FDA ECG Warehouse

Jose Vicente

ORISE Fellow, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

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Disclaimer

• I have no conflicts of interest.

• The opinions expressed in this presentation are mine and do not necessarily reflect the official views of the U.S. Food and Drug Administration.
FDA ECG Warehouse

• On-line database of electrocardiograms
• Technical response
  – Drug-induced QT prolongation and torsade de pointes (potentially fatal arrhythmia)
• An example of success
  – Community effort (ECG standards developed)
  – No new marketed drugs removed from market because torsade/QT prolongation
  – Large database of effects of drugs on the ECG
  – Allowed the assessment of new ECG biomarkers and generate new hypothesis
History

- 2001: Digital ECG Initiative
- 2002-03: Community develops annotated ECG data standard
- 2004: Implementation of the ECG warehouse
- 2005: Guidelines for clinical evaluation of QT
- 2006: Implementation of the ECG warehouse
- 2007-09: Expansion of the ECG Warehouse
- 2010: >4 million ECGs

- 2011: Continuous ECG Initiative
- 2012: Option for long term (Holter) ECGs (e.g. 24Hrs)
- 2013-15: Novel ECG biomarkers
- 2016-17: Baseline
- 2017: ECG signature of drugs from 34 clinical trials
- 2018-20: Analysis of ECG signatures in a large number of studies

>400 Thorough QT Studies, 9.5 million ECGs
Data collection

• ECGs acquired during clinical trial
  – 10-second 12-lead at multiple time-points
  – Continuous ECGs (Holters)
• Cardiologists annotate the ECGs
• Digital files of annotated ECGs are uploaded to the ECG warehouse
  – aECG HL7 data standard
ECG warehouse services

• Storage
  – Sponsor cannot access other sponsors’ ECGs
• Web-based user interface
• Quality metrics
• Review and format validation tools
Regulatory Review at FDA

- Web-based user interface to review ECG data in the warehouse
  - Display ECG waveforms with or without sponsor’s measurement annotations
  - Zoom in on parts of the ECG recording
  - Multiple views (individual leads, overlaid…)
  - Make measurements using on-screen calipers
Screen shots

- Search box
- Studies tree
- Protocol and ECGs tree
- Study data and ECGs summary statistics
- Quality metrics
Screen shots
Screen shots
Screen shots
Screen shots
Continuous Recordings (Holters)

• Supported since 2012
• Allow for extended analysis outside the pre-specified windows
  – Arrhythmia analysis (e.g. in non-thorough QT studies)
  – Assessment of trends
  – Enhanced quality metrics
• Research and development of novel methods
  – Improve characterization of drug-induced effects on ECG biomarkers as function of time
  – Beat-to-beat, bin methods
  – Improve automation
Recent research

Analysis of ECGs from 34 clinical studies showed that drugs that prolong QT by different mechanisms have different ECG signature in \( J-T_{\text{peak}c} \) and \( T_{\text{peak}}-T_{\text{end}} \) subintervals.

Johannesen et al., Clin Pharmacol Ther 2014
Next steps

• Extend ECG biomarkers analysis to a larger number of studies
• Incorporate/link preclinical information
  – drug effects on multiple ion channel currents
• Develop and assess new methods using data from multiple studies
• Develop new analytical methods based on continuous data
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FDA ECG Warehouse

• On-line database with +9 million ECGs
• An example of success
  – Community effort
  – Large database of effects of drugs on ECG
• On-going analysis of ECG signatures in a large number of drug studies
Thank you

Jose.Vicente@fda.hhs.gov

ORISE Fellow, Center for Drug Evaluation and Research, U.S. Food and Drug Administration