese NDA (continued)

- **Non clinical data**
  in vivo, in vitro

- **Japanese data**
  Phase I concentration - QT data
  Phase II, III ECG data for QT prolongation adverse events

- **The availability of foreign data used to assess the delay of cardiac repolarization or necessity of additional data is judged on a case by case basis.**

Dosage used in TQT studies

- **E14 guideline statement:**

"If not precluded by considerations of safety or tolerability due to adverse effects,

the drug should be tested at substantial multiples of the anticipated maximum therapeutic exposure. "

Dosage used in TQT studies

①If supratherapeutic dose in the foreign TQT was covered in the “worst case scenario” for Japanese patients:

- the foreign TQT study NEGATIVE

→・minimum Japanese ECG data is required.

ex. Phase I concentration- QT data

Phase II, III ECG data for QT prolongation adverse events

Dosage used in TQT studies

②If supratherapeutic dose in the foreign TQT was covered in the “worst case scenario” for Japanese patients:

- the foreign TQT study POSITIVE

→・During clinical studies after the TQT study, Japanese ECG data as well as foreign ECG data should be collected appropriately.

・The risk of QT prolongation and proarrhythmia when using the drug in Japanese patients, particularly in clinical settings, should be evaluated.

Dosage used in TQT studies

②If supratherapeutic dose in the foreign TQT was covered in the “worst case scenario” for Japanese patients:

- the foreign TQT study POSITIVE (continued)

・Adverse events regarding arrhythmia should be collected .

・Integrated QT prolongation and proarrhythmia risk assessment is needed using all available information including the foreign TQT and Japanese data.

Dosage used in TQT studies

②If supratherapeutic dose in the foreign TQT was covered in the “worst case scenario” for Japanese patients:

- the foreign TQT study POSITIVE (continued)

・One of the risks of the drug is QT prolongation, and decision for approval or non-approval is made by considering all of the risks and benefits of the drug.

・Labeling will include the result of the TQT study, and a precautionary statement regarding the risk should be considered.

Dosage used in TQT studies

③If supratherapeutic dose in the foreign TQT was NOT high enough, and was not covered in the “worst case scenario” for Japanese patients:

→・Additional Japanese ECG data, particularly data regarding higher exposure than supratherapeutic dose setting, is extremely important.

・We would encourage PMDA consultations, as the appropriate method of collecting the additional Japanese data will be judged on a case by case basis.

Dosage used in TQT studies

③If supratherapeutic dose in the foreign TQT was NOT high enough, and was not covered in the "worst case scenario" for Japanese patients:

(continued)

・The amount and quality of additional Japanese ECG data, which should be obtained during clinical studies, depends on many factors:

ex. Non clinical data - in vivo, in vitro

TQT study results - positive, negative

the degree of QT prolongation effect

the difference between the supratherapeutic dose of TQT study and the Japanese high exposure scenario

Future directions

- We need to learn more regarding the details of the additional Japanese data necessary to evaluate the risk of QT prolongation and proarrhythmia in Japanese patients for appropriate drug use in clinical practice

  - when supratherapeutic dose in the foreign TQT was NOT covered in the “worst case scenario” for Japanese patients

  - and also when foreign TQT studies are positive

Future directions

(continued)

- Since QT interval prolongation is not a perfect marker for detection of drug induced proarrhythmia, establishment of better methods for evaluating proarrhythmic risk of drugs is needed.

Conclusions

- The E14 guideline has been implemented in Japan since November 1st, 2010.
- The Japanese situation surrounding the E14 guideline is different from other countries.
- We have limited experience in reviewing extrapolation of foreign TQT study results.
- More and more Japanese TQT studies will be conducted in the future.
- However, the majority of Japanese NDAs will use the non- Japanese TQT studies.

Conclusions (continued)

- To promote efficient new drug development, the available data related to the effects of the drug on QT should be used appropriately.
- It is extremely important to clarify the efficient use of non- Japanese TQT data in Japanese NDAs.
- PMDA clinical trial consultation meetings are encouraged to avoid replication of studies and to construct clinical data packages efficiently.

Conclusions

(continued)

- We need more knowledge regarding the contents of additional Japanese data necessary to evaluate the risk of QT prolongation and proarrhythmia in Japanese patients when Japanese NDAs include non- Japanese TQT studies.

Thank you for your attention