May 13, 2010

FDA Critical Path Initiative Research Project
PI: Christine Garnett, Pharm.D.
Co-PI: Norman Stockbridge, M.D., Ph.D.

Research Fellowship: $50–60K / year (duration 2 years)

Requirements: Ph.D. or other professional doctorate in electrophysiology, engineering, or related field. The candidate shall have good communication skills and hands-on experience with quantitative electrocardiography, quantification of drug-induced changes in electrocardiograms, and advanced programming skills. US Citizenship or US Permanent residency needed, J-1 visa processing possible. Specify immigration status in CV.

Please send cover letter and CV via email to Dr. Jeffrey Tworzyanski, Senior Project Management Officer, by June 15, 2010.
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Delays in cardiac repolarization (QT/QTc prolongation) are associated with lethal arrhythmias. Evaluation of the QT/QTc prolonging effects of new compounds has been challenging for drugs with pronounced effects on the autonomic nervous system, which can have secondary effects on cardiac repolarization. To identify drug-induced QT/QTc prolongation while adjusting for drug-induced changes in autonomic tone, scientists and experts have proposed analytic strategies relying on continuous Holter monitor recordings [1]. These methods include: 1) the evaluation of individual QT/RR coupling (QTci)[2-5]; 2) the definition of a normal 24-hour range of QT/RR couplets (QT beat-to-beat)[6-9], and 3) the design of rate-related referential QT benchmark (RR bin method)[10]. These three approaches are considered to be improved analytic strategies to evaluate the effects of a new compound on the QT/QTc interval in situations where the drug also changes the autonomic regulation of the heart. More importantly, these methods can be applied to data recorded in thorough QT studies (TQT studies, adhering to ICH E14 recommendations) if they were designed to use data from continuous 24-hour ECG recordings.

These methods require the analysis of long-term multi-lead continuous recordings, each including on the order of 10^5 cardiac beats on which these measurements are made. The current capacity of the Agency to receive, process, and evaluate this information is insufficient, and the primary objective of the proposed work is to develop these capacities inside the Center for Drug Evaluation and Research (CDER).

The project proposes a two-year research fellowship position at the FDA Campus in Silver Spring, Maryland, for the development of internal quality evaluation, analysis, and collation tools for Holter data submitted to the FDA by pharmaceutical companies. This data will encompass ECG raw signal (technical specifications of the signal to be defined) and a list of Holter-related information. This data will include:

Fiducial locations

1. QRS onset location

2. R peak location
3. QRS complex location,
4. T-end location

Interval duration

5. RR interval duration
6. QT interval duration
7. Cardiac beat annotation- HL7 ECG xml annotation

Signal quality

8. Noise content – all frequencies, low-frequency (LF) and high-frequency (HF)
9. Amplitude annotations (R and T wave amplitudes)

It is expected that the candidate will perform the following tasks:

1) Develop quality metrics for Holter annotation: cardiac beat annotation, fiduciary point evaluation (*e.g.*, R peak, onset of QRS, J point, T-wave end). The candidate will evaluate the variability of these parameters in reference to cardiac beat annotation, heart rate, and signal-noise content;
2) Develop quality metrics for RR and QT interval measurements;
3) Develop quality metrics for the selection of Holter segments on which the RR and QT interval measurements are to be measured (for protocols not requiring each beat to be accurately measured);
4) Develop quality metrics for QTci, QTb2b, and RR binning output (may include minimal requirements for data representation and reports content);
5) Present the above quality metrics and the associated process, as well as train FDA CDER employees in their application;
6) Recommend to the FDA staff the technical requirements for Holter data submissions by pharmaceutical companies to the Agency;
7) Develop a set of benchmarks for the QTci, QTb2b, and RR binning methods, based on available data (*e.g.* from sources such as the THEW at www.thew-project.org). These benchmarks will be released to private and public organizations as references for the validation of their Holter analysis processes for FDA submission. This will strengthen the confidence of submitting organizations while ensuring a minimum level of quality in data to be reviewed by the Agency.

Importantly, development of these processes should be done with the idea of extending the review capacities of the Agency to other electrocardiographic parameters beyond QT and QTc, which may bring to light new biomarkers for drug safety and efficacy.

In conclusion, the proposed project would benefit from an individual already familiar with the ECG methods described above, as well as expertise in quantitative electrocardiography. Candidates not familiar with fundamental principles of quantitative electrocardiography, Holter technology, and associated methods, are invited to participate in the THEW training class (RES950) at University of Rochester Medical Center, or other similar training programs, prior to joining the CDER/FDA.

Bibliography

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[3] M Malik. "Problems of heart rate correction in assessment of drug-induced QT interval prolongation." Journal of Cardiovascular Electrophysiology 12 (2001): 411-420.

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[10] F. Badilini, P. Maison-Blanche, R. Childers, and P. Coumel, "QT interval analysis on ambulatory electrocardiogram recordings: a selective beat averaging approach," *Med Biol. Eng Comput.*, vol. 37, no. 1, pp. 71-79, Jan.1999.