E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

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PhRMA Topic Leader

ICH E14 Milestones

Topic Adopted	**June, 2009**
Current Status	**Prior E14 IWG discontinued and Q&A mailbox closed** **Informal Discussion Group initiated in Yokohama**
Current Draft	**E14 version 1, May 2005** **E14 Q & A issued June 2008**
Next Draft Expected	**E14 Q & A concept paper March 2010**
Date Expected	***E14 Q & A concept paper Accepted - April 2010 ICH SC***
Rapporteur	**Dr. Daniel Bloomfield, PhRMA**
Last Meeting	**June 2011, Cincinnati, OH USA**
Next Meeting	**November 2011 Seville, Spain**

Concentration-Response Relationships

- **Question: The E14 guidance states (section 3, page 12) that analysis of the relationship between drug concentration and QT/QTc interval changes is under active investigation. Has this investigation yielded a reasonable approach to concentration response modeling during drug development? What is the role of CR Relationship and the TQT study?**

Gender

- **Question: Should we enroll both sexes in a TQT study, and does the study need to be powered for independent conclusions about each sex?**

New Technology

- **How does one validate new methodology, for example, to acquire ECGs or to measure ECG intervals?**

HR Correction

- **The E14 states that QT interval corrected by Fridericia's and Bazett's correction should be submitted in all applications; is this still necessary? Is there a recommended approach to QT correction that is different than that specified in E14?**

Late Stage QTc Evaluation

- **The E14 describes in section 2.3 (Clinical Trial Evaluation After the 'Thorough QT/QTc Study) that 'adequate ECG assessment to accomplish this [monitoring] is not fully established.' Is there now a reasonable approach to evaluating QTc in late stage clinical development in the case of a finding of QT prolongation prior to late phase studies?**

QTc Evaluation when TQT not feasible

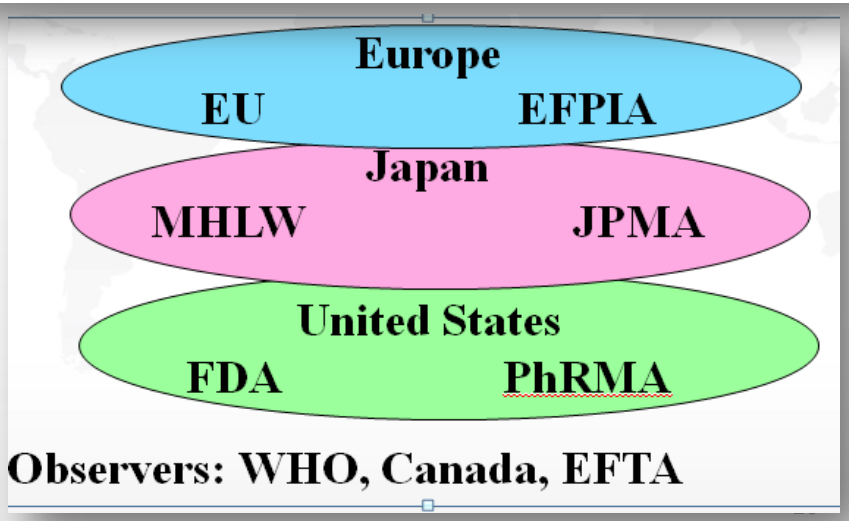
- **The E14 states that in certain cases conventional design QT studies may not be feasible. In such cases what other methods should be used for evaluation of QT/QTc and proarrhythmic potential?**

Extra Slides

Background Material on ICH Processes

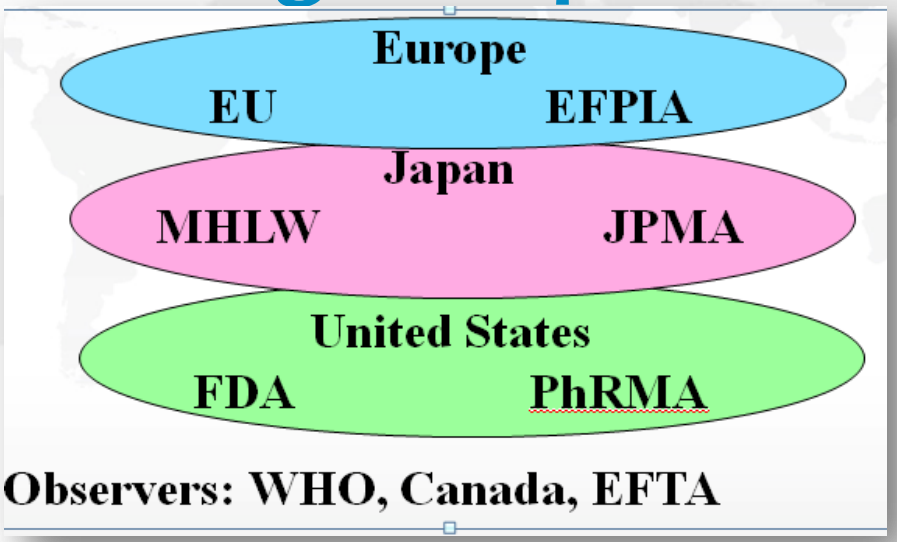
The ICH Steering Committee

- **Governs the ICH**
- **Determines ICH policies and procedures**
- **Decides on the adoption of ICH projects**
  - Selects topics for harmonisation
  - Endorses the creation of ICH Working Groups
- **Monitors and facilitates the progress of ICH Working Groups**
- **Signs off ICH documents**



Technical Working Groups Structure

Interested Parties
- IGPA
- WSMI
- Biotechnology Industry
- IPEC



DRAs/DoH
- DRA of Australia
- DRA of Brazil
- DRA of China
- DoH of Chinese Taipei
- DRA of India
- DRA of Korea
- DRA of Russia
- DRA of Singapore

Pharmacopoeias
- Europe
- Japan
- United States

RHIs
- APEC
- ASEAN
- EAC
- GCC
- PANDRH
- SADC

**Experts are nominated by their regional Coordinators*

ICH Products

- **Over 50 Guidelines on technical requirements on:**
  - Quality - 20 Guidelines
  - Safety - 14 Guidelines
  - Efficacy - 21 Guidelines
- **Electronic Standards for the Transfer of Regulatory Information (ESTRI, E2B)**
- **Common Technical Document (CTD & eCTD)**
- **Medical dictionary for adverse event reporting and coding of clinical trial data (MedDRA)**
- **Consideration documents**

Steps in the ICH Process

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- ***A formal sign-off can be achieved only when consensus is reached within the 6 ICH Parties.***
- *The Secretariat should be contacted to initiate the sign-off process.*
- *At **Step 2,** six Parties are requested to sign-off the consensus text. The topic leaders from all Observers / Interested Parties / RHIs/DRAs/DoH may also sign in recognition of their contribution, if they wish.*
- *At **Step 3,** the comments received by each of the three Regulatory Parties shall be consolidated.*
- *At **Step 4,** the topic leaders from Regulatory Parties are requested to sign the Step 4 final document.*
- *Upon reaching Step 2 or Step 4, the Rapporteur shall develop a presentation to be published along the Guideline on the ICH website, as training material.*

Biannual Face to Face meeting

Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday
ICH MedDRA Management Board		Regulators Forum	ICH Global Cooperation Group	ICH Steering Committee*	
ICH Technical Working Groups*					

**Evening Caucuses*

All ICH Parties must be represented for a face to face meeting to be considered official.

- *ICH EWGs/IWGs are invited to submit a work plan ahead of the meeting*
- *Alternate expert(s) may be nominated if needed*
- *ICH EWGs/IWGs are invited to present its work at the SC*
  - *Concise and clear and issues or specific steps forward that need SC approval should be stated at the end of the presentation*
  - *This presentation should be provided to the Secretariat on site according to the printing schedule distributed prior to the meeting*

In between Meetings

All ICH Parties must be represented for a teleconference/web-conference to be considered official.

- *Between face-to-face meetings ICH EWGs/IWGs are encouraged to make use of modern communication technologies (e-mail, web-conferences, teleconferences, etc.) to progress draft Guidelines.*
- *Interim face-to-face meetings (should be exceptional)*
- *The ICH Secretariat is primarily concerned with preparations for, and documentation of, meetings of the Steering Committee as well as coordination of preparations for Working Group (EWG, IWG, Informal WG) meetings.*

ICH: Keys to success

- **Effective management and administration**
  - Through ICH Steering Committee and Secretariat
- **Joint participation of regulators and industry**
- **Science based and consensus driven**
- **Frequent, concurrent meetings of SC and Working Groups that are outcomes based**
- **Commitment of all parties to implement harmonised Guidelines**
- **Well-defined process and procedures**