SEX-SPECIFIC REPORTING OF SCIENTIFIC RESEARCH

US FDA Perspective

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Regulatory History

1977 Guidelines: General Considerations for the Clinical Evaluation of Drugs

‘...women of childbearing potential should be excluded from the earliest dose-ranging studies.’

.....under representation or exclusion
Sex was **NOT** recognized as:
- A **variable** in health research
- A **factor** that could affect health and illness

Adapted from Moncher & Douglas, Importance of and Barriers to Including Women in Clinical Trials. In: Principles of Gender-specific Medicine
The FACTS

- 2010 US census population estimates:
  - 50.7% women

- Women outlive men (80.7 years vs 74.8 years)

- Many diseases place heavy burden on women compared to men
  - Heart disease
  - Cancer
  - Rheumatoid arthritis
  - Lupus
  - Osteoporosis

- Women rely more on medical system than men

- For many diseases treatment guidelines are largely based on data in men
DRUG INDUCED ECG CHANGES

- QT prolongation
- Torsades de pointes

Women are:
2-3 times more likely to develop TDP than men
more likely to have LQT/TDP secondary to drug therapy
Prescription Drugs WITHDRAWN from the US Market 1997-2000

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of Drug</th>
<th>Patient Population</th>
<th>Primary Health Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prescription Drugs with Evidence of Greater Health Risks In Women</strong></td>
<td></td>
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<tr>
<td>Pondimin</td>
<td>Appetite suppressant</td>
<td>Women</td>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Redux</td>
<td>Appetite suppressant</td>
<td>Women</td>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Rezulin</td>
<td>Diabetic</td>
<td>Women</td>
<td>Liver failure</td>
</tr>
<tr>
<td>Lotronex</td>
<td>Gastrointestinal</td>
<td>Women</td>
<td>Ischemic colitis</td>
</tr>
<tr>
<td>Seldane(^a)</td>
<td>Antihistamine</td>
<td>Women and Men</td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td>Posicor</td>
<td>Cardiovascular</td>
<td>Women and Men</td>
<td>Lowered heart rate in elderly women and adverse interactions with 26 other drugs</td>
</tr>
<tr>
<td>Hismanal</td>
<td>Antihistamine</td>
<td>Women and Men</td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td>Propulsid(^b)</td>
<td>Gastrointestinal</td>
<td>Women and Men</td>
<td>Torsades de Pointes</td>
</tr>
</tbody>
</table>

\(^a\)Seldane-D was also withdrawn from the market.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
Kaplan-Meier estimates of the cumulative incidence of fractures at 5 years in all patients (A), men (B), and women (C). Fractures were as reported by the clinical site and the HRs (95% CI) for these events are listed for comparisons by treatment group. Bars represent 95% CIs.

FRACTURE RISK  
ADOPT study 
Avandia (rosiglitazone) 

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone</th>
<th>Metformin</th>
<th>Glyburide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MALE</strong></td>
<td>(3.95)</td>
<td>(3.36)</td>
<td>(3.35)</td>
</tr>
<tr>
<td>rate/100PY</td>
<td>1.16</td>
<td>0.98</td>
<td>1.07</td>
</tr>
<tr>
<td><strong>FEMALE</strong></td>
<td>(9.30)</td>
<td>(5.09)</td>
<td>(3.47)</td>
</tr>
<tr>
<td>rate/100PY</td>
<td>2.74</td>
<td>1.54</td>
<td>1.29</td>
</tr>
</tbody>
</table>

*Majority of fractures in upper arm (humerus), hand or foot. Number with hip or spine fractures was similar among the 3 treatment groups.

GSK Dear HealthCare Professional Letter, February 2007
Women were not adequately included in clinical studies.

60% of drugs – representation of women less than prevalence with disease.

Data not analyzed for sex differences consistently.

Lack of understanding of sex/gender differences.
**Guidances and Regulations**

<table>
<thead>
<tr>
<th>1993 GUIDELINE: Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs</th>
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<tbody>
<tr>
<td>1998 REGULATION: Require Investigational New Drug Applications (INDs) and New Drug Applications (NDAs)</td>
</tr>
<tr>
<td>“Demographic Rule”: 21 CFR 314.50 and 21 CFR 312.33</td>
</tr>
<tr>
<td>2000 REGULATION (amendment): Clinical Hold Regulations for Products Intended for Life-Threatening Diseases</td>
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<tr>
<td><strong>β</strong> Reversed the 1977 Policy: Collection and analysis of data on sex differences Effectiveness, Adverse effects, PK</td>
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<tr>
<td><strong>β</strong> NDA submission: information on trial participation, safety, effectiveness</td>
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<tr>
<td><strong>β</strong> IND submission: to tabulate the number of participants according to age race sex</td>
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<tr>
<td><strong>β</strong> Permits FDA to stop studies under an IND for treatment of a life-threatening disease if women are excluded due to reproductive potential</td>
</tr>
</tbody>
</table>
Where are we?

Women's Participation in Late Phase Clinical Trials for Drugs

Women's Participation in Early Phase Clinical Trials for Drugs

*trials enrolling both sexes have 38.8% women

Data Analysis by Sex in Clinical Trials for Drugs

Recent data on women’s participation and analysis (2007-2009)
Recent data on review of approved labels (2007-2009)

Yang, et.al., Journal of Women’s Health, Vol 18, No.3, 2009
Pinnnow et.al, Women’s Health Issues, 29, 2009
Ongoing Initiatives

- Data Standardization Initiative
- Guidances in development
- Internal Review Templates
- Other (Sentinel, Medwatch, REMS)
FDA Mission:
Protecting and Promoting Public Health

OWH Mission:
Protecting and Advancing the Health of Women