PMDA comments for CIPA

Kaori Shinagawa, MD, PhD
Pharmaceuticals and Medical Devices Agency

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Considerations from a Japanese regulatory viewpoint

- The purpose of ICH E14/S7B guildelines is to assess the proarrhythmic risk of drugs appropriately
- Success of ICH E14/S7B guidelines: ICH E14 and S7B guidelines have provided a high level of safety assurance.
  - No QT- related withdrawals after the implementation of ICH E14/S7B Guideline
  - Reduction in post-marketing reports of TdP for non-anti-arrhythmic drugs
  - Continued to approve some drugs with QT liability where benefits clearly outweigh apparent risks

- ***A novel approach must retain the same threshold of safety assurance.***

Possible advantages of CIPA

- CIPA is a promising initiative with parts that we clearly support

  - Looking at more cardiac ion channels than hERG
  - Potentially more specific proarrhythmic risk assessment
  - Increased role of stem cell derived cardiomyocytes, which may improve clinical predictability

Various possible approaches for proarrhythmic risk assessment

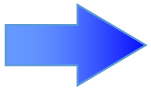
- In Vivo/ in Vitro QT assay (ICH S7B)
- Early phase QT evaluation and CR modeling (ICH E14)
- Thorough QT study (ICH E14)
- CIPA

- CIPA might be useful in the case of:
  - Compounds that prolong QTc in humans
  - Compounds that are positive in current S7B assessment
    Give additional information regarding mechanism of these findings
- CIPA might not be needed in the case of:
  - Compounds that are negative in S7B assessment and not prolong QTc in clinical studies (TQT/ CR modelling)

- ***An expanded non-clinical assessment like CIPA will still require high-confidence clinical ECG assessment***

Prerequisites for CIPA implementation as a tool for regulatory risk assessment

- Clear scientific basis
- Standardized protocols
- Validated
  - ➢ By many sponsors and researchers independently
    - clear information of the differences between operators, test systems and sites
  - ➢ For a wide range of compounds;
    - that prolong QT through various mechanisms
    - that are positive in S7B assessment but not prolong QT
- Clear information of the limits and pitfalls of each components
  - characteristics of false negative cases
- Clear information of the predictability of TdP risk
  - Assay sensitivity, specificity, accuracy



Substantial experience is needed

Points to consider for CIPA implementation

- Cannot provide information on effects on haemodynamic changes, autonomic changes, hormones, etc.
  → physiological response might be different
- iPS cell derived cardiomyocyte (hiPSC-CM):
  - Concerns regarding immaturity of hiPSC-CM phenotype compared to native adult cardiomyocyte
- In silico assessment:
  - Single cell model → cannot assess drug effects on the regional heterogeneity of refractory period and conduction between the myocytes
- Clinical ECG Biomarker:
  - Concerns in respect to the level of validation of the J-Tpeak as a potential biomarker of proarrhythmic risk

→ Totality of evidence assessment of the proarrhythmic risk

An expanded non-clinical assessment like CIPA will still require high-confidence clinical ECG assessment