

# Changing E-14

Easy or difficult?

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# ICH E14

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

EMA/CPMP Points to Consider 1997

Work begun on ICH S7B in 3/2001, E14 in 2003

Finalized both in May 2005

Implemented in

EU May 2005

US October 2005

Japan October 2009

# ICH E14

- Parent document has never been reopened.
- Clarifications and changes have been implemented through a series of Q&As
  - Initial version; June 2008
  - Version R1; April 2012
  - Version R2; March 2014

# Changes implemented through Q&A

- Holters discouraged → embraced (long after most studies were Holter-based)
- Bazett → “clearly ... inferior”
- Blinding → “not ... essential”
- Concentration-response
  - “component of a totality of evidence”
  - more compelling with pre-specified methods

# E14 Q&A on Exposure-response

“In some cases in which there is a large margin of safety between therapeutic exposures and the exposures that result in significant ECG interval changes, an intensive ECG follow-up strategy might not be warranted.

...

“CRR modeling applied on early clinical QT data from healthy volunteers seems promising in terms of enhancing our confidence to characterise QTc prolongation.”

# E14 next step

- Existing Q&A on exposure-response seems the logical place to amend E14.
- Would need to specify properties of an assessment whose negative findings will be considered dispositive.
  - Design
  - Analysis
  - Results
  - Documentation