Regulatory Science at the US Food and Drug Administration: Enhancing SCIENCE-based regulation of medical products

Carolyn A. Wilson, Ph.D.
Associate Director for Research
Center for Biologics Evaluation and Research
My comments are an informal communication and represent my own best judgment.

These comments do not bind or obligate FDA.
FDA’s Regulatory Scope:
25 cents of every GDP dollar
Using Science and Regulation to Advance Medical Product Development

- Post-market Surveillance
- Licensed Product
- Improved Data – Benefit/Risk
- Regulatory Policy/Decision
- Regulatory Science
- Discovery New Tools
- Regulatory Challenge
- Novel Product

Public Health
FDA’s Regulatory Science

- Product Centers oversee and conduct intramural laboratory and non-lab (i.e., epidemiology and biostatistics) research
- Office of the Commissioner and Office of the Chief Scientist:
  - Coordination/communication via working groups
  - Intramural funding programs
  - Extramural funding programs
FDA Regulatory Science:
Regulatory Product Center Programs

Commissioner

Office of Foods and Veterinary Medicine

Office of Medical Products and Tobacco

ORA
CFSAN
CVM
CBER
CDER
CDRH
CTP
2016 CBER Goals
Regulatory Science and Research

Goal 1. Advance the scientific basis for regulation of biologics, human tissues and blood to enhance safety, effectiveness, quality and consistency through development and evaluation of new concepts, methods, models, and reagents.

Goal 2. Develop and assess nonclinical models and methods with improved predictive value, and, as feasible, reduce, refine, or replace the use of animals, for evaluation of safety and effectiveness of CBER-regulated products.

Goal 3. Improve clinical evaluation related to CBER-regulated products through the use of new biomarkers, large scientific and healthcare datasets, and innovative design and analysis of clinical studies by applying new statistical, epidemiological, and mathematical modeling approaches, and considering patient input to inform benefit-risk assessment of general and special populations.

Goal 4. Prepare for future regulatory and public health challenges through investments in emerging science and technology, and develop and sustain varied scientific expertise.
What about Zika Virus?

Initial focus: protect the blood supply:

- **December 2015**: Local mosquito-transmitted in Puerto Rico
- **February 2016**: FDA issued guidance: No blood collection without screening in affected regions
- **March 2016**: Continental US blood provided to Puerto Rico
- **April 2016**: Testing of blood implemented in Puerto Rico
Zika and Protecting the Blood Supply....

April 2016

FDA developed RNA Reference materials

July 2016

Local mosquito-transmitted Florida

August 2016

FDA revised Guidance: Universal testing or Inactivation

October 2016

WHO adopted FDA developed RNA Reference materials
CBER: Mesenchymal Stem Cells Consortium

• Objective: Develop ways to identify quality attributes that predict safety and effectiveness.

• Outcomes
  – Demonstrated that Consensus MSC Markers do not Correlate with Functional Heterogeneity
    • Donor or Tissue Culture Age Differences
  – Developed assays to identify and qualify predictive product characteristics for cell therapy products
  – Published findings

Lo Surdo JL et al., Cytotherapy, 2013.

Sponsors have used some of CBER’s published methods to characterize their products; data provided in INDs
MSC Consortium Publications

**Differentiation**

**Proteomics**

**Immunomodulation**

**Genomics**

**Epigenetics**

**Sector Overview**
CDER: 7 Regulatory Science Topics

I. Improve Access to Post-market Data Sources and Explore Feasibility of Their Use in Different Types of Analyses

II. Improve Risk Assessment and Management Strategies to Reinforce the Safe Use of Drugs

III. Evaluate the Effectiveness and Impact of Different Types of Regulatory Communications to the Public and other Stakeholders

IV. Evaluate the Links among Product Quality Attributes, Manufacturing processes, and Product Performance

V. Develop and Improve Predictive Models of Safety and Efficacy in Humans

VI. Improve Clinical Trial Design, Analysis, and Conduct

VII. Enhance Individualization of Patient Treatment

http://www.fda.gov/Drugs/ScienceResearch/ucm264327.htm

www.fda.gov
Supporting evaluation of biosimilars: Analytical technologies to evaluate recombinant proteins

2D-NMR analysis of the higher-order structure of filgrastim (G-CSF, biosimilar for Neupogen): approval of this first biosimilar in 2015

• Originator product, Neupogen, and three unapproved drug products evaluated at four labs on 6 instruments
• Same analytical software applied to all data
• Sufficient resolution to obtain high degree of similarity with quantitative analysis revealing shifts tracking to variations in temperature, pH/ionic strength of solvent, or change in higher order structure.

http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm436648.htm
National Center for Toxicological Research: Supporting Multi-Agency Tox21
FDA’s Modernizing Toxicology

• Develop better models of human adverse response
• Identify and evaluate biomarkers and endpoints that can be used in non-clinical and clinical evaluations
• Use and develop computational methods and *in silico* modeling
Bioimaging: Replace?

Predictive Pharmacology *in silico*

**QSAR** (Quantitative Structure Activity Relationship)

- 50 years - Traditional drug discovery tool
- Based on classical (large body) mechanics
- Regression/classification outcomes based on measurement of 2D and 3D structural/reactive chemical descriptors.
- E.g. EDKB

**QSDAR** (Quantitative Spectral Activity Relationship)

- QSDAR patent 2004
- 3D QSDAR* patent 2011
- Based on quantum (very small body) mechanics; e.g. NMR chemical shift data
- Partial least squares and discriminant analysis of experimental or *in silico* generated NMR data
- E.g. PLD and hERG binding

*incorporates inter-atomic distance

* "All models are wrong but some are useful”  George Box 1978
Experimental Validation Of the hERG and PLD 3D-QSDAR *in silico* Model

- $^{15}$N- and $^{13}$C NMR 3D-QSDAR
- NCATS experimental PLD testing (n=1070; acc=83%), used a HepG2 cell line while the hERG assay (n=1385; acc=86%) used U-2 OS viral transduced cells
- Tendency 3D-QSDAR to predict false positives/ No tendency to predict false negatives

![ROC for 3D-QSDAR classification](image)

PLD  n=1070  

hERG  n=1385

PLD (AUC = 0.90)  

hERG (AUC = 0.88)
Office of Regulatory Science and Innovation

- Oversees two major **extramural** programs in regulatory science:
  - **Broad Agency Announcement**
    http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm301667.htm
  - **Centers of Excellence in Regulatory Science (CERSI)**
    http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm301667.htm
    - University of Maryland
    - Georgetown University
    - Johns Hopkins University
    - UCSF/Stanford
    - Yale/Mayo
Objective: Develop an anatomical and functional population model of the musculoskeletal system to facilitate virtual clinical trials
Collaboration with Dr. Thor Besier, Auckland Bioengineering Institute and CDRH

Overview and Outcomes:

- Open source software enables users to visualize the musculoskeletal system; create computational models of anatomical structures based on patient data.
- Database enables access to raw medical image data, motion capture and muscle performance data gathered in the international Physiome Project. Includes pelvis, femur, tibia, fibula and patella.
- Users query database for similarities and differences in range of anatomical data.

BAA example: The Musculoskeletal Atlas Project (MAP)
https://simtk.org/home/map
CERSI Program

Joint efforts between FDA and academic institutions to collaborate on projects that promote regulatory science, including innovative research, education, and scientific exchange under a cooperative agreement grant (U01).

- Address scientific challenges arising from new medical product development and regulatory activities
- Collaboration with academic partners on research that supports FDA’s regulatory mission & improves public health.
- Support training needs for FDA, new scientists, & scientific community.
- Enhance extramural partnerships and expand scientific exchanges.
CERSI Example:
Eliciting Patient Preferences to Enhance Regulatory Science Research Project

Johns Hopkins University

Objective
• Advance and apply stated preferences among people with type 2 diabetes

Overview & Outcomes
• National survey assessed priorities for diabetes self management and treatment preferences
• Collaborated with patient organizations to create patient-centered studies for lung cancer, acute myeloid leukemia and Duchenne muscular dystrophy
• Direct impacts of patient organizations – pilot results from collaboration with Leukemia and Lymphoma Society to be presented at FDA patient preference meeting
FDA Regulatory Science: OC Programs

Office of the Chief Scientist

National Center for Toxicological Research

Office of Regulatory Science and Innovation

Office of Counter-Terrorism and Emerging Threats

Office of Women’s Health

Office of Minority Health
Medical Countermeasures Initiative
Regulatory Science Program
www.fda.gov/medicalcountermeasures

• Established in 2010 under the Medical Countermeasure Initiative (MCMi) to support intramural and extramural research

• Priority research areas
  – Identifying, developing, and qualifying drug development tools (e.g., animal models, biomarkers)
  – Developing methods to assess product quality and related product release assays
  – Validating next-generation in vitro diagnostics platforms
  – Assessing the performance of emergency medical equipment
  – Enhancing emergency preparedness and response capabilities, including risk communication and tracking and evaluating the safety and clinical benefit of MCMs used during public health emergencies
MCMi extramural regulatory science example: Cross-Species Immune System Reference  
Garry Nolan, Stanford University

**Objective:** Conduct a comprehensive cross-species analysis of immune system function to inform the choice of appropriate models for MCM development

**Overview & Outcomes**

- Universal antibody panels for humans, macaques, African green monkeys, and mice
- Exposed blood from humans, three species of non-human primates, and mice to cytokines, viral and bacterial antigens, or receptor ligands; analysis via CyTOF mass cytometry
- Species- and gender-specific differences in immune response, the effect of anesthesia on NHP immune function and blood chemistry, and macaque-specific sensitivity to bacterial threat agent
- Open access cross-species immune response database: [http://immuneatlas.org](http://immuneatlas.org)

OWH-funded research has contributed to FDA policy and advanced knowledge of **SEX DIFFERENCES IN HEART DISEASE**
Higher Risk for Drug-Induced Arrhythmias for Women

Investigator: David Strauss – FDA CDER

- Between 1991 and 2003, 6 drugs were withdrawn from marketing in the US because of Torsade de Pointes (TdP) tachycardia
- Women are at higher risk
- Project assessed the ability of novel ECG biomarker strategies to differentiate benign from malignant drugs that prolong the QT and sex difference in QTc prolongation

**Regulatory Impact:** Understanding the mechanisms of QTc prolongation and determining if drug-induced abnormal heart rhythms may be prevented by combining drugs will ensure safety of approved drugs for women and men.
Vision: A world where health equity is a reality for all

Mission: The Office of Minority Health advances FDA’s regulatory mission in addressing the reduction of racial and ethnic health disparities and in achieving the highest standard of health for all.

- Goal 1- To improve and strengthen regulatory science informing the research and evaluation of sub-population data associations with race and ethnicity.

- Goal 2- To strengthen FDA capacity to address minority health and health disparities across the Agency.

- Goal 3- To promote effective communication and the dissemination of information to the public, particularly underserved, vulnerable populations.
Research and Collaboration Strategies

Support/Fund Research Projects
- Intramural Challenge Grants
- Intramural ORISE Fellows
- Extramural ORISE Fellows

Collaborations
- FDA Centers for Excellence in Regulatory Science and Innovation Program
- 2015 Genomics and Health Disparities Lecture Series with the National Human Genome Research Institute (NHGRI)

Training/Workshops
- OMH Speaker Series
- CDER Scientific Seminars
- Pharmacy Intern Program
- Institute of Medicine Roundtable on Promotion of Health Equity and the Elimination of Health Disparities
- Part 15 Hearings/CERSI Workshop
Objective: Evaluate how health information is relayed by examining health literacy and cultural competency of Food and Drug Administration (FDA) consumer materials on HIV/AIDS and Hepatitis B/C

Outcomes:
• Majority of pages scored at the college or graduate reading level (>12).
• Epidemiology of population health and health care disparities are key components of cultural competency training for health professionals
• Although many websites contain data and statistics, statistics presented are not representative of the intended audience and material is not useful
• Publication: Health Literacy and Cultural Competency of FDA Consumer Materials
Summary

Science-based regulation is improved when FDA engages in research *proactively and reactively* to address critical knowledge gaps that reduce uncertainty in regulatory decision-making.
With Thanks

• Robert Fisher, OCET, OCS
• York Tomita, Khaled Bouri, Shaila Shaheed, ORSI
• Martin Mendoza, OMH
• Emmanuel Fadiran, OWH
• Steve Bauer, Maria Rios, CBER
• Ruth Barratt, CDER
• Tom Flammang, NCTR