FDA Perspective: Women in CVD Clinical Trials

Katie O'Callaghan
Biomedical Engineer & Scientific Reviewer
Division of Cardiovascular Devices
FDA/CDRH/ODE

Disclaimer

- The comments made in this presentation represent my personal opinions and views. This does not necessarily reflect the official position held by the Government or the FDA, and does not bind or otherwise obligate or commit the Agency to the views expressed.

Objectives

1. Primer: FDA 101
2. Summarize guidance development efforts (with public input) for improving study and analysis of women in CVD device trials
3. Highlight opportunities for WIN collaboration and impact

Objectives

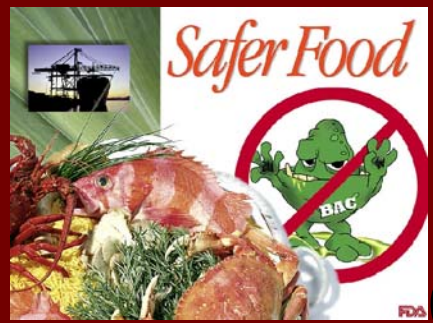
1. Primer: FDA 101
2. Summarize guidance development efforts (with public input) for study and analysis of women in CVD device trials
3. Highlight opportunities for WIN collaboration and impact

Food & Drug Administration

- Regulatory Agency
- Oldest Consumer Protection Agency
- Oversight & regulation of over $1 trillion worth of products annually
- ~ $0.25 of every consumer dollar spent
- NOT a research agency

Regulatory Oversight

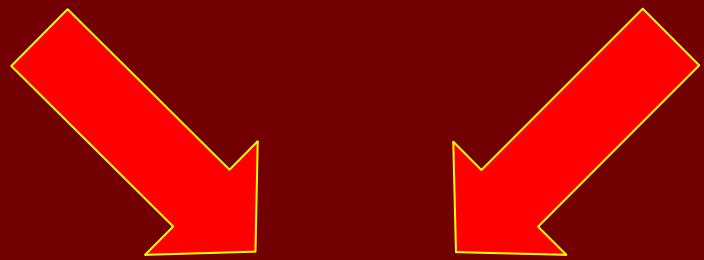
- Pharmaceuticals (prescription & OTC)
- Vaccines, blood products
- Medical devices
- Food (not meat)
- Veterinary products
- Cosmetics



What does CDRH do?

Premarket Application (PMA)

- Pre-clinical data
  - Bench testing
    - Product characterization
    - Reliability
    - Biocompatibility
  - Animal studies
- Clinical trial results
  - Feasibility
    - Safety (hint of effectiveness)
  - Pivotal
    - Establish safety and effectiveness



Reasonable Assurance of Safety and Effectiveness

Investigational Device Exemption (IDE)

- Studies subject to regulation:
  - If used to support a marketing application: PMA, HDE or 510(k)
  - Collection of safety and effectiveness information (e.g., for new intended use of a legally marketed device)
  - Sponsor-investigator studies of unapproved devices or new intended use of approved device (even if no marketing application planned)

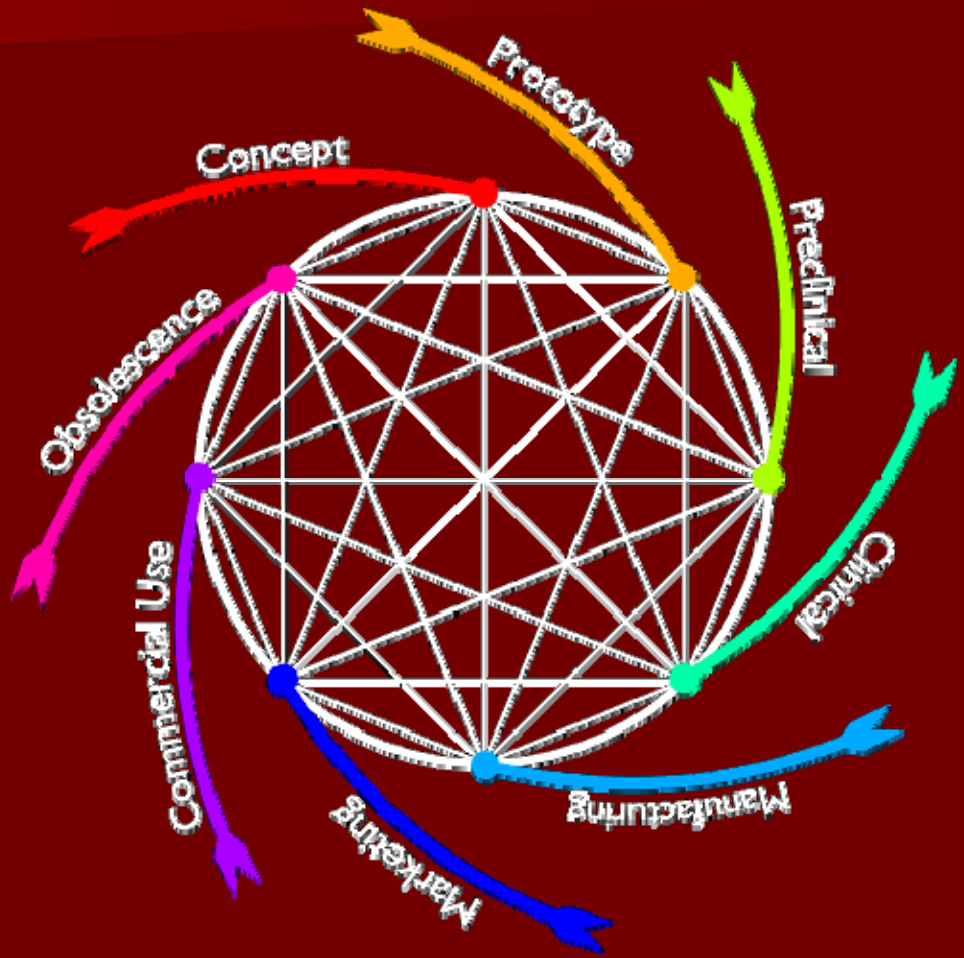
Required Elements of an IDE

- U.S. sponsor (manufacturer or investigator)
- Prior investigations
- Preclinical animal and bench testing
- Investigational plan (detailed protocol, informed consent, case report forms)
- Manufacturing information
- Investigator (CV, agreement) and IRB information
- Sales information (can recover cost of study but not more)
- Labeling (INVESTIGATIONAL)

Other types of applications

- 510(k) = pre-market notification
  - Analogous to PMA but for devices which are similar ("substantially equivalent") to existing legally marketed 510(k) devices and/or pre-amendment devices
  - Typically reserved for lower risk devices
  - Rarely include clinical data
- HDE = humanitarian device exemption
  - Analogous to PMA but for devices intended for use in a "medically plausible subset"
  - Demonstrate safety and "probable benefit" (instead of effectiveness)
  - May or may not include clinical trial data
  - No comparable PMA-approved device

Total Product Life Cycle



Post-Market

- Passive surveillance: Medical Device Reporting – MAUDE database
- Active surveillance: MedSun
- Post-approval studies
- Signal detection

Other

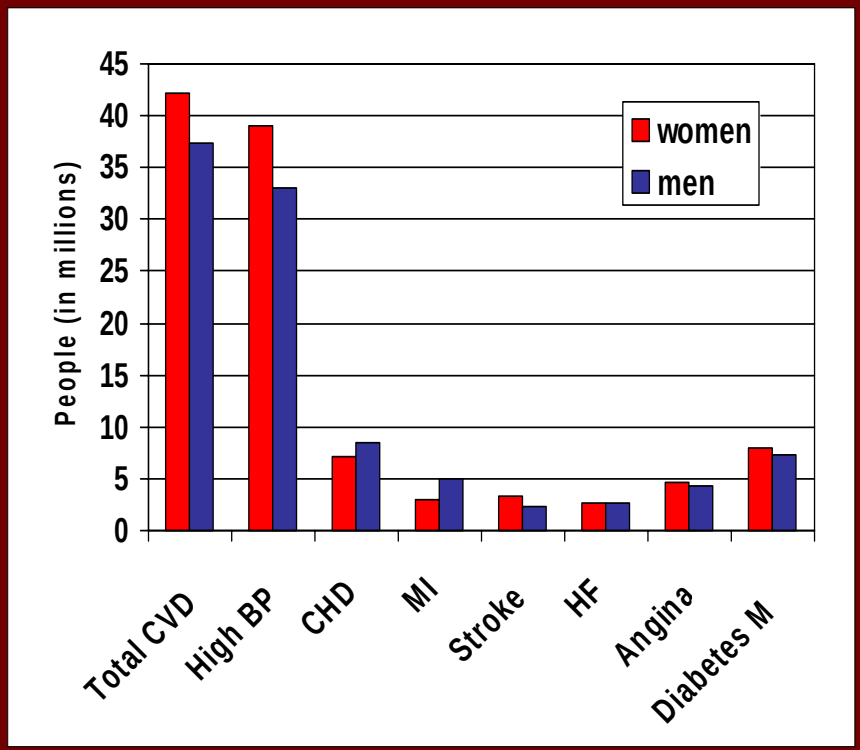
- Scientific research (regulatory impact)
- Public communication, education and outreach
- Enforcement, site inspections (manufacturing or preclinical/clinical research sites)
- Imports/exports of regulated products

Objectives

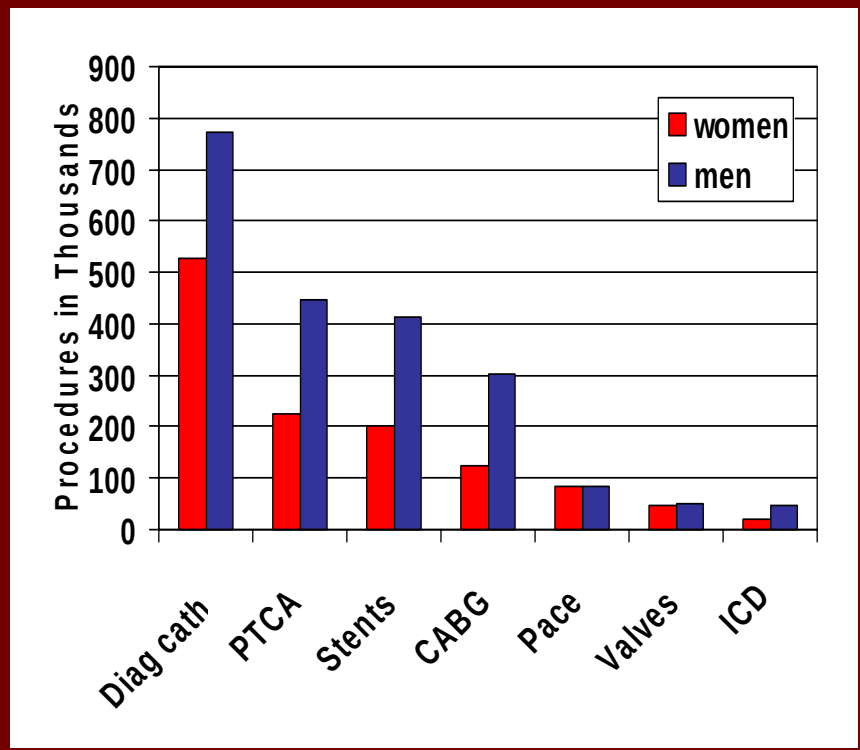
1. Primer: FDA 101
2. Summarize guidance development efforts (with public input) for study and analysis of women in CVD device trials
3. Highlight opportunities for WIN collaboration and impact

Prevalence vs. Utilization

CVD PREVALENCE BY TYPE



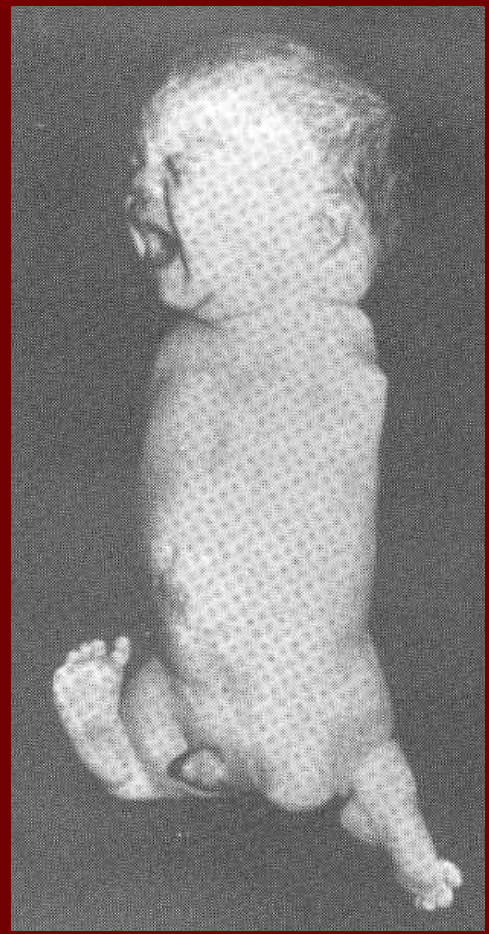
PROCEDURE/DEVICE UTILIZATION



2004 data, American Heart Association. Heart Disease and Stroke Statistics – 2007 Update

Historical Exclusion of Women

- Thalidomide tragedy leads to ***exclusion*** of women of child-bearing potential (1977 – FDA policy for drug trials)



Prescription Drugs WITHDRAWN from the US Market 1997-2000

Drug	Type of Drug	Patient Population	Primary Health Risk
Prescription Drugs with Evidence of Greater Health Risks In Women			
Pondimin	Appetite suppressant	Women	Valvular heart disease
Redux	Appetite suppressant	Women	Valvular heart disease
Rezulin	Diabetic	Women	Liver failure
Lotronex	Gastrointestinal	Women	Ischemic colitis
Seldane[a]	Antihistamine	Women and Men	Torsades de Pointes
Posicor	Cardiovascular	Women and Men	Lowered heart rate in elderly women and adverse interactions with 26 other drugs
Hismanal	Antihistamine	Women and Men	Torsades de Pointes
Propulsid[b]	Gastrointestinal	Women and Men	Torsades de Pointes

[a]Seldane-D was also withdrawn from the market. Terfenadine was the active ingredient in both Seldane and Seldane-D; Seldane-D also contained the decongestant pseudoephedrine.

[b]Propulsid remains minimally available on a patient-by-patient basis for those with severely debilitating conditions.

Source: *GAO analysis in GAO-01-286R Drugs Withdrawn From Market*

What FDA is doing

- Public Workshops:
  - Objective: to brainstorm ways to increase female participation in studies and availability of sex-specific results
  - Stakeholders: physicians, investigators, patient groups, industry, and other government health agencies (NIH, CMS, AHRQ)
- Guidance Document (in drafting stage): FDA recommendations regarding the study and analysis of sex differences in CV device trials

Planned Guidance: Analysis

- Sex-specific analysis:
  - Test for interaction between treatment and sex. Significant result suggests data should be analyzed separately by sex.
  - Examine sex differences in treatment effect (effectiveness) as well as serious adverse events (safety)
- Prospectively plan for these in study protocol
- Further study (including PAS): Where clinically significant sex differences are found or suspected

Planned Guidance: Reporting

IDE

- Report trial inclusion demographics in IDE annual progress reports
- Track & report reasons for non-inclusion (don't meet study criteria, don't give consent, lost to follow-up, etc.)

PMA

- Report results of sex-specific analyses, whether positive or negative (publicly accessible)
- For post hoc analyses, report descriptive statistics only (no p-values)

Planned Guidance: Trial Conduct

- Explore reasons for under-representation (via screening logs, etc.); develop ways to minimize barriers to female participation
- Consider methods of increasing female enrollment (e.g., women heart clinics, female investigators, maintain open enrollment, parallel registries if don't meet all inclusion criteria)
- Consider enrollment targets to include more women in clinical trials
- Evaluate existing evidence for signs of difference in disease or treatment...further study

WITH HELP FROM WIN

What do we hope to accomplish?

More clear information for physicians and patients, regarding diagnosis and treatment of CVD in women

To improve the quality of care for women with CVD

Policy alone is not enough!

Who's responsible?

- Industry and FDA
- Researchers and NIH
- Patients and Medical Providers
- Payers (insurance, CMS)
- Others

What others are doing

- Patient Awareness Campaigns – not just re: CVD in women, but also re: importance of participating in research
- Provider Awareness – is there a need for tailored diagnosis & treatment strategies for women?

What others are doing (2)

- Pre-clinical Research – discovering biological reasons for sex differences (in health, disease, and responses to treatment)
- Clinical Research – more consistency in sex-specific data analysis (e.g., for publication in journals)

Special Role for WIN

- Female investigators in clinical trials
- Help solve systemic problems – Why aren't women sufficiently included in studies?
  - Diagnostic challenges? Referral bias? Exclusion criteria? Refuse consent? Loss to follow-up?
- Evaluation:
  - For differential response which may be associated with sex
  - Of sex-specific questions (interaction of HRT or oral contraceptives; effects of radiation exposure on pregnancy; etc.)

Potential Opportunities at FDA

- Medical Device Fellowship Program (term)
- Special Government Employee (confidential consultation on project basis)
- Grant funding for collaboration projects with FDA employee (Office of Women's Health; Critical Path Initiative)

Thank You

Questions or copies of this presentation:
kathryn.ocallaghan@fda.hhs.gov

Resources:

- FDA Office of Women's Health: http://www.fda.gov/womens/default.htm
- Device Advice (submissions & regulations): http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm