AMPS-QT

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AMPS-QT is a quarterly journal dedicated to all the people and organizations involved in the world of cardiac safety. Published by AMPS LLC, it covers all aspects of methodology and software technology related to clinical trials and Thorough QT studies.

Editorial

Our readers will certainly remember the RFQ "ECG WAREHOUSE FOR CONTINUOUS 12-LEAD HOLTER RECORDING" issued by the FDA at the end of July 2010, which was subsequently awarded to Mortara Instruments, as we reported in the 8th issue of AMPS-QT. We have been involved in the warehouse development, and in particular concerning the definition of a new standard format for Holters and Dr Badilini was in attendance of the public meeting on this subject that was held at the FDA Headquarters earlier in March. We were positive that this would be a subject of great interest to our readers but rather than providing Dr. Badilini's summary on the meeting we went one step further and are proud to welcome in this issue a contribution written by Dr. Christine Garnett, Pharm D, and reviewed by Dr. Norman Stockbridge, MD, PhD. For our readers who never had a chance to meet her, Dr. Christine Garnett is currently Associated Director of Operations and Team Leader Pharmacometrics at the FDA, which she joined in 2005. We thought there was no better way to learn about the progress of the FDA Holter warehouse than straight from the horse's mouth, so to speak. We are convinced you will find, as we did, her contribution extremely relevant.

A Noteworthy Contribution:

FDA Expands the ECG Warehouse to Include Continuous Recordings.

By Christine E. Garnett, PharmD; Office of Clinical Pharmacology, OTS/CDER/*FDA,* Silver Spring, MD.

Thorough QT studies are conducted by sponsors of new drugs to evaluate their potential to cause cardiac arrhythmias such as Torsade de Pointes. As described in ICH E14 Guidance (www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html), a QTc prolongation of greater than 10 ms can be clinically relevant, making these studies quite challenging to conduct. To evaluate the data quality from the thorough QT studies, the FDA must have access to the digital ECGs from which the QT measurements are made.

After an appropriate data standard was developed, Mortara Instrument and FDA executed a Cooperative Research and Development Agreement in 2004 for the development and support of the ECG Warehouse. This multi-year public-private partnership has resulted in the creation of a digital ECG repository that contains approximately 6.1 million ECGs and has enabled FDA on-line review of over 250 thorough QT studies. The ECG Warehouse provides for on-line data submission, validation, and reporting of problems with data loads. The underlying database stores the annotated ECGs from all submissions in an online system. The FDA reviewer is provided with a web-based interface to these data that allows for navigation to the submission, subject, and time point of interest. It allows the reviewer to plot the data with or without the sponsor's measurement annotations, to zoom in on parts of the recording, to view the leads separately or overlaid, and to make their own measurements using on-screen calipers. In addition, the supporting system provides additional data quality assessments, some of which are based upon comparison of the reported results with the Mortara VERITAS™ algorithm for QT quality and signal assessment. The ECG Warehouse facilitates the organization and easy retrieval of ECGs resulting in efficient review of ECGs within the FDA's submission review process. The ECGs are easily accessible by authorized FDA reviewers on any system within the FDA's network. The ECG review software is easily integrate into existing or planned submission review tool suites at the FDA and is harmonized with the submission models being formalized by CDISC (www.cdisc.org). Furthermore, the ECG Warehouse supports research-

related queries and investigations. The physical and computer access security of the system are managed by a commercial web services facility, which has been reviewed by FDA IT personnel, giving sponsors the same level of secure submission that they have for applications sent directly to FDA.

Although frequently the ECG data in thorough QT studies are obtained from Holter recordings, the ECG Warehouse currently only stores a series of 12-lead, 10-second recordings taken at protocol-specified time points. This is not optimal for several reasons: the process for selecting the 10-second recording within the protocol-defined analysis window is not subject to audit; the pre-specified nominal time points may not be adequate to discriminate real signals from random variation; and there is inherently more information in the recordings than can be captured in 10-second snapshots. Furthermore, there are other settings in which the review of continuous ECG data would be invaluable, for example, in the assessment of new devices or antiarrhythmic therapy. From a research perspective, new analytical methods based on continuous data in the ECG Warehouse will increase the efficiency of thorough QT studies and allow for the evaluation of new biomarkers for cardiovascular safety.

Mortara Instruments initiated the expansion and upgrade of tools for submitting continuous ECG data to the ECG Warehouse in 2010. As part of this initiative, the FDA held a public meeting (Docket No. FDA–2012–N–0084) on March 12, 2012 to discuss changes in how continuous digital ECG data are gathered and submitted to the ECG Warehouse and new tools for visualizing the annotated continuous ECG recordings.

An extension of the Health Level-7 Annotated ECG standard data format is proposed. The new data format is intended to facilitate electronic submission and sharing of ECG data from continuous recordings. When the continuous ECG Warehouse is implemented, digital ECGs will be provided using the existing HL7 annotated ECG format with additional enhancements. The annotated ECG XML file will carry non-waveform data and the storage of ECG waveforms will be in separate external files using a binary format. These proposed changes will need to be approved by HL7 Standards in a process which takes up to 2 years to complete. In the meantime, the ECG Warehouse will accept the proposed extensions, and continue to accept them even after the HL7 process is finished.

A new feature of the continuous ECG Warehouse is analysis window annotations. Analysis windows indicate time windows defined in the study protocol where the sponsor has measured the ECGs as evidence of drug effects. The analysis window will contain the sponsor's QT interval annotations. Selecting analysis windows close to the protocol-specified nominal time point in such a way as to avoid noise or other problems in the signal should not affect the results of the study. If analysis windows are, however, chosen so the QT measurement has the shortest value, this may introduce bias and affect the study's outcome. Therefore, the ECG Warehouse will include novel tools to assess bias of the analysis window compared to neighboring regions of the recording.

Another new feature is the Trend View to support detection of anomalous events and arrhythmias, and to provide context to the continuous recordings. The Trend View will enable FDA reviewers to navigate to different time points to identify events of interest. The Trend View will capture on a timeline ECG measurements (*e.g.*, HR, QT), ECG quality assessments (*e.g.*, QT bias, signal quality), arrhythmias (*e.g.*, VPB rate/counts, ST segments, AF onset) and protocol events (*e.g.*, dosing, peak drug concentrations).

A decade ago, regulatory interest in digital ECGs led to development of data standards, greatly improved conduct and interpretability of thorough QT studies, and enabled development of new analytic tools. There are now new opportunities to do better with continuous ECG recordings and to improve the cardiovascular safety evaluation of new medical products.

Products News

Latest Releases

- TrialPerfect v. 2.8.0, with enhanced ECG workflow and updated BRAVO algorithm;
- CalECG v. 3.3.0 and v. 3.4.0, with updated BRAVO algorithm;
- Fat-QT v. 1.1.0, with updated BRAVO algorithm.

Looking forward

In Q2 of 2012 AMPS is planning to release:

- FDAEcg Suite v.2: enhanced graphical interface, with advanced scoring display, new scoring metrics and optimized ECG management.

AMPS Notebook

As reported in the previous issue of AMPS-QT, Fabio Badilini is the chairman of the 37th **ISCE conference** that will be held in Birmingham, AL from April 20 to April 24,

2012. Here he provides for our readers a peek to what attendees may expect:

… "I look forward to a very interesting, stimulating, and productive meeting. This year's scientific program includes a number of very exciting highlights. The meeting will start with a tutorial, on April 20th, which will focus on the fragmented QRS, a topic that has received increased attention in the most recent literature. The main conference will start on April 21st; as previously announced, I am very pleased and honored to confirm a session, chaired by Dr. Marek Malik, which will feature three invited speakers directly from the FDA and which represent a unique opportunity to talk about aspects of drug studies within a highly technical ECG context. Another key session, chaired by Dr. Arthur Moss, will give a comprehensive overview of the most important digital ECGs collections, including epidemiological databases and research-oriented repositories. Other sessions will cover clinical aspects of ECG associated with ventricular hypertrophy and with the management of patient monitoring alarm fatigue. Finally, a full session will be dedicated to the state-of-the-art technology for surface-to-implantable cardiac devices".

AMPS People

We continue our round of staff introductions with Giovanni Franco Treccani.

Franco obtained his Economics degree at Parma University in Italy. He then continued his studies in France, at INSEAD business school. Later he attended a Senior Management Program at MIT in Boston. Though the years, he held several management functions with multinational companies such as L'Oreal, Revlon Inc, Avon Products Inc, Lavipharm Laboratories and Giorgio Armani.

Since 2000 Franco is AMPS President and head of finances and humane resources. He is also responsible for setting the Company strategies and exploring new venues of activities.

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