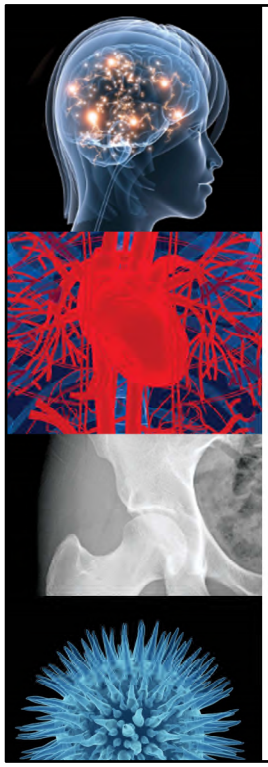

Sex Considerations in the FDA Drug Review Pipeline and Drug Trial Snapshots

Marjorie R. Jenkins, M.D., M.Ed.H. P., F.A.C.P.
Director
Medical Initiatives & Scientific Engagement
U.S. Food and Drug Administration
FDA Office of Women's Health

- Thank you for inviting me to speak with you today about some the progress made related to the inclusion of women in clinical trials for FDA-approved products.

Disclosure

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.

No relationship or financial conflicts of interests to disclose.

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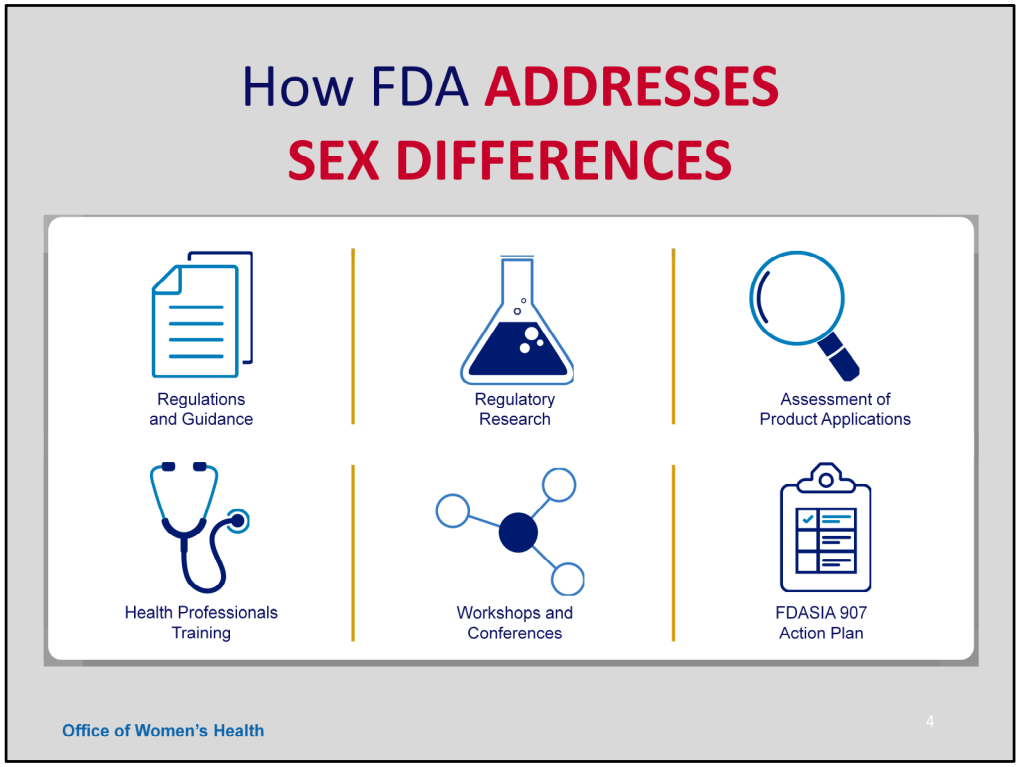
Outline

Related to Sex Influences

- Brief Review of Policy
- Requirement and Expectations in the FDA Drug Review Process
- Real-World Example of Impact
- Increasing Transparency
  - Drug Trial Snapshots
    - CV Demographics

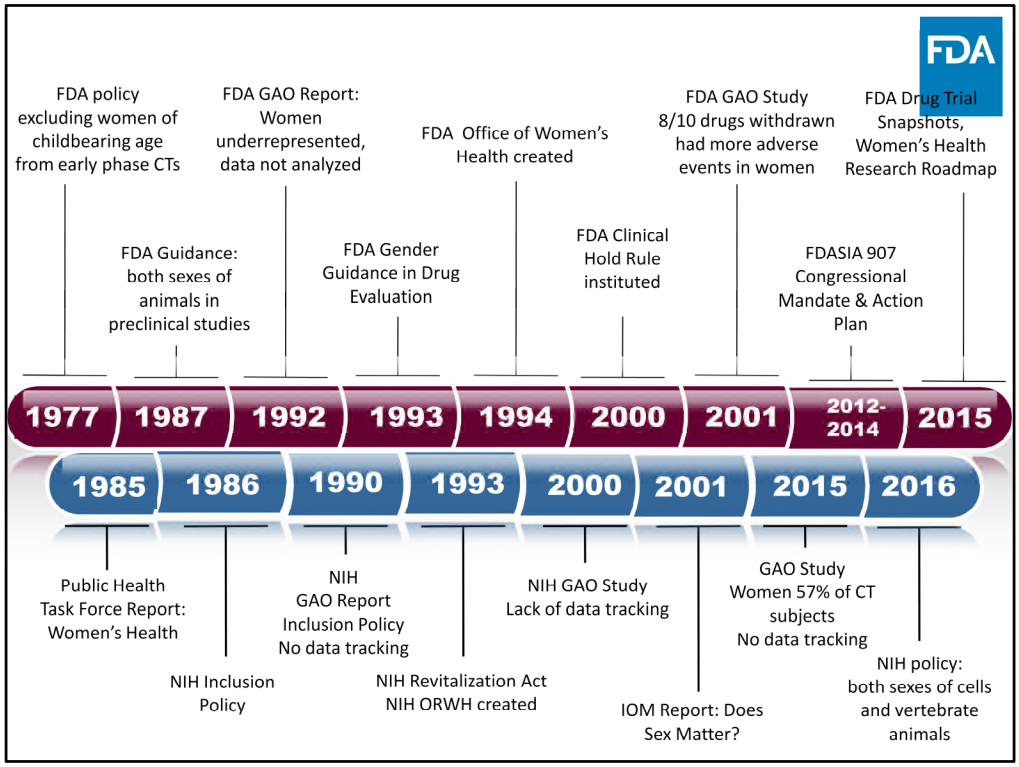


- FDA uses several approaches to help identify, understand, and educate the public about sex differences related to the products we regulate.

- FDA encourages diverse participation in biomedical research. It is clear when diverse populations of participants are involved in clinical research, we all benefit from a more complete knowledge base related to safety and effectiveness.

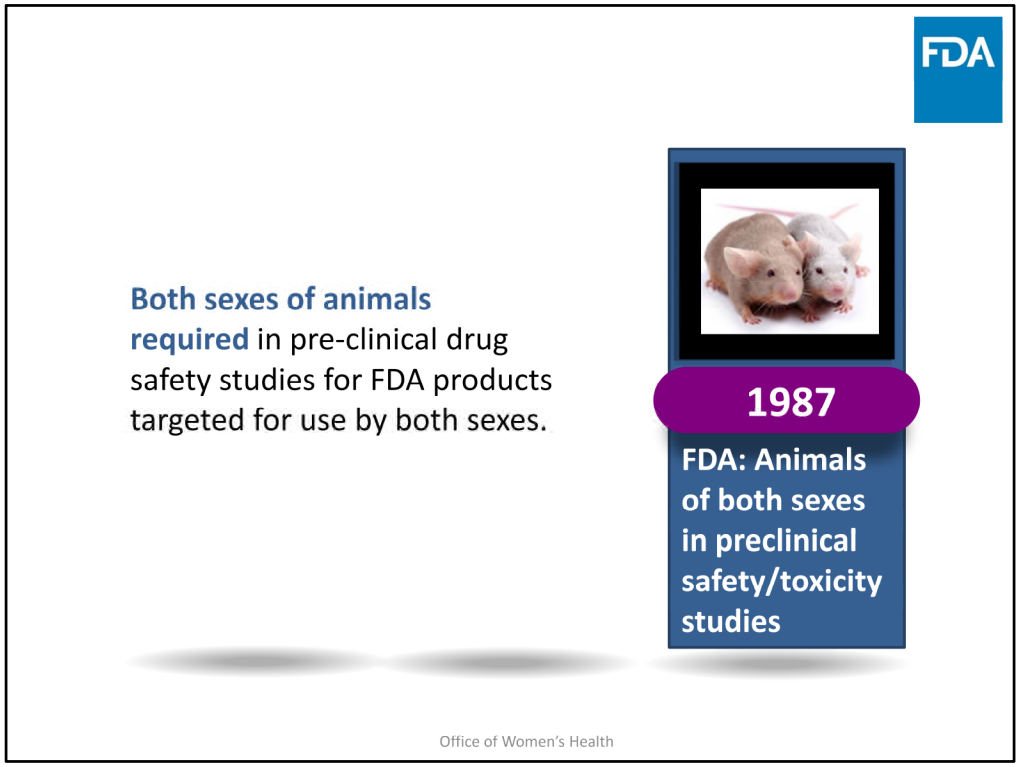
- We accomplish this through:
  - Regulations and guidance
  - Regulatory research
  - Assessment of product applications and communications
  - Health professional training
  - Workshops and conferences
  - Action Plan

- I will be highlighting some existing practices in each of these areas as well as outlining new activities that the FDA Centers and Offices have implemented as part of our 2014 Food and Drug Safety Innovation Act (FDASIA) Action Plan.

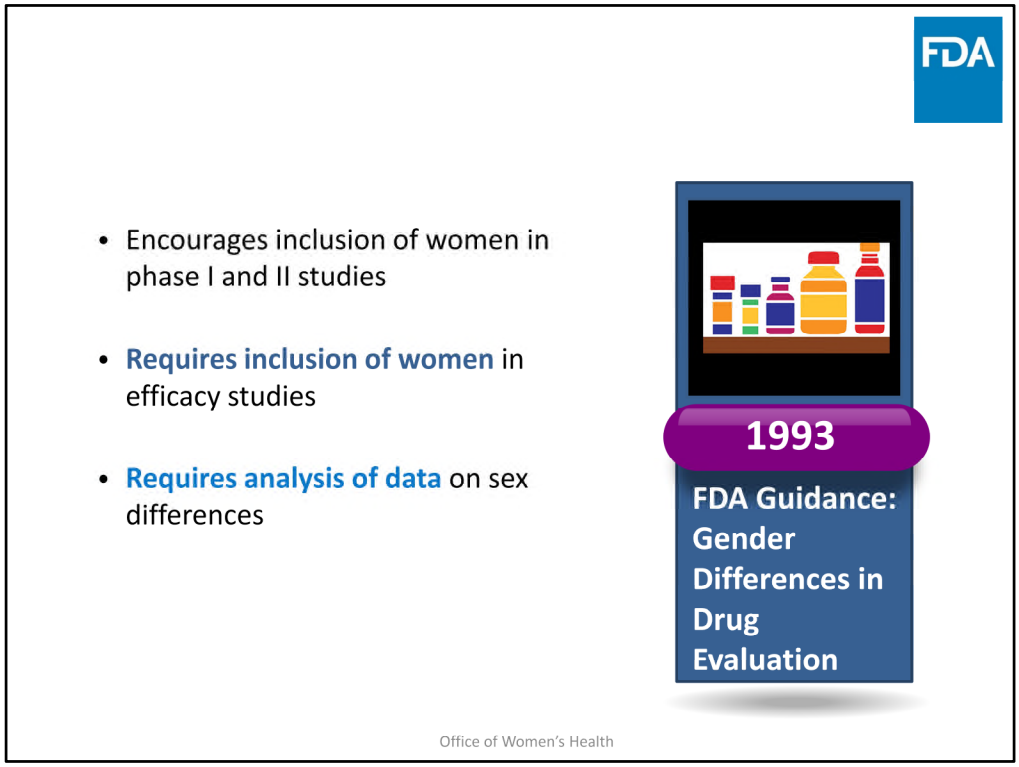


Quick overview of the policy pipeline as we move toward integration of sex and gender evidence into research, education, and regulatory process

SEX: WHAT IS REQUIRED OR EXPECTED IN THE APPLICATION PROCESS



FDA Pharm/Tox Guidance 1987
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065014.htm



1993 Gender Guidance

Reverses stance of 1977 policy that recommended exclusion of women of childbearing potential from early phase clinical trials

Applies to biologics and devices as well as drugs

Studies of effectiveness and adverse events should by analyzed by gender

PK of a drug should be defined for both genders, preferably before conducting "definitive" controlled trials

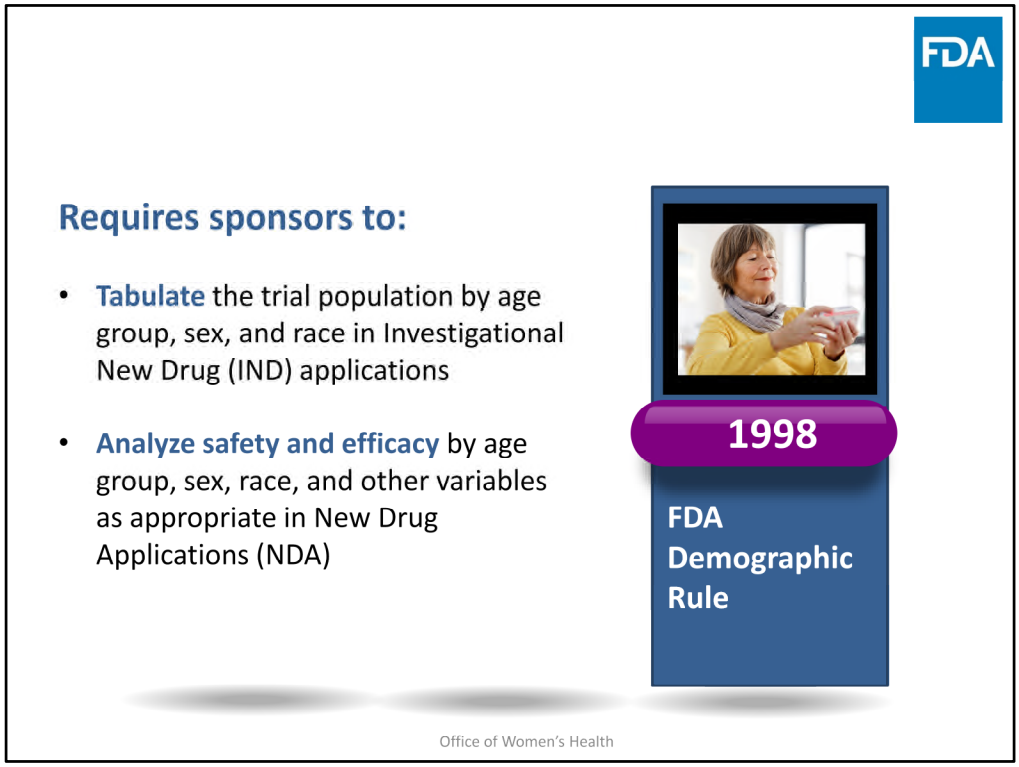
Issues to consider during drug development:

Effect of menstrual status on drug PK

Influence of concomitant estrogen treatment or systemic contraceptives on drug PK

Influence of drug on PK of oral contraceptives

Source: U.S. Food and Drug Administration. (1993). Guideline for the study and evaluation of gender differences in the clinical evaluation of drugs. In Federal Register (Ed.), *Notices (Vol. 58).* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126835.pdf



1998 FDA Demographic Rule

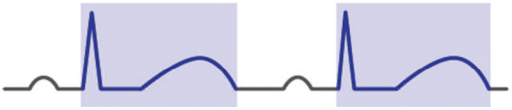
The Demographic Rule requires sponsors to tabulate the trial population by age group, sex, and race in Investigational New Drug (IND) applications, and to analyze safety and efficacy by age group, sex, race, and other variables as appropriate in New Drug Applications (NDAs).

Source: Federal Register. (1998). *The Investigational New Drug Applications and New Drug Applications Regulation. Retrieved from http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm133181.htm.*

EXAMPLE: POLICY IMPACT IN DRUG APPROVAL

QT Prolongation and *Torsades de Pointes*

Normal QT interval

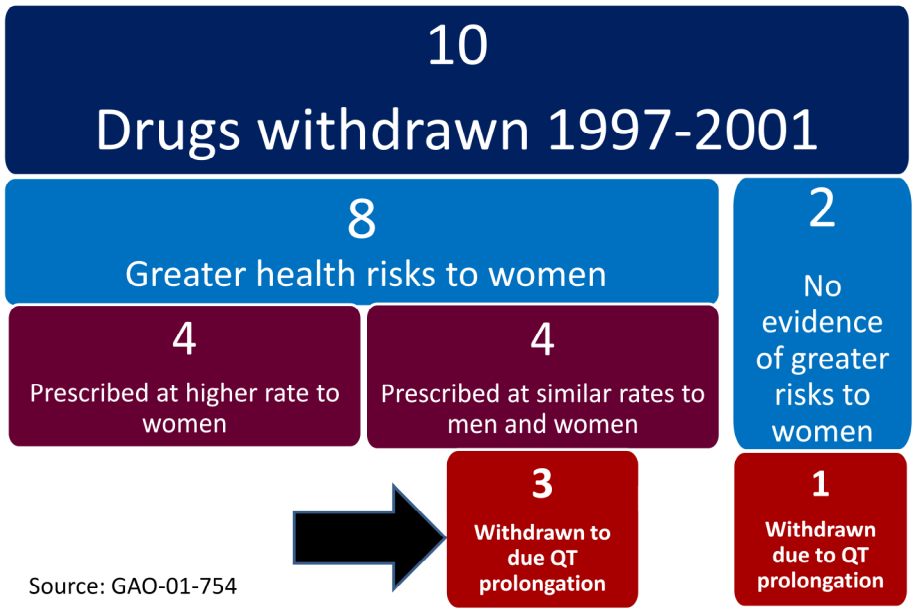


Prolonged or abnormal QT interval

Prescription Drugs Withdrawn From the U.S. Jan. 1, 1997-Dec. 31, 2000

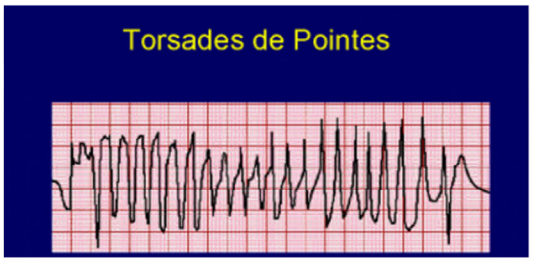
Drug	Type of Drug	Primary Health Risk
Prescription Drugs with Evidence of Greater Health Risks in Women		
Pondimin	Appetite suppressant	Valvular heart disease
Redux	Appetite suppressant	Valvular heart disease
Rezulin	Diabetic	Liver failure
Lotronex	Gastrointestinal	Ischemic colitis
Seldane[a]	Antihistamine	Torsades de Pointes
Posicor	Cardiovascular	Lowered heart rate in elderly women and adverse interactions with 26 other drugs
Hismanal	Antihistamine	Torsades de Pointes
Propulsid[b]	Gastrointestinal	Torsades de Pointes
Prescription Drugs Without Evidence of Greater Health Risks in Women		
Raxar	Antibiotic	Torsades de Pointes
Duract	Analgesic and anesthetic	Liver failure

2001 FDA GAO Study



Source: GAO-01-754

Why This is So Important



- Torsade de Pointes: potentially fatal arrhythmia
- Associated with long QT interval in the ECG
- 70% of drug-induced torsade cases in women

Source: Makkar et al JAMA 1993

- OWH-funded research
  - CVD related research comprise 17% of portfolio
  - 25% of CVD projects deal with QT interval and Torsade de Pointes
  - QT Prolongation

What's our motivation for funding research in this area?

- TdP is a potentially fatal arrhythmia
- Associated with longer QT interval in the ECG
- 70% of drug-induced torsades cases in women

QT Prolongation:
Drugs Withdrawn from the Market Worldwide

Potential QT prolongation and/or torsade

Drug	Year of introduction	Therapeutic class	Year of withdrawal
Prenylamine	1960s	Antianginal	1988
Lidoflazine[a]	1979	Antianginal	1989
Terodiline	1986	Antianginal/urinary incontinence	1991
Terfenadine	1982	Antihistamine	1998
Sertindole[b]	1996	Antipsychotic	1998
Astemizole	1986	Antihistamine	1999
Grepafloxacin	1997	Antibiotic	1999
Cisapride	1988	Gastric prokinetic	2000
Droperidol	1960s	Tranquilizer/analgesic	2001
Levacetylmethadol	1997	Methadone substitution	2001
Dofetilide[a]	1999	Class III drug for atrial fibrillation	2004
Thioridazine	1958	Antipsychotic	2005
Clobutinol	1960s	Antitussive	2007
Dextropropoxyphene [c]	1960s	Opioid analgesic	2009

Stockbridge et al Drug Saf 2013

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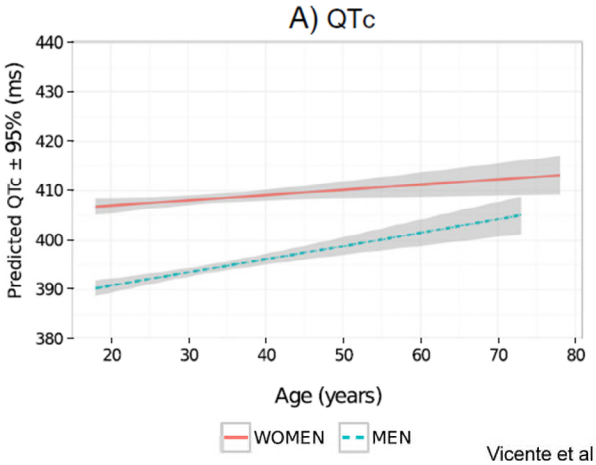
Fourteen drugs have been removed from the market worldwide because they cause an abnormal heart rhythm that leads to sudden death and up to **70% of the cases occur in women.**

Sex Differences at Baseline

Healthy women have longer QT intervals at baseline than men



Vicente et al Am Heart J 2014

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What do we know?

Before puberty:
Boys and girls have the same QT

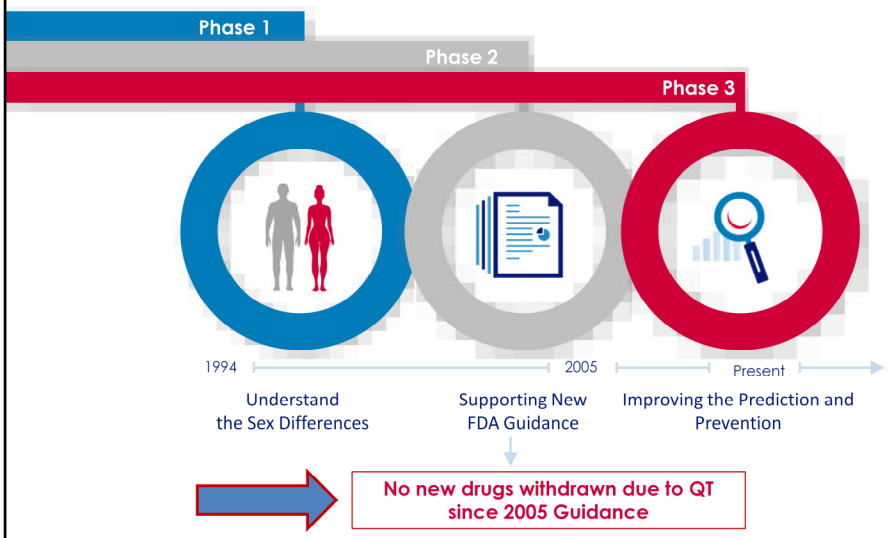
After puberty:
This sex difference is apparent only after puberty

OWH-funded research shown that:

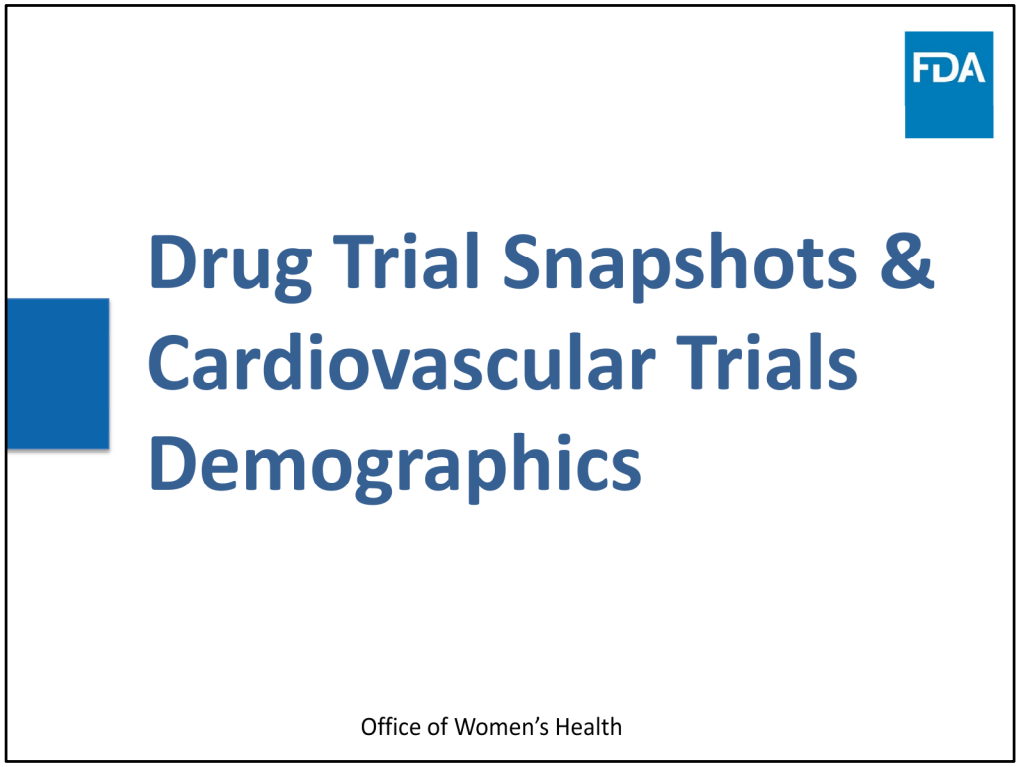
- *Healthy* women have longer QT at baseline *than men.*

- Men
    - QT shorten or decreases in men when they reach puberty
    - As men age, *testosterone levels decrease* and QT goes back up to the level of women
    - Testosterone may be protective

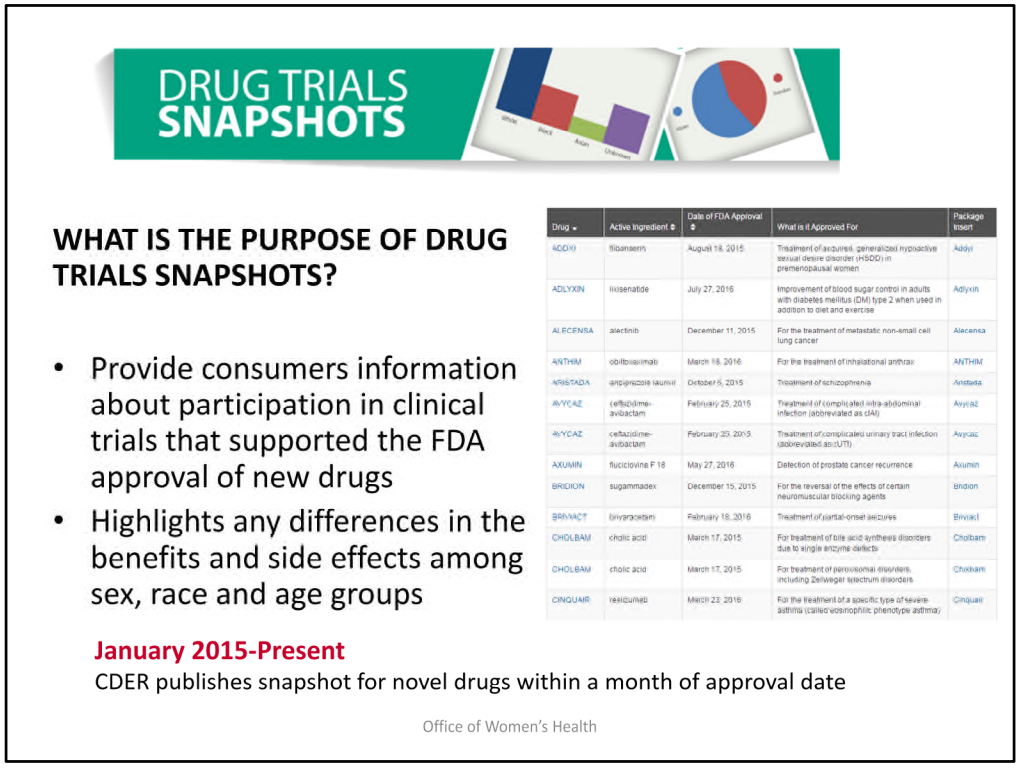
FDA and OWH QT Research
Making a Difference



No new drugs withdrawn due to QT since 2005 Guidance

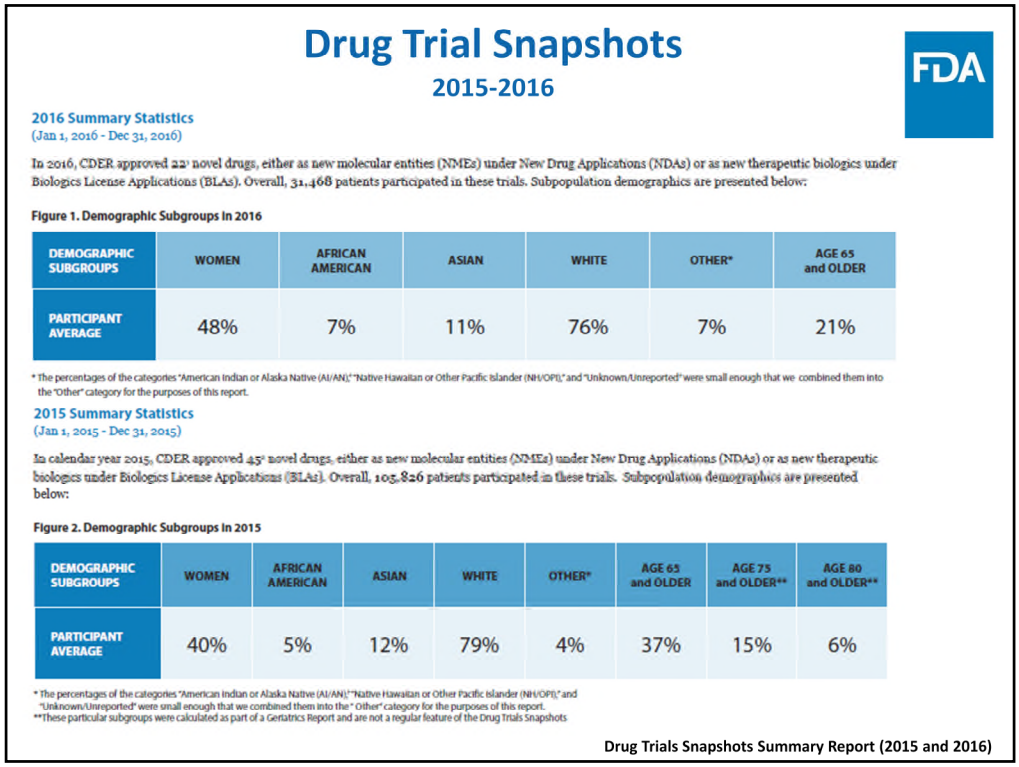


- CVD is the leading cause of death for women
- And CVD is an example of a targeted area that FDA looking more closely into the participation of women in trials.
- A lot of the previous studies conducted by FDA has used aggregate data to look at demographics and across a broad therapeutic area.
- Now, we are taking a more granular approach and taking a look at more targeted areas such as cardiovascular disease, an area where there have been concerns about lower participation of women.



- As part of the FDASIA section 907 Action Plan, FDA has implemented steps to improve the reporting of sex based analyses such as the Drug Snapshots which makes demographic data more available and transparent to the general public.

- The Snapshots show who participated in the pivotal clinical trials used to approve the drug and stratify the data by sex, race, and age subgroups.



Drug Trial Snapshots

2015-2016

FDA

2016 Summary Statistics

(Jan 1, 2016 - Dec 31, 2016)

In 2016, CDER approved 22[1] novel drugs, either as new molecular entities (NMEs) under New Drug Applications (NDAs) or as new therapeutic biologics under Biologics License Applications (BLAs). Overall, 31,468 patients participated in these trials. Subpopulation demographics are presented below:

Figure 1. Demographic Subgroups in 2016

DEMOGRAPHIC SUBGROUPS	WOMEN	AFRICAN AMERICAN	ASIAN	WHITE	OTHER*	AGE 65 and OLDER
PARTICIPANT AVERAGE	48%	7%	11%	76%	7%	21%

* The percentages of the categories "American Indian or Alaska Native (AI/AN)," "Native Hawaiian or Other Pacific Islander (NH/OPI)," and "Unknown/Unreported" were small enough that we combined them into the "Other" category for the purposes of this report.

2015 Summary Statistics

(Jan 1, 2015 - Dec 31, 2015)

In calendar year 2015, CDER approved 45[2] novel drugs, either as new molecular entities (NMEs) under New Drug Applications (NDAs) or as new therapeutic biologics under Biologics License Applications (BLAs). Overall, 105,826 patients participated in these trials. Subpopulation demographics are presented below:

Figure 2. Demographic Subgroups in 2015

DEMOGRAPHIC SUBGROUPS	WOMEN	AFRICAN AMERICAN	ASIAN	WHITE	OTHER*	AGE 65 and OLDER	AGE 75 and OLDER**	AGE 80 and OLDER**
PARTICIPANT AVERAGE	40%	5%	12%	79%	4%	37%	15%	6%

* The percentages of the categories "American Indian or Alaska Native (AI/AN)," "Native Hawaiian or Other Pacific Islander (NH/OPI)," and "Unknown/Unreported" were small enough that we combined them into the "Other" category for the purposes of this report.
**These particular subgroups were calculated as part of a Geriatrics Report and are not a regular feature of the Drug Trials Snapshots

Drug Trials Snapshots Summary Report (2015 and 2016)

- The report also includes an overview of the two years of the Snapshots program.

- 2016: 48% women – overall
- 2015: 40% women

Drug Trial Snapshots

Table 1. Women and Men in Pivotal Trials[a] of Cardiovascular Snapshots (2015) Compared With Percentage of Women in Disease Population[b]

Drug	Indication	Participants, No. (%)		Cardiovascular Disease Area	Women in the Disease Population, %[b]
		Women 22 621	Men 41 990		
Ivabradine	To reduce hospitalization from worsening heart failure	1535 (24)	4970 (76)	Heart failure	53[c]
Secubitril/valsartan	Treatment of heart failure	1847 (22)	6595 (78)	Heart failure	53[c]
Cangrelor	For prevention of coronary artery blood clot formation in patients undergoing PCI	3121 (28)	8024 (72)	Acute coronary syndrome	39[d]
Alirocumab	Treatment of certain patients with high cholesterol	1507 (40)	2245 (60)	Hypercholesterolemia	58[e]
Idarucizumab	Reversal of the anticoagulant effects of dabigatran during emergency situations or when there is a need to reverse its blood-thinning effects	58 (47)	65 (53)	Reversal agent	NA
Evolocumab[f]	Treatment of certain patients with high cholesterol	2079 (50)	2098 (50)	Hypercholesterolemia	58[e]
Evolocumab[g]	Treatment of certain patients with high cholesterol	24 (49)	25 (51)	Hypercholesterolemia	58[e]
Edoxaban	Prevention of stroke in patients with atrial fibrillation	8006 (38)	13020 (62)	Atrial fibrillation	43[h]
Edoxaban	Reduction of risk of VTE in patients with previous VTE	3524 (43)	4716 (57)	VTE	52[i]
Selexipag	For the treatment of adults with PAH	920 (80)	232 (20)	PAH	80[j]

Source: Whyte et al.

Office of Women's Health

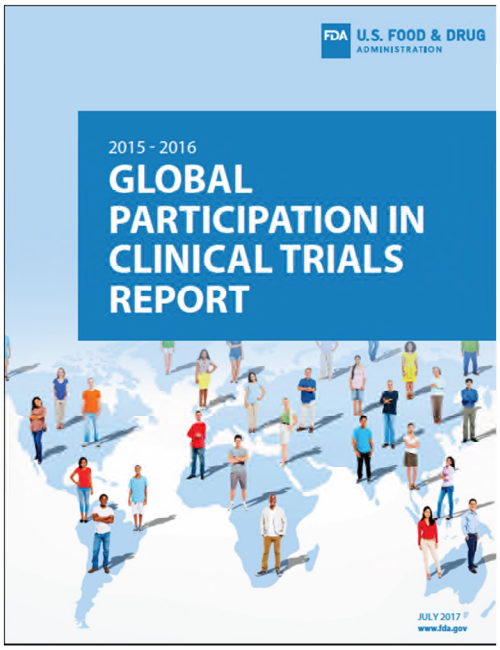
- Using Drug Trial Snapshots, FDA looked at the demographics of CVD NMEs approved in 2015 in pivotal trials.

Results from Whyte et al:

- In 2015, there were 9 NMEs with cardiovascular indications.
- Of these, the number of women enrolled in the trials was 22621, accounting for 35% of the 64611 total participants (Table 1).
- Inclusion of women ranged from 24 participants to 8006 (mean of 2262 and median of 1691).

- Participation: Concluded that "Cardiovascular disease appears to be an area where enrollment of women is disproportionately low. The FDA plans to work with the cardiology community to address this issue"

- The author's state that with only a year of data, it is difficult to understand if this data is comparable to those of other years.
- Which brings us to another project that we have been working on at FDA where we have looked at the participation of women in pivotal CVD trial data for drugs approved 2005-2015. The submitted paper is currently under review. I will come back to this project later in my presentation.



Developed by FDA Center for Drug Research and FDA Office of Women's Health

https://www.fda.gov/downloads/Drugs/InformationOnDrugs/UCM570195.pdf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