FINAL REPORT

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)

Science Exchange and Conference Grants

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Co-Chairs: Wenlei Jiang, PhD,
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James E. Polli, Ph.D.
Professor and Ralph F. Shangraw/Noxell Endowed Chair in Industrial Pharmacy and Pharmaceutics University of Maryland SOP

Gregory Krauss, MD
Professor of Neurology
Johns Hopkins University School of Medicine

Title of conference:

Questioning the bioequivalence standards for antiepileptic drugs: implications for regulation of narrow therapeutic index drugs

Date of conference: **May 12, 2014**
Time: 9:00 am - 4:00 pm, with lunch provided
Location: White Oak Campus of the FDA Monday, May 12, 2014 beginning at 9:00 am in the Great Room Section-A, 10903 New Hampshire Ave

Attendance: **82 total participants** (26 participants on-line)
Invited speakers and participants included neurologists with expertise in epilepsy, pharmacologists, generic manufacturers, representatives of epilepsy patient-advocate and professional societies (EFA/Abilities Network, American Epilepsy Society, American Academy of Neurology) and FDA representatives.

Opening remarks were made by Janet Woodcock, MD, Director of FDA Center for Drug Evaluation and Research. Closing remarks were made by Robert Lionberger, PhD, FDA Acting Deputy Director for Science, Office of Generic Drugs.

Speakers, Tricia Ting MD and James Polli PhD, discussed results of the completed Bioequivalence in Epilepsy (BEEP) study. Michel Berg MD, University of Rochester SOM, provided an update of the ongoing Equivalence Amoung Generic AEDs (EQUIGEN) study and the results of Q-pulse survey on AED dosing practices of epileptologists. Wenlei Jiang PhD, gave an overview of FDA OGD historical and current approach to ensuring generic AED safety and efficacy, including the MedWatch program, supporting research in epilepsy patient BE studies (BEEP and EQUIGEN), evaluating classification of NTI drugs, and adopting reference scaled average bioequivalence and variability comparison for NTI drugs. William Clarke PhD, Johns Hopkins University, and Michael Cohen-Wolkowiez MD, Duke University SOM, introduced current FDA research on extracting clinical use data from EMR to examine physician practices for NTI classification. James Cloyd PharmD, University of Minnesota College of Pharmacy, discussed dose sensitivity considerations for AEDs. Jack Cook PhD, Vice President Clinical Pharmacology Specialty Care Pfizer, Inc., proposed criteria for establishing BE and testing on the basis of compound pharmacology and PK, including NTI compounds. Angela Men, MD PhD, FDA Clinical Pharmacology for Neurology Products, outlined an ongoing FDA Critical Path Project for extrapolating efficacy of AEDs in adults to estimate drug dose-exposure response (DER) relationship in pediatric patients. Gregory Krauss MD, Johns Hopkins University SOM, discussed concerns for BE standards of modified release AED generics including the performance of generics of different delivery technologies and whether absorption variability may contribute to clinically significant concentration changes. A final panel of speakers, Drs. Polli, Ting, Berg, Jiang, Cloyd, Cook, Men, and Krauss, opened a forum for interdisciplinary discussions with participants on the effectiveness of current regulatory standards governing generic drug approval and the most appropriate and acceptable approach for assessing generic bioequivalence to ensure therapeutic equivalence. Conclusions drawn from this conference may be relevant for the regulatory oversight of other drugs as well, such as immunosuppressant drugs. Speakers and discussants in the conference met objectives for the following focus areas:

- Assess the emerging data, including case evidence (3) and postmarketing surveillance, e.g. MedWatch, suggesting that patients with epilepsy may have issues of tolerability for generic AED switching

- Review data from ANDA submissions to survey average differences in the rate and extent of drug absorption between generic and innovator products including a comparison of immediate and modified release product performance

- Explore criteria for an AED to be considered a NTI drug based on efficacy and toxicity profiles with consideration of within-patient variability (e.g. in the generic brittle), therapeutic drug monitoring, and clinical dose adjustment

- Review results and conclusions from current single- and multiple-dose AED bioequivalence trials of brand and generic lamotrigine tablets in epilepsy patients