

Panel Discussion: HTE Across Diverse Populations

MODERATOR:

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OFFICE OF WOMEN'S HEALTH

Session Outline

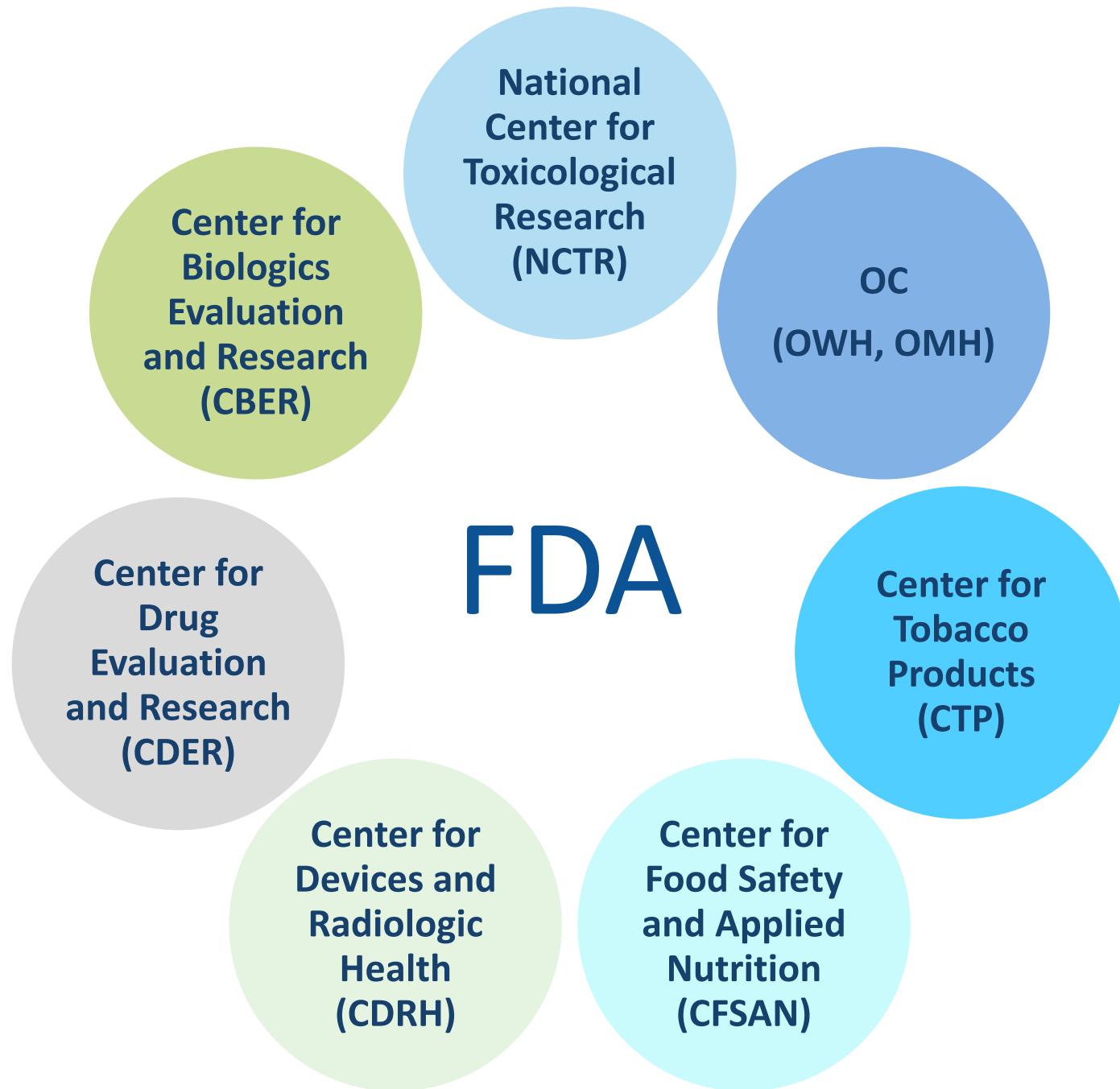
➤ **Moderator Presentation**

- ❑ FDA Overview
- ❑ Panel Goals and Objectives
- ❑ Panelists
- ❑ Review Panel Subtopics
 - PK/PD
 - Biologics
 - Devices
 - Drugs/Aging
 - Sex as a Biological Variable
 - Race/Ethnicity and Disease Prevalence

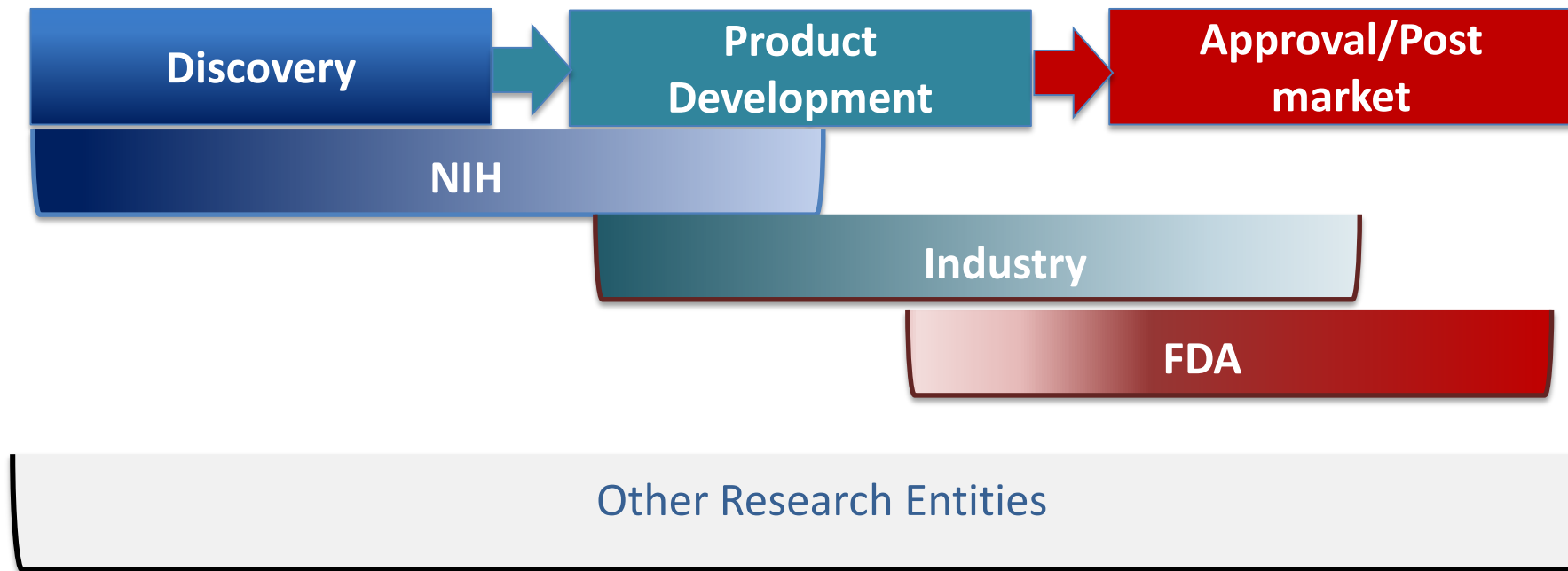
➤ **Panelists Remarks**

➤ **Moderated Q&A**



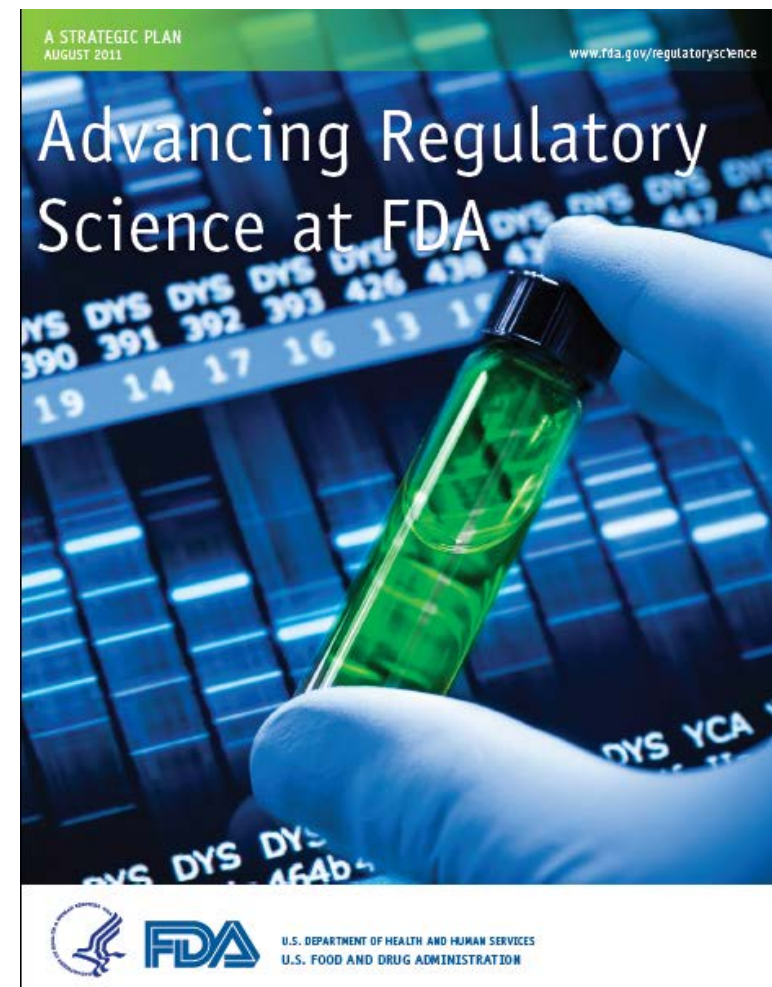


Research Environments

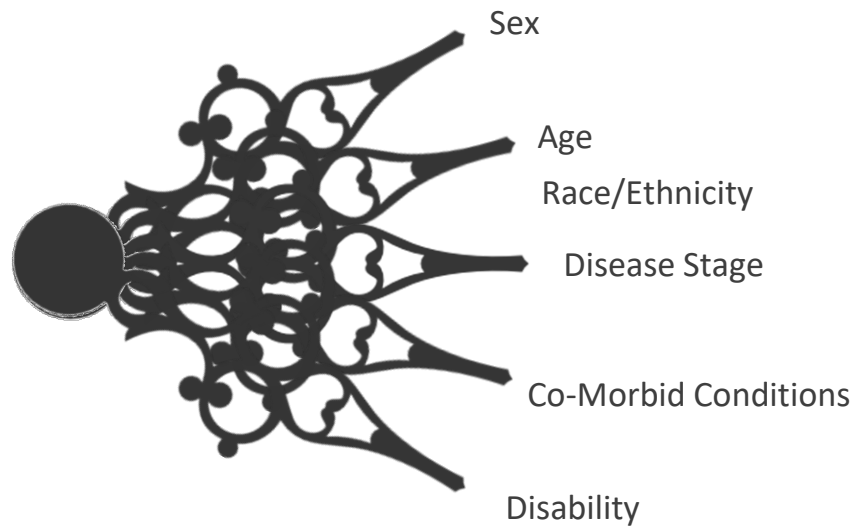


FDA and Regulatory Science

The science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA regulated products.



FDA is interested in patient or population characteristics that might impact the safety or effectiveness of a product such as:



All Differences Are Not Equal

Zolpidem

Sedative hypnotic

Approved in 1995

Maximum approved dose 10mg in adults

Early PK studies revealed a 40% sex difference in metabolism

Is the PK difference clinically meaningful?



Today's Panel

Overarching Goal

HTE related to demographic groups and pharmacotherapy principles.

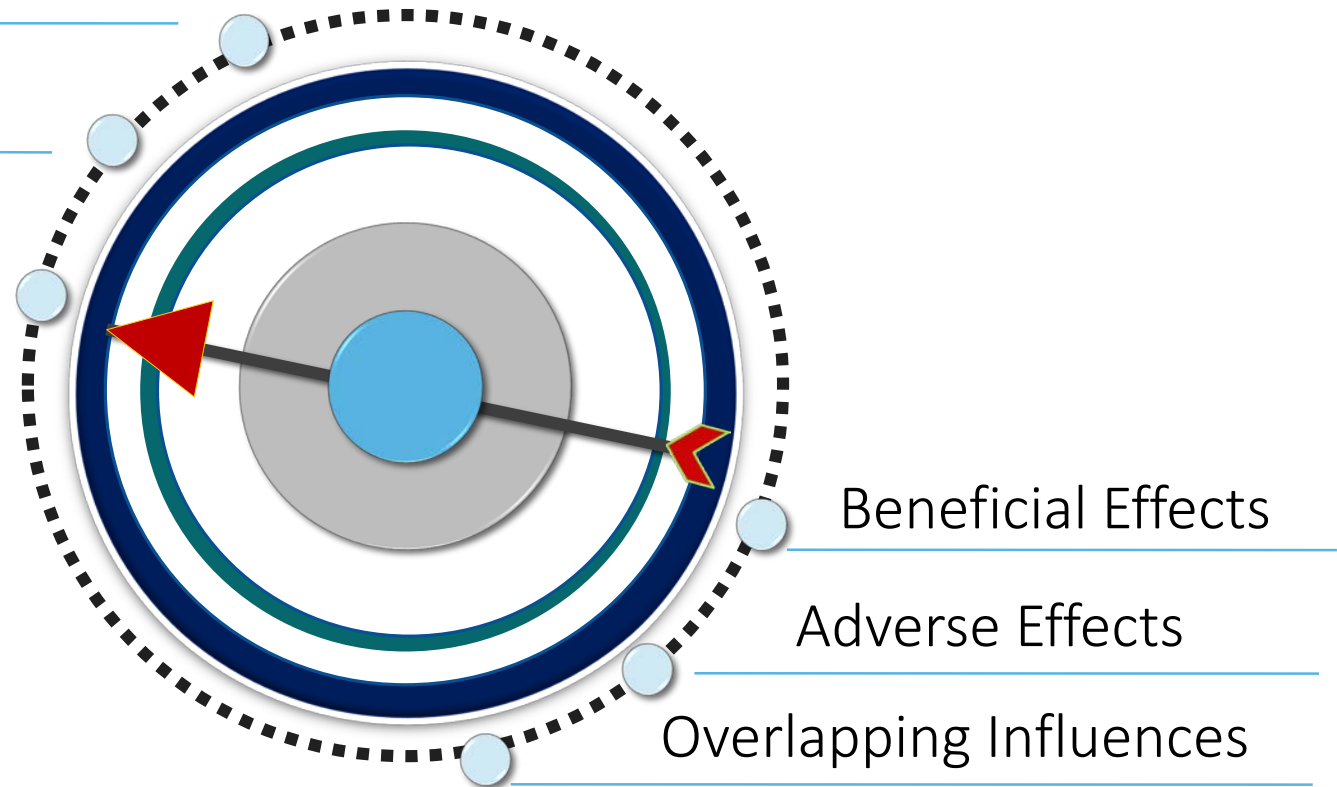
Heterogeneity of Treatment Effect



Differences Across Subjects

Magnitude of Effect

Optimal Conditions

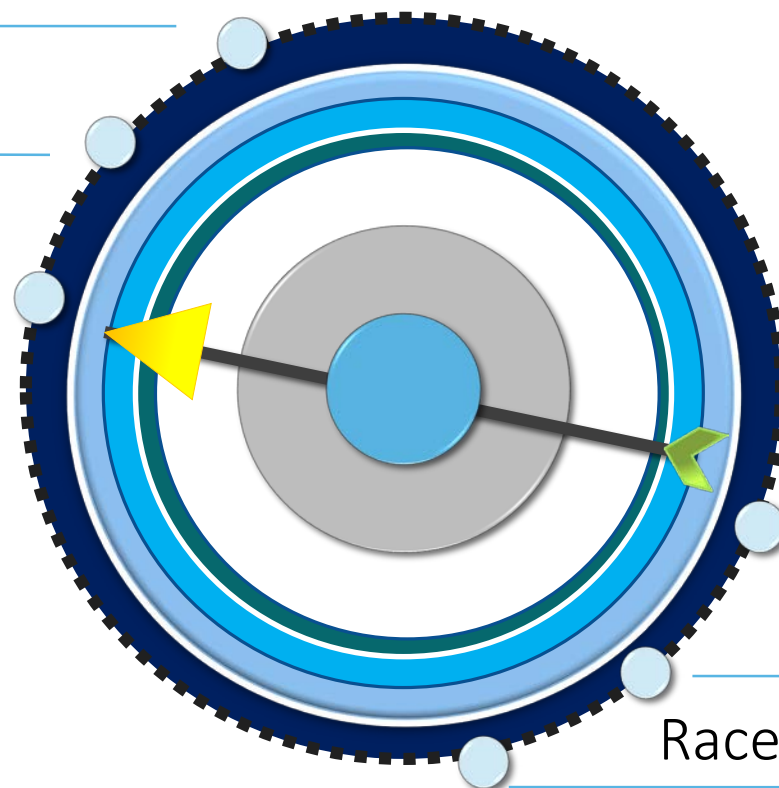


Panel Subtopics

Devices: Pediatrics

Biologics

PK/PD



Drugs: Aging

Sex /Gender

Race/Ethnicity

Panel Objectives: Challenge Questions

1. Why is it critical to account for clinical pharmacology when interpreting and mitigating heterogeneity in treatment effects?
2. What are some challenges that biologics present when interpreting and mitigating heterogeneity in treatment effect?
3. How long can a neonate tolerate a heart rate of 220 beats per minute?
4. How does aging mechanistically contribute to heterogeneity of treatment effects?
5. Why is it critical to account for biological sex in all analyses of drug effects?
6. Can clinical trials address the realities of disease prevalence data?

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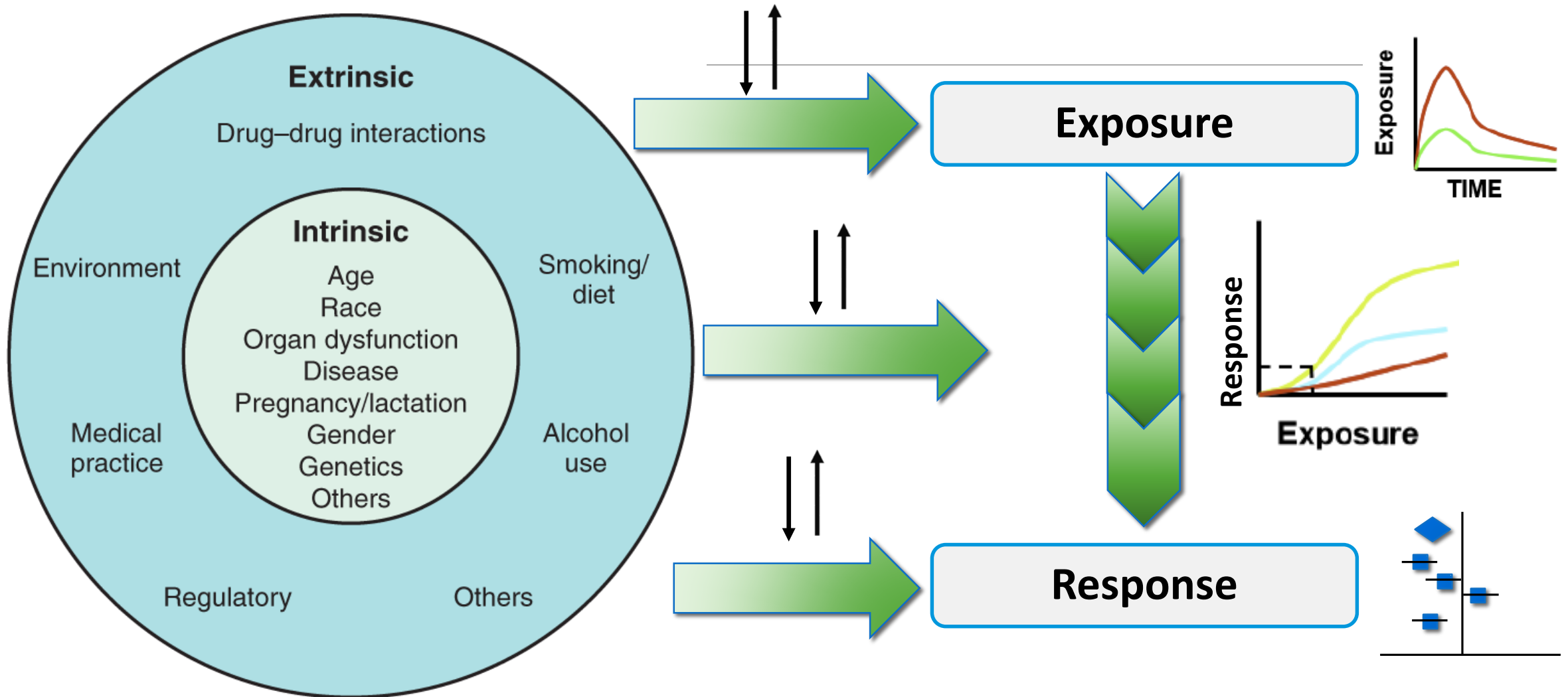
PANELISTS



Pharmacokinetics & Pharmacodynamics

Understanding Response Variability

Clinical Pharmacology Perspective



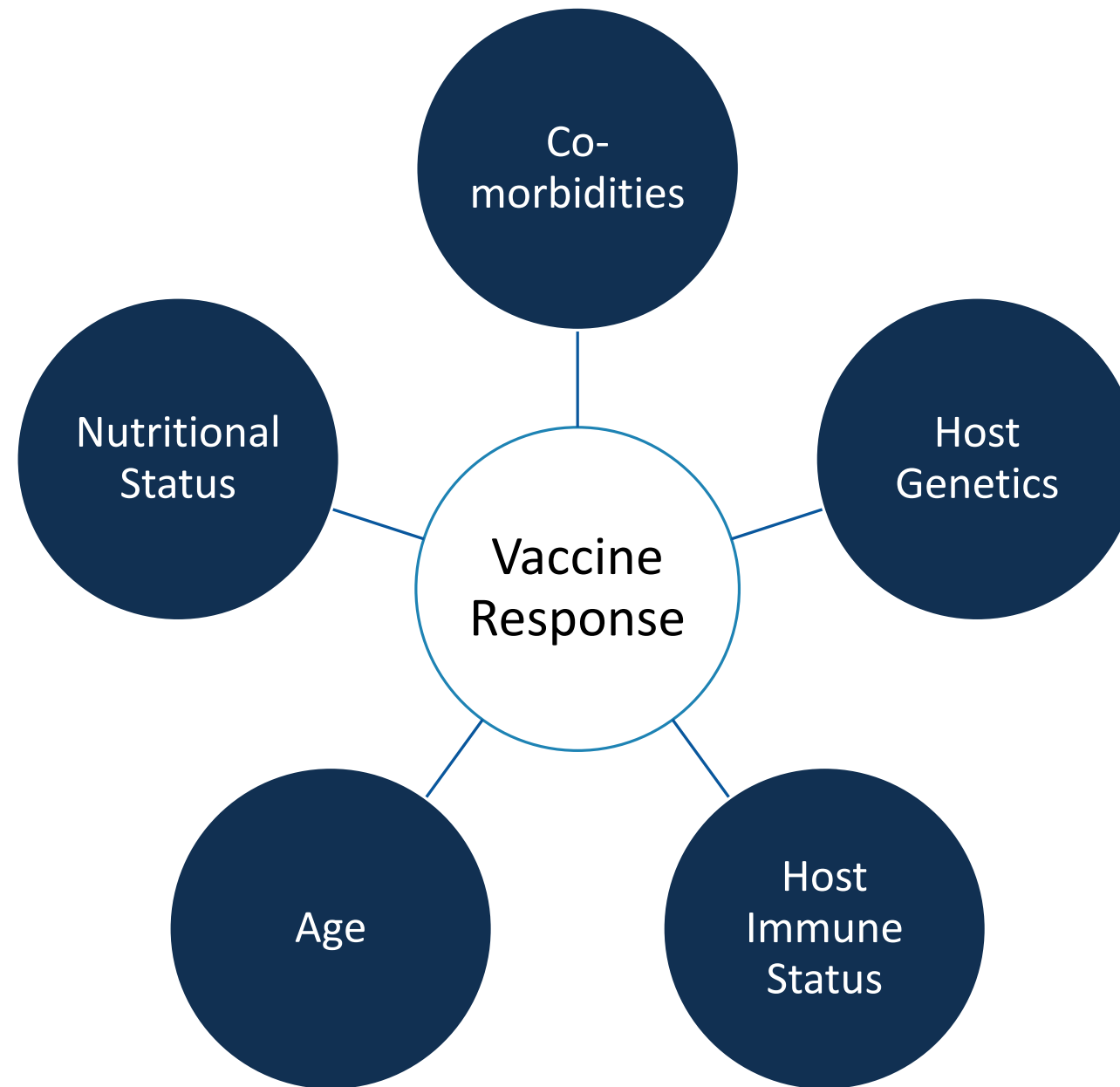
Regulatory Note

Impact of Osmotically Active Excipients on Bioavailability and Bioequivalence of BCS Class III Drugs

Mei-Ling Chen,^{1,2} Nakissa Sadrieh,¹ and Lawrence Yu¹

Received 23 April 2013; accepted 28 June 2013; published online 19 July 2013

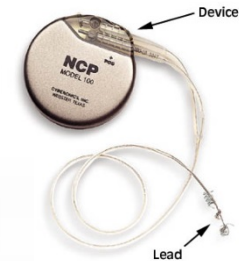
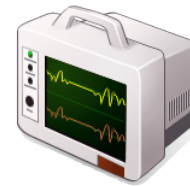
KEY WORDS: BCS; bioavailability/bioequivalence; drug absorption; excipient; osmotic potential.



Devices: Pediatric

It is a Medical Device if it:

- Diagnoses, Cures, Mitigates, Treats or Prevents a Disease or Condition, or
- Affects the Function or Structure of the Body, and
- Does Not Achieve Intended Use Through Chemical Action, and
- Is Not Metabolized

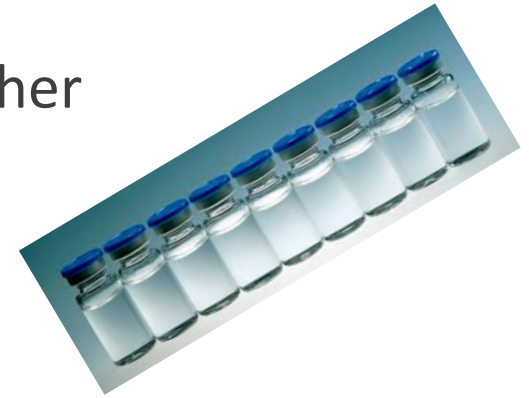


Drugs: Aging

What is a Drug?

The FD&C Act defines drugs, in part:

- ✓ by their intended use, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease"
- ✓ "articles (other than food) intended to affect the structure or any function of the body of man or other animals"



Example: PORTRAZZA (necitumumab)

Approval date: November 24, 2015

- **FDA Drug Trial Snapshots:**

- The risk of overall side effects was similar in patients below and above 65 years of age. The risk of venous thromboembolism was higher in patients age 70 and over compared to those who were younger than age 70.

- **Drug Label (PORTRAZZA (necitumumab) injection, for intravenous use Initial U.S. Approval: 2015):**

- 8.5 Age: The risk of overall side effects was similar in patients below and above 65 years of age. The risk of venous thromboembolism was higher in patients age 70 and over compared to those who were younger than age 70.

Sex as a Biological Variable

SEX is a BIOLOGICAL VARIABLE



- Chromosomal
- Physiological
- Typically binary
 - Male/Female

GENDER is a SOCIAL CONSTRUCT

- Environmental
- Society
- Spectrum
 - Masculine/Feminine
 - Man/Woman
 - Both
 - Neither



How FDA LOOKS FOR SEX DIFFERENCES

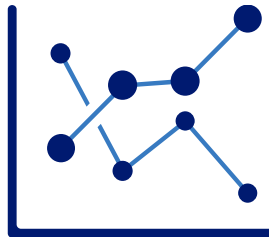


PRE-CLINICAL STUDIES

Using Both Male and Female Animals



POST-MARKETING MONITORING AND SAFETY ALERTS



DATA ON SAFETY AND EFFECTIVENESS

for Women and Men (required since 1998)



SEX ANALYSES

Almost Always Done

Office of Women's Health

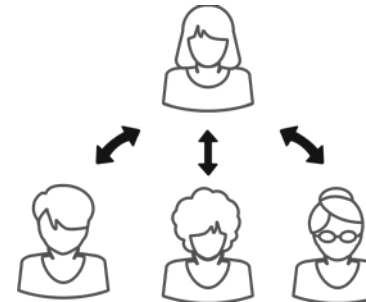
SCIENCE



EDUCATION



OUTREACH



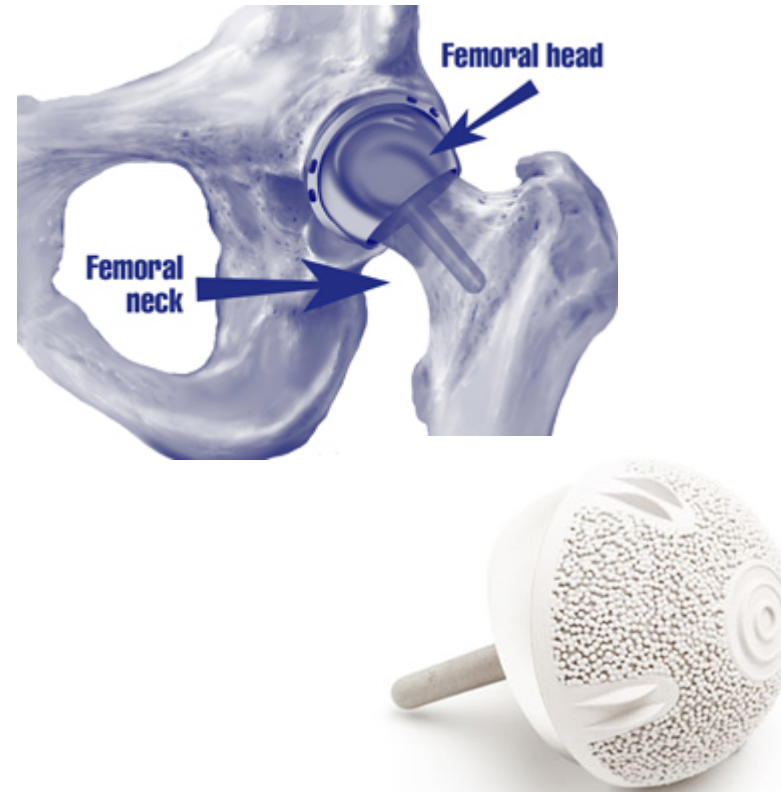
OWH achieves its mission through the foundational principle that Sex as a Biological Variable (SABV) should be factored into research design, analysis, reporting and education.

Examples of devices with sex differences in outcomes

HeartMate II VAD



Birmingham Hip Resurfacing System

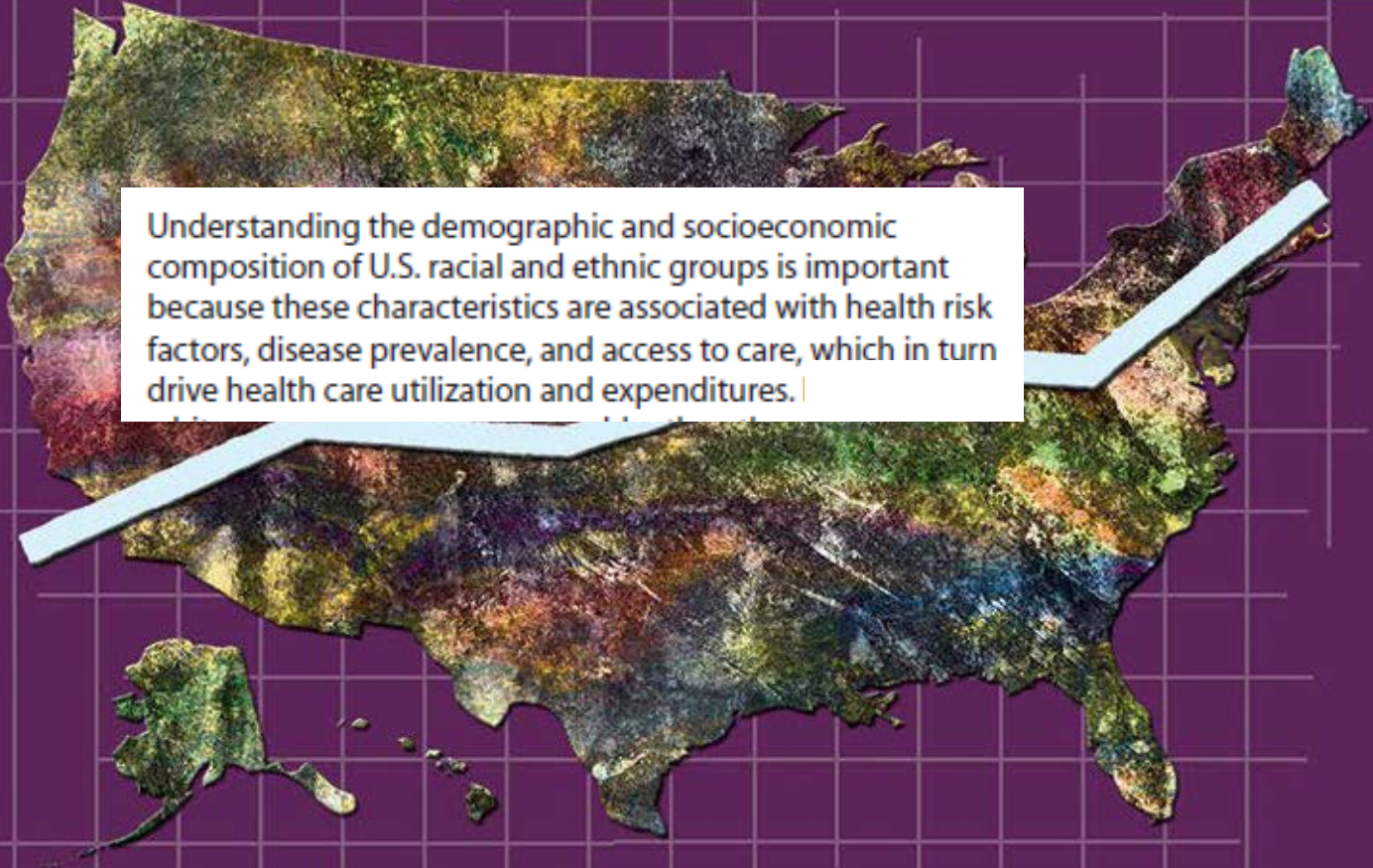


Race/Ethnicity, Clinical Trials & Disease Prevalence

Health, United States, 2015

With Special Feature on Racial and Ethnic Health Disparities

This report was updated on June 22, 2017 to reflect corrections to the 2014 mortality data. Changes appear in the highlighted areas of the individual PDF and spreadsheet versions of Tables 17, 18, 19, 20, 29, 30, and 31, and Figure 3 (also updated in the PPT file). For more information about the corrections to the 2014 mortality data, please refer to "Deaths: Final Data for 2014," available from: https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_04.pdf.



Understanding the demographic and socioeconomic composition of U.S. racial and ethnic groups is important because these characteristics are associated with health risk factors, disease prevalence, and access to care, which in turn drive health care utilization and expenditures.

Why Is Subgroup Analysis Important?

Examining specific subgroups can also deepen our understanding of age-, sex-, and race/ethnicity-based differences in prognosis and response to therapy.
(Pang et al. 2016)

In order for outcomes from RCTs to be generalizable to the real world, greater consideration needs to be taken to include patient populations that are more representative of those awaiting treatment in the clinical setting. (Gray et al. 2017)

Gray et al. 2017. Journal of Comparative Effectiveness Research. 6(1): 65-82.

Pang et al. 2016. Journal of Clinical Oncology. 34(33): 3992-3999.

Thank you

