Duke UNIVERSITY | Duke-Margolis Center *for* Health Policy

Biologic Variability to Drug Response: Sex Differences in Clinical Trials

Marriott Renaissance • Washington, DC

May 16, 2016

We know there is biologic variability to drug response. What we don't know is what those major causes of variability are. The U.S. Food and Drug Administration (FDA) is being asked to ensure pivotal trials are adequately powered to detect demographic differences of sex, race, age, and ethnicity on drug safety and efficacy. Yet the hypothesis-driven, population-mean-based results of randomized clinical trials (RCTs) are not designed to yield definitive insights into the differential responses of subgroups, or for that matter, any individual.

Given that a randomized clinical trial cannot test every subgroup, how do we determine which subgroups actually matter? If we believe there is a biologic plausibility that a certain subgroup will respond differently to the same drug, how do we design a trial to capture that difference? How much confidence do we have in that finding? How much uncertainty are we comfortable with? How can we as a scientific community, improve the nature of the "learn-confirm" clinical trial process to better understand variability in drug response? And are there viable alternatives to RCTs that may be more useful in identifying meaningful differences in drug response?

Acknowledging that the randomized control trial is not the only solution, and may not even be the best approach, the FDA is calling a meeting to discuss best practices to understanding variability to drug response. Duke is hosting this day-long meeting in collaboration with experts from government, academia, industry, and patient advocacy groups to discuss biologic variability in regard to FDA CDER-approved drugs and biologics.

8:30 a.m. **Registration**

9:00 a.m. **Welcome, Overview, and Meeting Objectives**

- **Mark McClellan,** Duke-Margolis Center for Health Policy
- **Greg Daniel**, Duke-Margolis Center for Health Policy

9:15 a.m. **Opening remarks from FDA**

- **John Whyte,** US Food and Drug Administration
- **Janet Woodcock,** US Food and Drug Administration

9:30 a.m. **Understanding the Known Causes of Variability in Response to Drugs**

Objective: Provide an overview of the current understanding of different sources of biologic variability in response to drugs

Opening presentation:

- **Garret FitzGerald,** University of Pennsylvania Perlman School of Medicine

10:00 a.m. **Session Ia: Determining Which Subgroups Matter**

Objective: Explore the current understanding of when subgroup analysis should be undertaken as part of a clinical trial, and discuss the regulatory approach to identifying variability in response to drugs.

Moderator: **Mark McClellan**, Duke-Margolis Center for Health Policy

Opening Presentations:
- **David J. Greenblatt,** Tufts University School of Medicine
- **Robert Temple,** US Food and Drug Administration

11: 00 a.m. **Break**

11:15 p.m. **Session Ib: Determining Which Subgroups Matter**
Objective: Explore current theories of sex differences in response to drugs, discuss the potential of including sex as a secondary endpoint in clinical trials, and identify methods for determining the correct balance of men and women in a given clinical trial.

Moderator: **Mark McClellan**, Duke-Margolis Center for Health Policy

Opening Presentations:
- **Rita Redberg,** University of California—San Francisco School of Medicine
- **Virginia Miller,** Mayo Clinic

12:15 p.m. **Lunch**

1:15 p.m. **Session II: Incorporating Variability in Drug Development**
Objective: Discuss current methods of understanding variability in drug response as a result of sex, and identify possible alternatives to randomized controlled trials (RCTs) that may be better suited to capture sex differences or other kinds of variability.

Moderator: **Mark McClellan**, Duke-Margolis Center for Health Policy

Panelists:
- **Issam Zineh,** US Food and Drug Administration (5-7 mins)
- **Ruthanna Davi,** US Food and Drug Administration (5-7 mins)
- **Richard Sax,** Quintiles (5-7 mins)
- **Jerald Schindler,** Merck (5-7 mins)

2:45 p.m. **Next Steps**
Objective: Recap major takeaways from the day's discussion, and prioritize for action key next steps.

3:15 p.m. **Closing Remarks**

3:30 p.m. **Adjournment**

Funding for this conference was made possible in part by a cooperative agreement UFD005197 from Food and Drug Administration, Center for Drug Evaluation Research. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsements by the U.S. Government.