# Trial Populations and Sex Differences

Clinical Investigator Training Course (CITC)
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# DISCLAIMER

The views expressed are those of the speaker and do not necessarily reflect official policy of the US FDA. No official endorsement by the US FDA is intended or should be inferred.

# OBJECTIVES

- FDA policy regarding demographic data.
- Sex differences and clinical trials.
- Recent data on representation in clinical trials.

# OWH MISSION

- Promote the inclusion of women in clinical trials.
- Identify and monitor the progress of crosscutting and multidisciplinary initiatives.
- Serve as the principal advisor to the Commissioner and other key Agency officials on scientific, ethical, and policy issues relating to the health of women.

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

# 1998 “DEMOGRAPHIC RULE”

NDA regulations, at 21 CFR 314.50(d)(5)(v), (vi)(a):

- Require sponsors of NDAs to include summaries of effectiveness and safety data presented by gender, age, and race.

IND regulations (21 CFR 312.33(a)(2)):

- Require that IND data regarding subjects’ participation in clinical trials be presented in annual reports by gender, age, and race.

# SEX ≠ GENDER

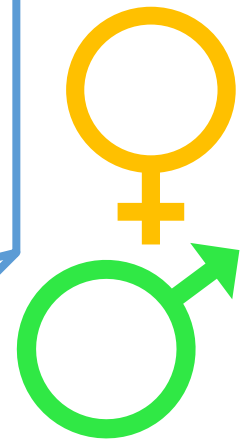
***Sex*** is the classification of living things, generally as male or female according to their reproductive organs and functions assigned by the chromosomal complement.

***Gender*** is defined as a person's self-representation, or how that person is responded to by social institutions on the basis of the individual's gender presentation.

Source: Exploring the Biological Contributions to Human Health: Does Sex Matter (2001)

# WHY SEX MATTERS:
## MALES AND FEMALES ARE *NOT* THE SAME

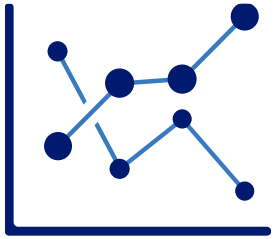
- **Biological**
  - Anatomy, physiology
- **Disease**
  - Onset, risk factors, prevalence, severity, signs/symptoms, comorbidities, etc.
- **Hormonal effects across life stages**
  - Menarche to menopause
  - Endogenous, HRT or contraceptive
- **Pharmacokinetics**
  - Drug metabolism
  - Renal function
- **Pharmacodynamics**
  - Efficacy
  - Safety



# HOW FDA LOOKS FOR SEX DIFFERENCES

**PRE-CLINICAL STUDIES**
Using Both Male and Female Animals

**CLINICAL STUDIES**



**DATA ON SAFETY AND EFFECTIVENESS**
for Women and Men (required since 1998)

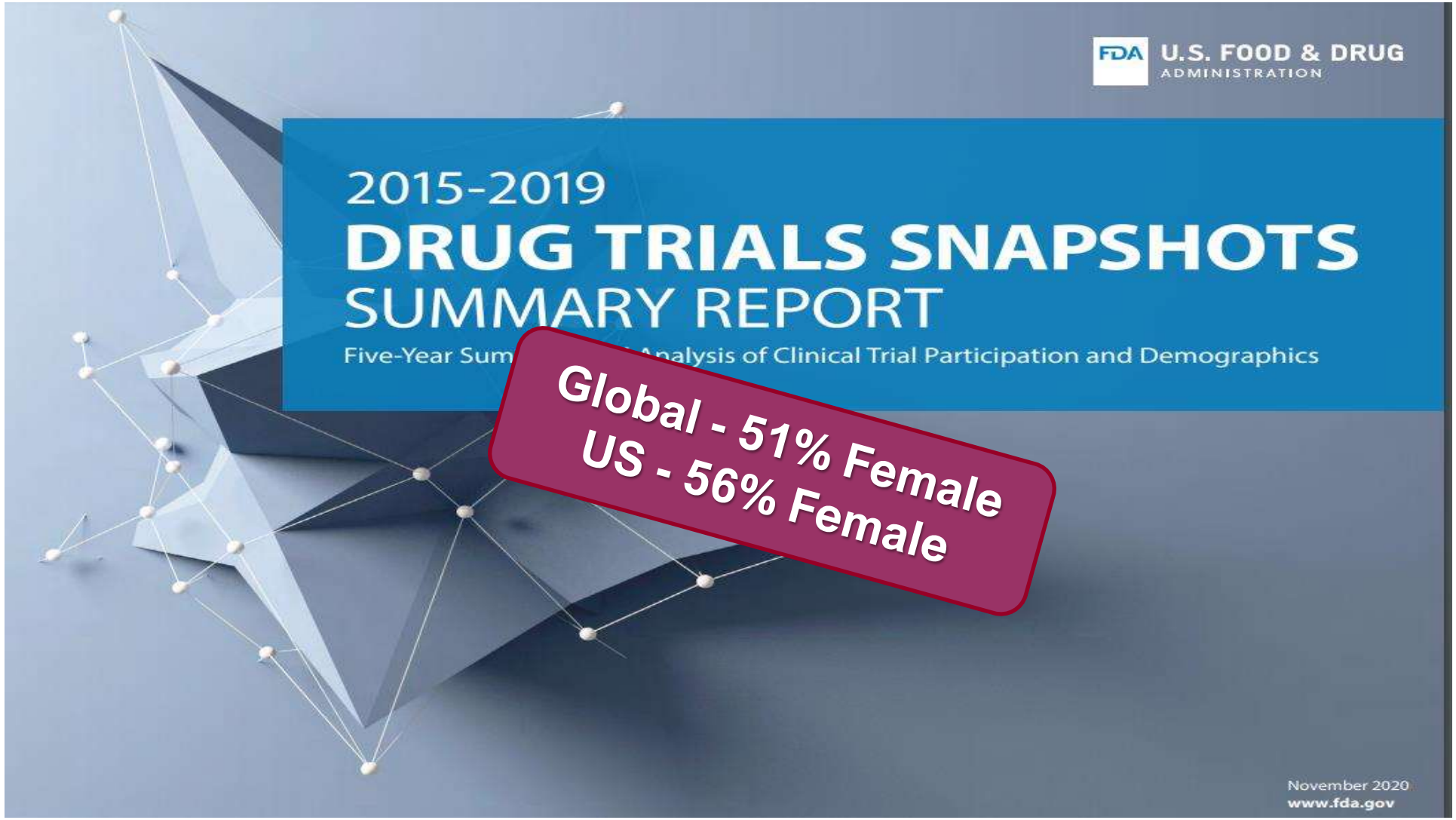
**POST-MARKETING MONITORING AND SAFETY ALERTS**

# LABEL EXAMPLES

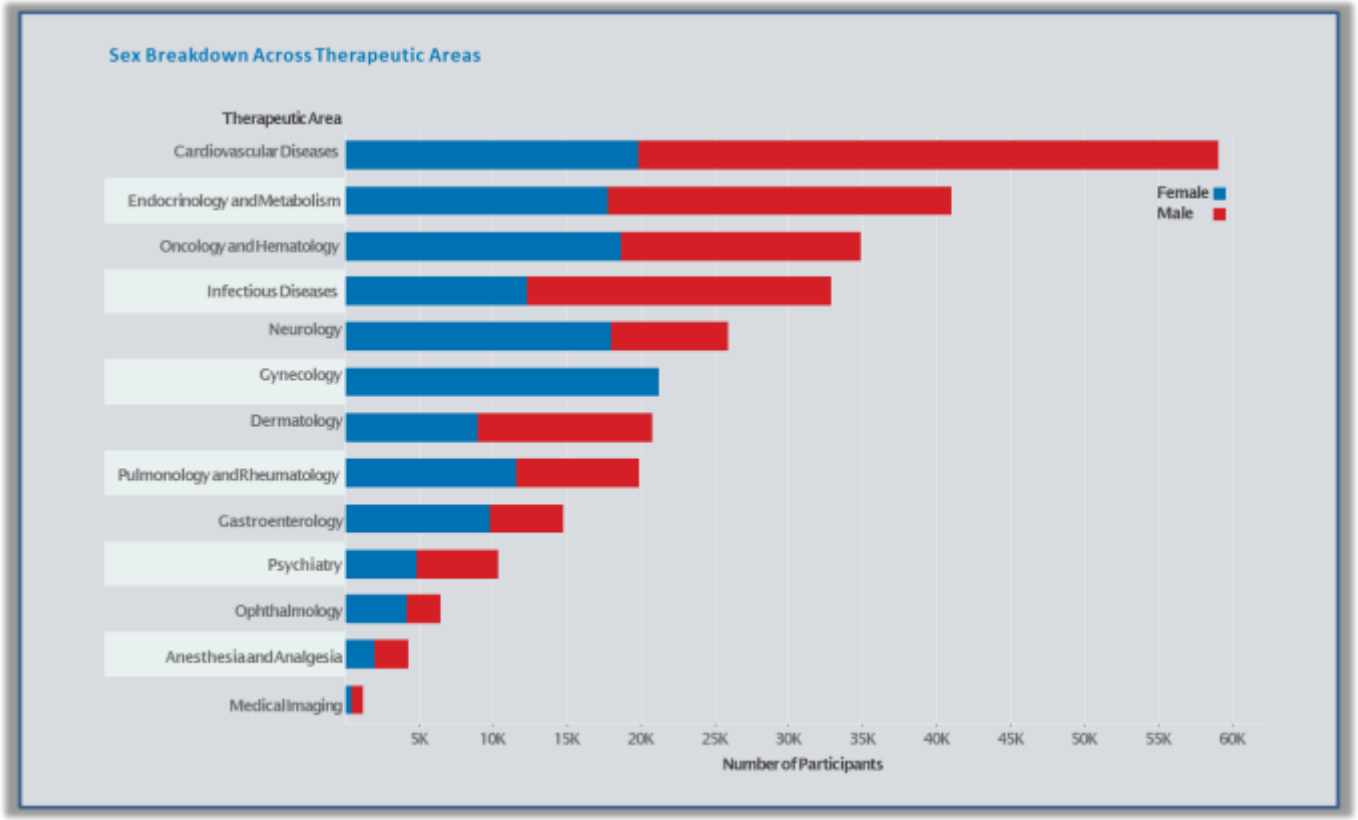
- **Olanzapine**
  - Clearance of olanzapine is *approximately 30% lower in women* than in men.
- **Amlodipine**
  - Drug-and dose-related adverse experiences - *greater incidence in women than men*.

# LABEL EXAMPLES

- **Zolpidem tartrate**
  - FDA changed the zolpidem labeling in 2013 *to reduce the maximum initial dose in women*.
- **Balsalazide disodium**
  - Mildly to moderately active ulcerative colitis *in male patients* 18 years of age and older.
  - *Effectiveness in female patients* was not demonstrated in clinical trials.

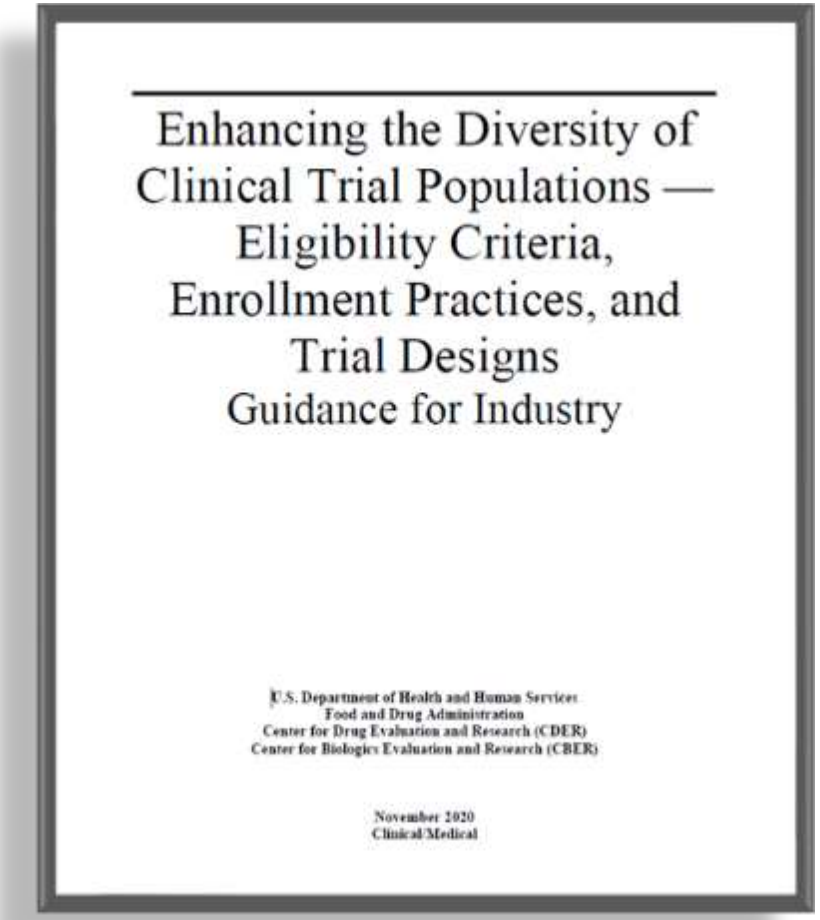

U.S. FOOD & DRUG ADMINISTRATION
2015-2019
DRUG TRIALS SNAPSHOTS
SUMMARY REPORT
Five-Year Sum
nalysis of Clinical Trial Participation and Demographics
Global - 51% Female
US - 56% Female
November 2020
www.fda.gov

# 2015-2019 Drug Trials Snapshots Summary Report



# 2020 FDA GUIDANCE FOR INDUSTRY

Representatives of both sexes should be included in clinical trials in numbers adequate to allow detection of clinically significant sex-related differences in drug response


Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2020
Clinical/Medical

# SUMMARY OF KEY POINTS

- One size does not fit all.
- Sex differences should be considered throughout medical product development.
- Progress in representation of women, but opportunities remain.
- Need the data for science to find the answer.

# CHALLENGE QUESTION

Which of the following statements about sex and gender is correct?

a) Sex is a biological variable
b) Gender is a binary variable
c) Sex and gender are synonymous terms

# *Thank you*

**www.fda.gov/womens**

**www.fda.gov/womenshealthresearch**

**@FDAWomen on Twitter**