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# WHISE

# Sex Considerations in Research and Drug Development

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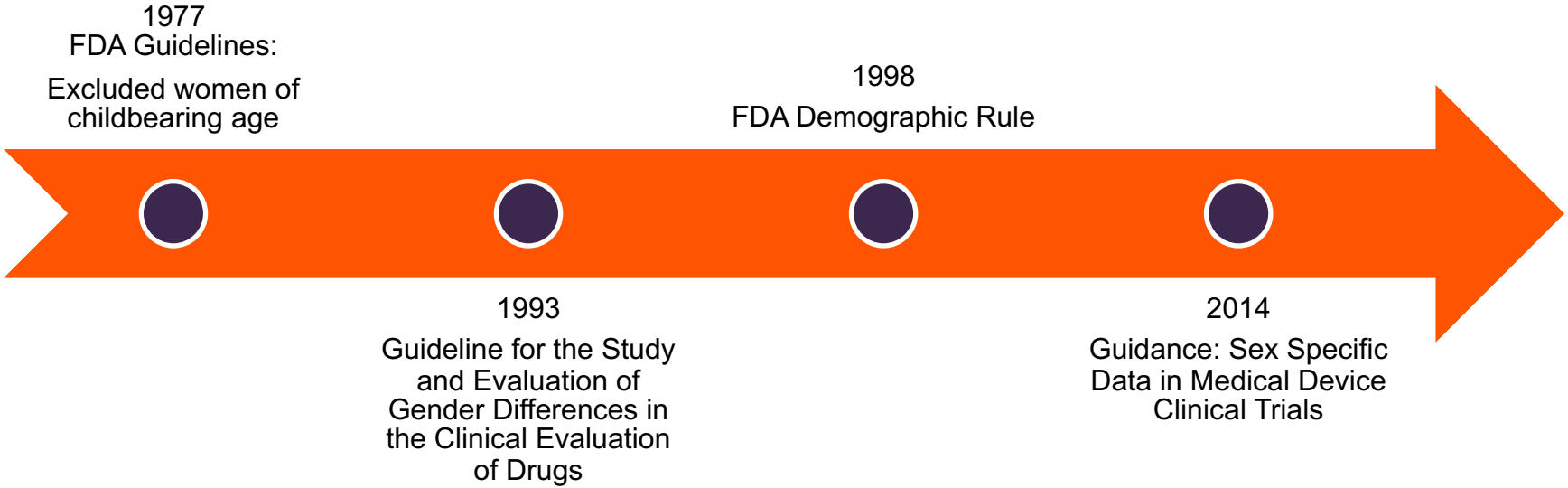
# Disclaimer

- Employee: FDA
- The views expressed are those of 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

# Historical Perspective



# Definitions:

- Sex vs. Gender
  - Sex is a biological variable (chromosomal, physiological, typically binary male/female)
  - Gender is a social construct that takes into account environmental, societal and may be on a spectrum (masculine/feminine, man/woman/both/neither)

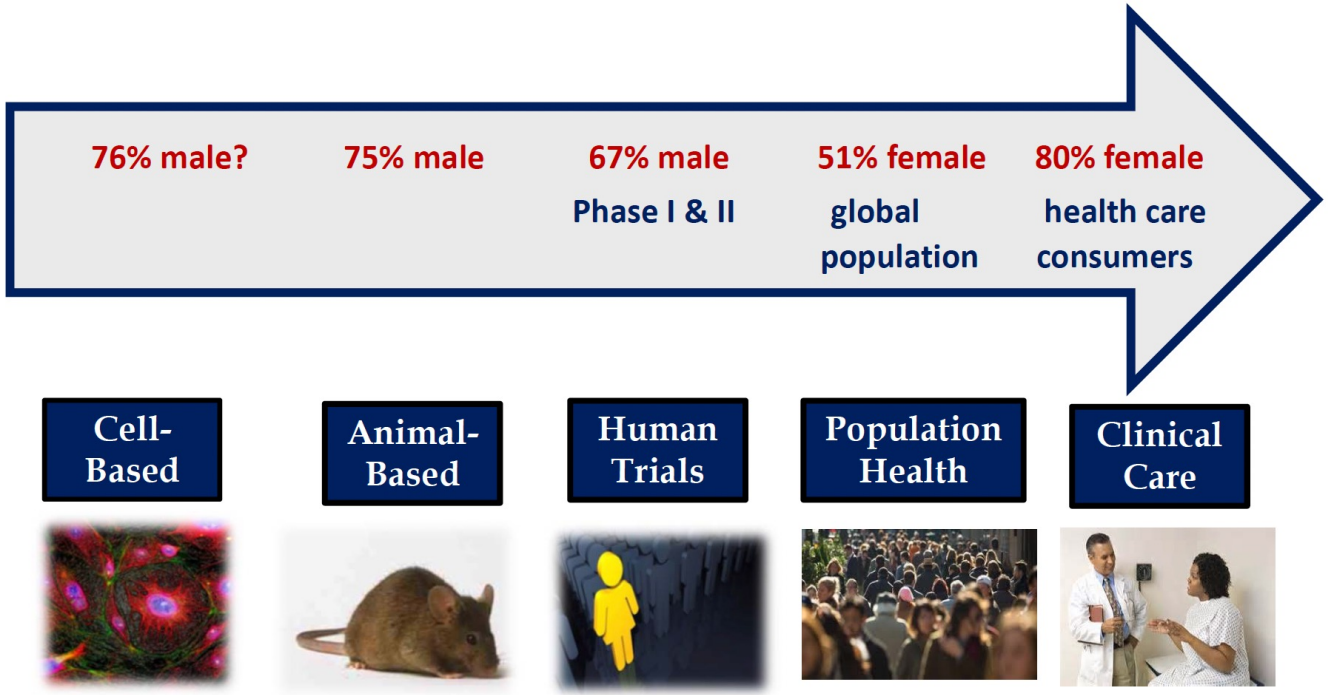
- Why sex matters:
  - Biological (anatomy/physiology)
  - Disease (onset, risk factors, prevalence, severity, signs/symptoms, comorbidities etc)
  - Hormonal effects across life stages
  - Pharmacokinetics (drug metabolism, renal function)
  - Pharmacodynamics (efficacy, safety)

2001 Exploring the Biological Contributions to Human Health: *Does Sex Matter*.

# Historical Perspective

- FDA 1977 Guideline “General Considerations for the Clinical Evaluation of Drugs”
  - Recommended excluding women of *childbearing potential* from participating in phase 1 and early phase 2 studies until reproductive tox studies were done
  - Broadly applied to “premenopausal female capable of becoming pregnant”
    - Ethical and legal questions around appropriateness of assuming women cannot avoid pregnancy
    - Deciding for a woman that protecting the fetus outweighed other possible interests
- Accelerated development and approval of experimental therapies that may be life-threatening →important to include women earlier in studies

- 1993 “Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs”
- FDA explicitly reversed the 1977 recommendation
  - Called for data to analyze and assess gender effect
  - Recognition of need for individualized pharmaceutical therapy
    - Gender
    - Age (eg elderly)
    - Body size
    - Hepatic or renal function
  - Rigid gender quotas are not expected in clinical trials
  - Preference for being included in the same studies, not separate single gender studies




Jenkins M et al. TTUHSC Laura W. Bush Institute for Woman's Health. *J Women's Health*. 2016 Feb 1; 25(2): 181-187.

# Percentage of women participating in new drug trials

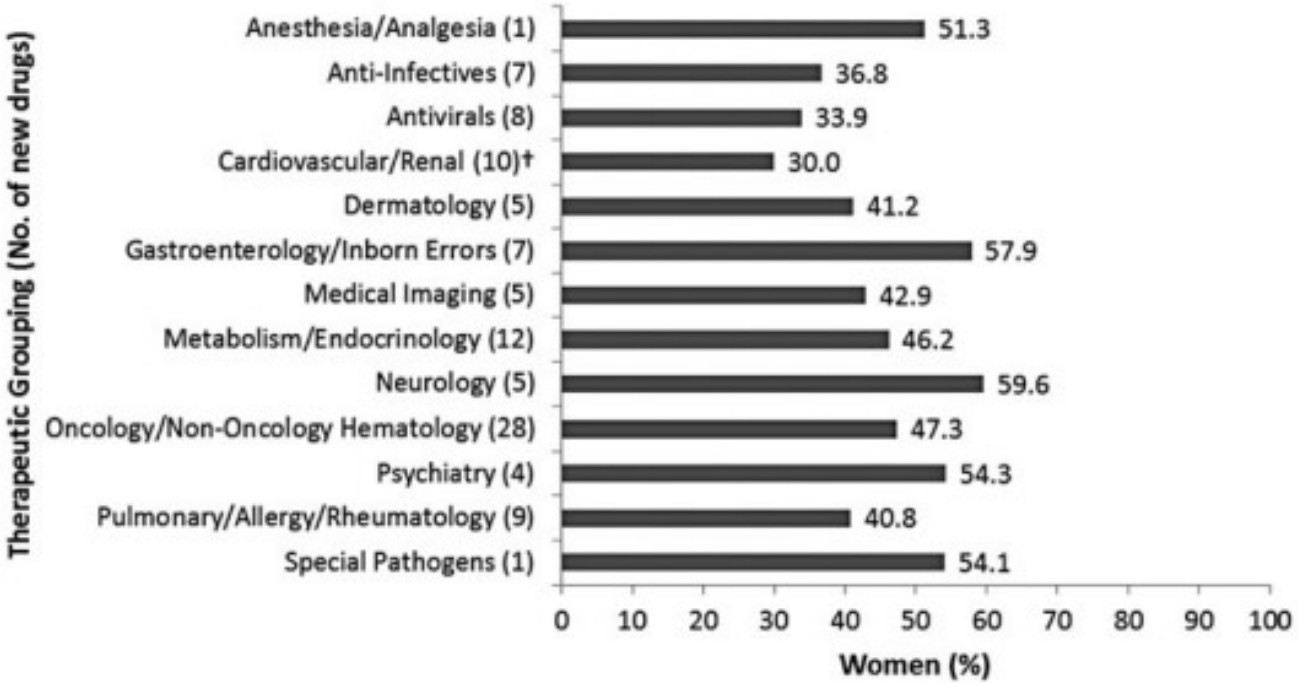
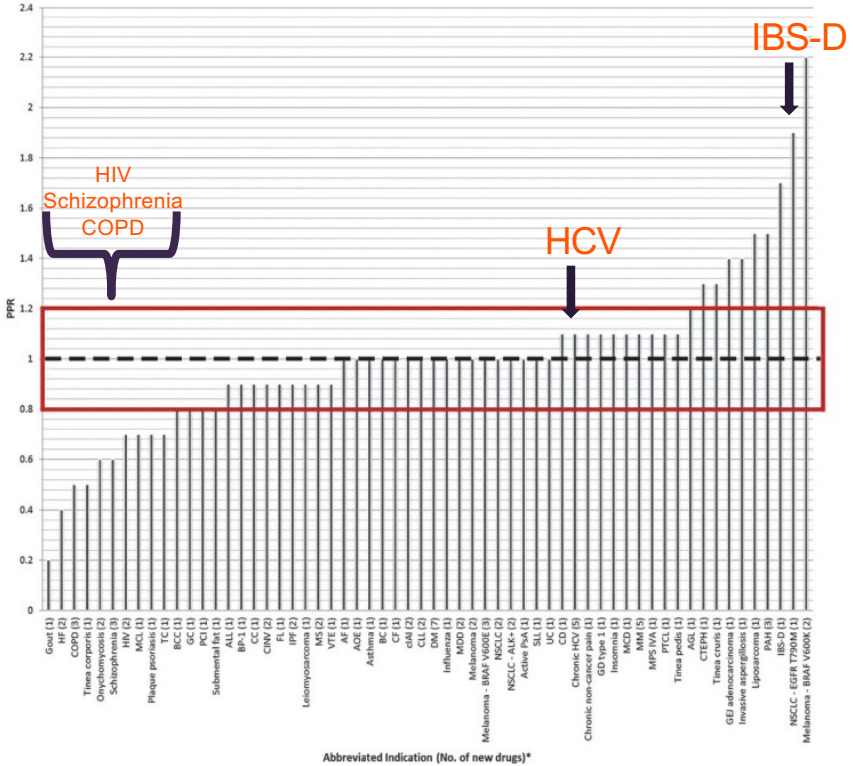



**FIG. 2.** Percent women participation in new drug trials by therapeutic grouping.

Chen et al. *Journal of Women's Health*. Vol 27; 4, 2018.




Ratio of women in clinical trials relative to estimated proportion of women in the disease population

Chen et al. *Journal of Women's Health*. Vol 27; 4, 2018.

# Informed Consent

- 1993 Guideline emphasized trial participants understand what is known and unknown about experimental agents
  - Need for women with childbearing potential to use contraception or abstinence
  - Recognition of using pregnancy tests as part of protocol design
  - Interest in protecting fetus while allowing potential benefit of women to participate in all phases of drug development

# Other Important Sex Factors

- Important of **pharmacokinetics** studies to assess contribution of
  - Body size
  - Smoking
  - Concomitant illness
  - Pre- or post- menopausal status
    - Decrease CYP3A4 activity by 20%
  - Concomitant medications (estrogens and OCP)
    - inhibition of multiple cytochrome P450 enzymes including CYP1A2, CYP3A4, CYP2C19, and CYP2C9-medi-ated metabolism
- Often these analyses are done as **integrated summaries of safety and efficacy**
  - Post-hoc
  - Descriptive
  - May be incorporated into the ultimate product label

Nazir Eur J Drug Metab Pharmacokinet 2016 Oct;41(5):505-9.

# Impact on NIH Studies

- 1993 NIH Revitalization Act and Guidelines
  - Ensure that women and members of minority groups and their subpopulations are included in all NIH-supported human subjects research and phase 3 trials
    - Numbers sufficient for valid analysis for intervention effect
    - Not allowed to use cost as a reason for excluding these groups
    - Programs and support for outreach to recruit into studies
- 2014 NIH policies to account for sex as a biological variable in research

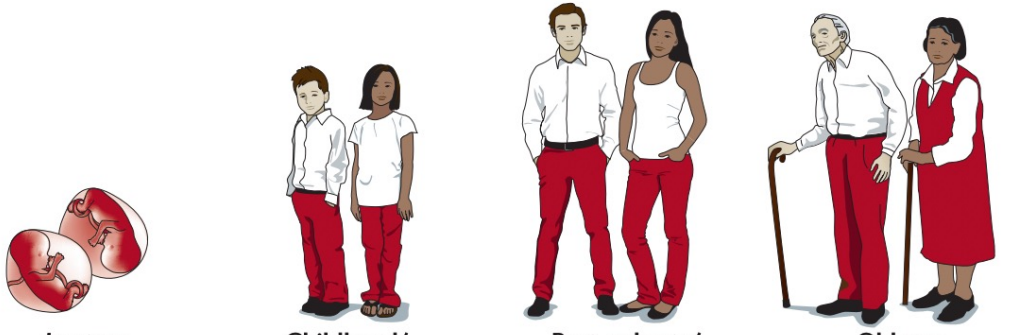
Clayton JA, Collins F, et al. *Nature*. 2014.

# Controversies

- Practical implementation that doesn’t impede research or impose data requirements that don’t have sound scientific reasoning
- Liability
  - Children adversely affected by the medical decisions of parent have the right to pursue litigation when they reach age of majority

# Practical Learnings: Sex and Impact on Disease/Rx

- Cardiovascular: response to ASA in women it reduces ischemic stroke, in men it reduces MI. Symptoms of MI different between men and women
- Bone/Joint: women more likely to injure knees due to knee and hip anatomy differences
- Psychiatric: differences in rates of depression, mode of suicide attempts and likelihood of seeking treatment
- Pharmacology: sex differences in absorption, metabolism, distribution, elimination and enzymatic processes
  - Flurazepam and zolpidem affects driving performance in women the next morning under the same administration conditions→slower elimination=lower labeled doses for women
- Liver is a highly sexual dimorphic organ accounting for 72% of sexually differentiated genes
- Affects differences in susceptibility, progression and outcomes of acute and chronic liver diseases




| | | | | |
|---|---|---|---|---|
| **Innate immunity** | • Increased inflammatory responses in males | ↑ Inflammation in males<br>↑ NK cells in males | ↑ Inflammation in females<br>↑ NK cells in males | ↑ Inflammation in males<br>↑ IL-10 in females<br>↑ NK cells in females |
| **Adaptive immunity** | • Increased IgE levels in males | • CD4/CD8 ratios and $CD4^+$ T cell numbers equal<br>• $CD8^+$ T cell numbers equal<br>• IgA levels in males ≥ females<br>• IgM levels in males ≥ females<br>• IgG and IgM levels equal<br>• B cell numbers equal<br>• $T_{reg}$ cell numbers in males ≥ females | • CD4/CD8 ratios and $CD4^+$ T cells ↑ in females<br>• $CD8^+$ T cells ↑ in males<br>• T cell activation/ proliferation ↑ in females<br>• $T_{reg}$ cells ↑ in males<br>• B cells ↑ in females<br>• Immunoglobulins ↑ in females | • CD4/CD8 ratios and $CD4^+$ T cells ↑ in females<br>• $CD8^+$ T cells ↑ in males<br>• T cell activation/ proliferation ↑ in females<br>• $T_{reg}$ cells ↑ in males<br>• B cells ↑ in females<br>• Immunoglobulins ↑ in females |

*Klein et al Nature Reviews Immunology* **volume 16**, pages626–638 (2016)

| Liver Disease | Relative Incidence Male:Female Ratio | Mechanisms of Sex Differences |
|---|---|---|
| **Acute liver injury** | | |
| DILI (according to RUCAM) | 1:2 | Sex-related different bioavailability and excretion of drugs e.g., due to sex hormone activity that affect CYP and P-gp expression<br>Difference in genetic backgrounds |
| **Chronic liver disease** | | |
| Viral hepatitis | Conflicting results, Female generally have higher rate of symptoms but increased viral clearance | Females display more efficient innate, humoral and cell-mediated immune response (higher cytotoxic T cells, higher CD4+/CD8+ ratio and higher CD4+ T cells), as well as more TLRs |
| ALD | 1:2 | Estrogen-induced activation of KCs after alcohol administration in female rats increases hepatocyte inflammation and necrosis<br>Alcohol exposure in female decreases upregulation of hepatoprotective genes, and genes involved in compensatory pathways, inflammation and oxidative stress |
| NAFLD | n.a. | Higher FA clearance and synthesis in females (increased FA transport protein expression)<br>Higher LDL-cholesterol in men and postmenopausal women<br>E2 seems to be protective for NAFLD |
| PBC | 1:10 | Estrogen-dependent alteration of HLA expression, cytokine release and cholangiocyte proliferation |
| PSC | 2.6:1 | Few evidences suggest a correlation between a good female reproductive health and childbearing and delay of PSC development |
| AIH | 1:3.5 | Female hormone-related modulation of immune system improving AIH-induced inflammation |
| Benign hepatic cancerous lesions | 1:5–15 (depending on types) | Estrogens improve the outcome of benign lesions |
| HCC | 3–4:1 | Estrogen-modulated IL6 decrease in females improves HCC progression, through regulating NRF2-antioxidant response<br>Increased expression of TLRs involved in the innate immune response,<br>Higher rate of CD4+ cells in females with respect to males<br>Males better respond than female to checkpoint blockade therapy since sex hormones control PD1-PDL1 expression. |

Estrogen activation of KC
inc inflammation and necrosis

Higher FA clearance and synthesis in females
Higher LDL post menopause
E2 protective for NAFLD?

Sayaf, K et al. The Role of Sex in Acute and Chronic Liver Damage. Int. *J. Mol*. Sci. 2022, 23, 10654.https://doi.org/10.3390/ijms231810654.

# Conclusions

- We need to better understand sex differences in many diseases especially in the lab and pre-clinical stages of research
- GI/Liver has done fairly well in our clinical trials but a lot remains to be understood
  - Alcoholic liver disease
  - Metabolic Associated Liver Disease
- Be involved as early as possible in clinical trial protocol development to best facilitate balanced development and subsequent analysis of data