Activity Outline

FDA Grand Rounds:
Developing a Mechanistic Model-Based Approach to Assess Cardiac Safety of New Drugs

September 14, 2017
12:00 PM-1:00 PM
FDA White Oak CSU 2031

Series Description

The FDA Grand Rounds is webcast every other month to highlight cutting-edge research underway across the agency and its impact on protecting and advancing public health. Each session features an FDA scientist presenting on a key public health challenge and how FDA is applying science to its regulatory activities.

Session Description

This presentation addresses the public health and regulatory need for:

- a new paradigm to assess cardiac safety of new drugs;
- the cutting edge science that underpins that paradigm;
- the current status of ongoing validation studies; and
- expected impact of this novel mechanistic, model-informed approach.

In the 1990s to early 2000s, multiple drugs were removed from the market because they caused arrhythmias and sudden death. In response, regulatory guidelines were implemented that have successfully prevented such occurrences by focusing on detecting hERG potassium channel block in cells and QT prolongation on the electrocardiogram. However, this approach is not very specific because some drugs are flagged as posing a risk and thus can be dropped from development when they are actually safe.

A new model, the Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative, aims to be a more accurate and comprehensive, mechanistic-based assessment of drug safety. It combines data that we get from multiple ion channels in the lab in a computer model to predict the risk in patients. The results are checked in an assay with human-induced pluripotent stem cell derived cardiomyocytes and using electrocardiographic biomarkers in standard phase 1 clinical trials.

Much of the development and validation work for CiPA has occurred in FDA labs, but this effort also involves our worldwide drug regulatory colleagues, academia, and industry through multiple public-private partnerships. In March 2017, this new model was presented to an FDA advisory committee, which endorsed this approach, pending ongoing validation studies.

Session References:

1. Gintant G, Fermini B, Stockbridge N, Strauss D. The Evolving Role of Stem Cell Derived Cardiomyocytes in Drug Safety and Discovery: Bridging Cardiac Safety Testing into the 21st Century. Cell Stem Cell 2017;21:14-17.
2. Colatsky T, Fermini B, Gintant G, Pierson JB, Sager P, Sekino Y, Strauss DG, Stockbridge N. The Comprehensive in Vitro Proarrhythmia Assay (CiPA) initiative – Update on progress. Journal of Pharmacological and Toxicological Methods. 2016;81:15-20.
3. Li Z, Dutta S, Sheng J, Tran PN, Wu W, Chang K, Mdluli T, Strauss DG, Colatsky T. Improving the In Silico Assessment of Proarrhythmia Risk by Combining hERG-Drug Binding Kinetics and Multi-Channel Pharmacology. Circulation Arrhythmia and Electrophysiology 2017 Feb;10(2):e004628.
4. Blinova K, Stohlman J, Vicente J, Chan D, Hortigon M, Rodriquez VZ, Smith G, Ross J, Brock M, Chvatal S, Millard D, Johannesen L, Galeotti L, Pang L, Lyn-Cook B, Crumb W, Stockbridge N, Strauss DG. Comprehensive Translational Assessment of Human Induced Pluripotent Stem Cell Derived Cardiomyocytes for Evaluating Drug-Induced Arrhythmias. Toxicological Sciences 2017 Jan;155(1):234-247.

5. Johannesen L, Vicente J, Mason J, Sanabria C, Waite-Labott K, Hong M, Guo P, Lin J, Sorensen JS, Galeotti L, Florian JA, Ugander M, Stockbridge N, Strauss DG. Differentiating Drug-Induced Multi-channel Block on the Electrocardiogram: Randomized Study of Dofetilide, Quinidine, Ranolazine and Verapamil. Clinical Pharmacology and Therapeutics. 2014;96: 549-58.

Meeting Materials for the Pharmaceutical Science and Clinical Pharmacology Advisory Committee that covered this topic:
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm535520.htm

Series Objectives:

1. Discuss the research conducted at the FDA.
2. Explain how FDA science impacts public health.

Session Learning Objectives After completion of this activity, the participant will be able to:

1. Describe the need for a novel cardiac safety regulatory assessment paradigm for drugs.
2. Discuss the different technologies being used to inform drug safety, including ion channel assays, in silico models, induced pluripotent stem cells and biomarkers.
3. Identify the potential for mechanistic, model-informed approaches to be used more broadly at FDA.
4. Talk about the benefit of research collaborations using public-private partnerships.

Target Audience

This activity is intended for physicians, pharmacists, nurses and other scientists within the agency and external community.

About the Presenter

David Strauss, MD, PhD is a leader in translational sciences regulatory research. Before serving in his current role as Director of the Division of Applied Regulatory Science in FDA's Center for Drug Evaluation and Research (CDER), Dr. Strauss was Senior Advisor for Translational and Experimental Medicine in CDER's Office of Clinical Pharmacology and a medical officer and premarket medical device reviewer in the Center for Devices and Radiological Health. He earned a B.A. in chemistry and medical degree (M.D.) from Duke University, and a Ph.D. in clinical physiology from Lund University, Sweden. Dr. Strauss also completed a postdoctoral fellowship at Johns Hopkins University. He has published over 100 peer-reviewed journal articles and book chapters related to assessing the safety and effectiveness of drugs and medical devices and predicting individualized response to therapies. He currently oversees research and review activities across the translational research spectrum, including in vitro and in vivo laboratory research, in silico computational modeling and informatics, and integrated clinical research covering clinical pharmacology, experimental medicine and postmarket analyses.

Schedule

Date/Time/Place	Lecture Title	Lecturer
Thursday, September 14, 2017 12:00 PM-1:00 PM FDA White Oak CSU 2031	FDA Grand Rounds: Developing a Mechanistic Model-Based Approach to Assess Cardiac Safety of New Drugs	David Strauss, MD, PhD

Continuing Education
Accreditation

In support of improving patient care, FDA Center for Drug Evaluation and Research is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC) to provide continuing education for the healthcare team.

CME

FDA Center for Drug Evaluation and Research designates this live activity for a maximum of 1 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CPE

This knowledge-based activity has been assigned ACPE Universal Activity Number 0601-0000-17-114-L04-P, for 1 contact hour(s).

CNE

FDA Center for Drug Evaluation and Research designates this activity for 1 contact hour(s).

Requirements for receiving CE credit
Physicians, pharmacists, nurses and those claiming non-physician CME: attendance is verified by a sign-in sheet and completion of the final activity evaluation. For multi-day activities, participants must sign in every day. Final activity evaluations must be completed within two weeks after the activity.

Pharmacy participants: partial credit cannot be awarded therefore you must attend the entire activity to receive CPE credit. No exceptions. Pharmacists will need their NABP e-profile ID number as well as their DOB in MMDD format in order to claim CE credit.

Statements of Credit
Physicians and Nurses Statements of Credit for CE will be issued 10 weeks after the last session of this activity. Pharmacists should log into the CPE monitor 10 weeks after the last session of the activity to obtain their CE credit.

Disclosure
Faculty
David Strauss, MD, PhD, Director, Division of Applied Regulatory Science, FDA/CDER, has nothing to disclose.

Planning Committee
Emannuel Fadiran, PhD, RPh, Intramural Research Program Director, FDA/OC/OWH, has nothing to disclose.
Virginia Giroux, MSN, ARNP, CE Program Administrator, CDER/DLOD, has nothing to disclose.
Eileen Parish, MD, Medical Officer, FDA/OC/OCS/OSPD, has nothing to disclose.
Leslie Wheelock, MS, RN, Director OSPD, FDA/OC/OCS/OSPD, has nothing to disclose.

CE Consultation and Accreditation Team

Traci Bryant, MAT, Education Specialist, FDA/CDER/OEP/DLOD, has nothing to disclose.
Karen Zawalick, CE Team Leader, FDA/CDER/OEP/DLOD, has nothing to disclose.

Registration Fees and Refunds
Registration is complimentary therefore refunds are not applicable.

Requirements for Certificate of Completion (Non CE)
Must attend 80% of the lectures (verified by a sign-in sheet).

Remote Access Instructions:

Webcast Registration: To register for the webcast, please click the link below and then follow the instructions on the registration page. After you register you will receive a link via email to access the live webinar. You must log in with your username and password which you create when you register. Please pre-register at least one day before the event to ensure you receive the access link email and outlook invitation for the session.
https://collaboration.fda.gov/sept172017grandroundsreg/event/registration.html

For technical assistance please contact Jeffery Rexrode at Jeffery.Rexrode@fda.hhs.gov.

LMS Registration link:
https://lms.learning.hhs.gov/Saba/Web/Main/goto/RegisterCatalog?offeringId=class000000000127159&oneClickLearningON=true

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