Biologic Variability to Drug Response: Sex Differences in Clinical Trials
Parsing Variability in Drug Response
A New Era in Clinical Research

• A shift from detection of large average effects to information relevant to individual patient decisions
• Harvest EHR and linked biobank at scale to uncover unexpected disease associations (e.g. AD – IBD) and interrogate mechanism
• Use of iPS cells and deep phenotyping to establish POC: **Human Phenomic Science**
• More focused and creative trial design
• Seek internal consistency from non – RCT data

FitzGerald GA Sci Transl Med. 2015 Apr 22;7(284):284fs15
Interindividual variability in the pharmacological response to PGHS-2 inhibition

Fries, Grosser, FitzGerald, Gastroenterology, 130(1):55-64. 2006
Genomic Variance is One Hand Clapping

• Comparison of intra vs inter individual variability of drug response permitted calculation of maximum contribution from fixed sources of variance – such as the genome (if we could measure it comprehensively)
• Maximal estimate ~30% in young male volunteers studied under controlled conditions
• Most variance from unrecognized environmental inputs interacting with our genomes – need for unbiased readouts of metabolome etc
• Imagine the maximal contribution of genomic variance in typical patient target populations…..
Gender and Age are Important Variables; Inclusion in Preclinical Research

Nature 2016
**APPROVe Study: Confirmed Thrombotic Endpoint**

*Kaplan-Meier Estimates (95% CI)*

RR(95% CI): 1.96 (1.20, 3.19)*

* p<0.05

**Patients at Risk**

<table>
<thead>
<tr>
<th>Month</th>
<th>Placebo</th>
<th>Rofecoxib 25 mg</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>1299</td>
<td>1287</td>
</tr>
<tr>
<td>6</td>
<td>1192</td>
<td>1123</td>
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<tr>
<td>12</td>
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<td>1050</td>
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<td>30</td>
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<td>898</td>
</tr>
<tr>
<td>36</td>
<td>470</td>
<td>411</td>
</tr>
</tbody>
</table>

PGL2 and COX-2 deletion accelerate the initiation of Atherosclerosis

Egan et al,
Science 10;306(5703):1954-7, 2004

Kobayashi et al,
JCI 114: 784-94, 2004

Translational Science of CV Risk

• Suppression of PGI$_2$ might foster atherogenesis and account for CV risk transformation; more striking in females
• Target population in arthritis trials
• Estrogen upregulates VSMC COX-2 dependent PGI$_2$ formation which restrains lipid induced oxidative stress
• Deletion of the Ip undermines atheroprotective effects of estrogen
• FDA approval of coxibs in juvenile arthritis
Interrogation of potential sources of variance

Variability in target enzyme expression
Consideration of the broader lipidome
Background genetics
Time of dosing
Drug interactions with the microbiome
Drug-drug and drug-diet interactions
Off target effects
Target Variability and the Broader Lipidome
Identification of genes that may contribute to variability in the NSAID response – gene expression variability

GEO search: Hapmap GSE #10824, #5859, #2552, #1485

Interindividual variability of COX 2 expression in immortalized B-cells
Distance Correlation Analysis

p-value < 0.05

Read counts 10 libraries ≥ 16

# Expressed Libraries ≥ 8
Multiple genes relevant to PG synthesis/action altered by COX-2 inhibition
O'Donnell's Expanded View of the Human Platelet Lipidome

thrombin → PAR 1/4 → aggregation → coagulation → thrombosis

aspirin → multiple lipids → mitochondrial β oxidation → Acetyl CoA → ATP

12-HETE → AA → TxA2 → cPLA2

COX-1

oxPL re-esterification → PI Assymetry

Background Genetics
### Background Genetics; Collaborative Cross

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Gene</th>
<th>Fold difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose</td>
<td>Lipg</td>
<td>1934</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>Ggt1</td>
<td>1469</td>
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<tr>
<td>Adipose</td>
<td>Ptgs2</td>
<td>1034</td>
</tr>
<tr>
<td>Spleen</td>
<td>Pla2g1b</td>
<td>968</td>
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<td>Adrenal gland</td>
<td>Slc27a2</td>
<td>761</td>
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<tr>
<td>Kidney</td>
<td>Akr1c18</td>
<td>553</td>
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<td>Adipose</td>
<td>Ptgds</td>
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<td>Kidney</td>
<td>Alox15</td>
<td>417</td>
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<tr>
<td>Skeletal muscle</td>
<td>Slc27a2</td>
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<td>Adipose</td>
<td>Lipa</td>
<td>274</td>
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<td>Adipose</td>
<td>Gpx6</td>
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<td>Adipose</td>
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<td>Skeletal muscle</td>
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<tr>
<td>Skeletal muscle</td>
<td>Ptger3</td>
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<td>Lung</td>
<td>Slc27a2</td>
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<td>Macrophage</td>
<td>Ptgs2</td>
<td>99</td>
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<td>Adipose</td>
<td>Pla2g5</td>
<td>93</td>
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<td>Liver</td>
<td>Akr1c18</td>
<td>90</td>
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<tr>
<td>Adrenal gland</td>
<td>Pla2g2f</td>
<td>76</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>Acsl4</td>
<td>74</td>
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<tr>
<td>Macrophage</td>
<td>Gpx3</td>
<td>66</td>
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<td>Adrenal gland</td>
<td>Pla2g12b</td>
<td>66</td>
</tr>
<tr>
<td>Lung</td>
<td>Alox15</td>
<td>63</td>
</tr>
</tbody>
</table>

- **Adipose**
- **Adrenal gland**
- **Spleen**
- **Kidney**
- **Skeletal muscle**
- **Lung**
- **Macrophage**
- **Liver**

**Gene Expression**
- High expression
- Low expression

**Diagram:**
- Heatmap showing gene expression across different tissues and conditions.
Heart rate and blood pressure measurements across the strains. Abbreviations: EDP = end diastolic pressure; ESP = end systolic pressure; MAP = mean arterial pressure.
Timing of Dosing
### Clock-regulated drug targets

<table>
<thead>
<tr>
<th>Rank</th>
<th>Sales</th>
<th>Trade name</th>
<th>Drug</th>
<th>Indications</th>
<th>Circadian-gene targets</th>
<th>Organs in which targets oscillate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>$1.46b</td>
<td>Nexium</td>
<td>Esomeprazole</td>
<td>Gastritis, GERD, Esophagitis</td>
<td>Ap4a</td>
<td>liver</td>
</tr>
<tr>
<td>5</td>
<td>$1.28b</td>
<td>Advair Diskus</td>
<td>Fluticasone + salmeterol</td>
<td>Asthma, Chronic obstructive pulmonary disease, Non-Hodgkin’s lymphoma</td>
<td>Agrp2b, Ms4a1</td>
<td>kidney, lung, skeletal muscle</td>
</tr>
<tr>
<td>11</td>
<td>$794m</td>
<td>Rituxan</td>
<td>Rituximab</td>
<td>Rheumatoid arthritis, Non-Hodgkin’s lymphoma</td>
<td>Kenma1</td>
<td>kidney, skeletal muscle</td>
</tr>
<tr>
<td>20</td>
<td>$538m</td>
<td>Diovan</td>
<td>Valsartan + hydrochlorothiazide</td>
<td>Hypertension, Heart failure</td>
<td>Adra1b</td>
<td>liver</td>
</tr>
<tr>
<td>27</td>
<td>$431m</td>
<td>Vyvanse</td>
<td>Lisdexametamine</td>
<td>Attention deficit hyperactivity disorder</td>
<td>Neu1, Neu2</td>
<td>liver, kidney, lung, cerebellum</td>
</tr>
<tr>
<td>32</td>
<td>$392m</td>
<td>Tamiflu</td>
<td>Oseltamivir</td>
<td>Influenza</td>
<td>Slc6a4</td>
<td>kidney, adrenal gland</td>
</tr>
<tr>
<td>33</td>
<td>$383m</td>
<td>Ritalin</td>
<td>Methylphenidate</td>
<td>Attention deficit hyperactivity disorder</td>
<td>Ar</td>
<td>brown fat, aorta, brainstem</td>
</tr>
<tr>
<td>37</td>
<td>$348m</td>
<td>AndroGel</td>
<td>Testosterone</td>
<td>Hypogonadism</td>
<td>Egrf</td>
<td>heart</td>
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<tr>
<td>38</td>
<td>$346m</td>
<td>Lidoderm</td>
<td>Lidocaine</td>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>$304m</td>
<td>Seroquel XR</td>
<td>Quetiapine</td>
<td>Bipolar disorder, Major depressive disorder</td>
<td>Htr2a, Drd4, Htr2c, ...</td>
<td>liver, kidney, lung, brown fat, heart, a...</td>
</tr>
<tr>
<td>45</td>
<td>$289m</td>
<td>Viagra</td>
<td>Sildenafil</td>
<td>Erectile dysfunction</td>
<td>Pde5a, Pde6g</td>
<td>brown fat, adrenal gland</td>
</tr>
<tr>
<td>48</td>
<td>$281m</td>
<td>Niaspan</td>
<td>Nicardipine</td>
<td>Hyperlipidemia</td>
<td>Qprt</td>
<td>kidney</td>
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<tr>
<td>49</td>
<td>$279m</td>
<td>Humalog</td>
<td>Insulin lispro</td>
<td>Diabetes mellitus T2</td>
<td>Igf1r</td>
<td>kidney</td>
</tr>
<tr>
<td>76</td>
<td>$274m</td>
<td>Alimta</td>
<td>Mitomycin</td>
<td>Mesothelioma, Non-small cell lung cancer</td>
<td>Tms, Gart, Atic</td>
<td>liver, lung, aorta</td>
</tr>
<tr>
<td>54</td>
<td>$267m</td>
<td>Combivent</td>
<td>Ipratropium bromide + salbutamol</td>
<td>Asthma, Chronic obstructive pulmonary disease, Breathing problems</td>
<td>Chrm2, Agrp2b, Agrp1b</td>
<td>kidney, lung, heart, skeletal muscle, br...</td>
</tr>
<tr>
<td>56</td>
<td>$262m</td>
<td>ProAir HFA</td>
<td>Salbutamol</td>
<td>Asthma, Chronic obstructive pulmonary disease, Breathing problems</td>
<td>Agrp2b, Agrp1b</td>
<td>kidney, lung, skeletal muscle</td>
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<tr>
<td>62</td>
<td>$240m</td>
<td>Janumet</td>
<td>Metformin + sitagliptin</td>
<td>Diabetes mellitus T2</td>
<td>Pkra1b, Dpp4</td>
<td>kidney, heart, brainstem, hypothalamus</td>
</tr>
<tr>
<td>66</td>
<td>$236m</td>
<td>Toprol XL</td>
<td>Metoprolol</td>
<td>Hypertension, Heart failure</td>
<td>Agrp2b, Agrp1b</td>
<td>kidney, lung, skeletal muscle</td>
</tr>
<tr>
<td>71</td>
<td>$220m</td>
<td>Vvtorin</td>
<td>Ezetimibe + simvastatin</td>
<td>Hyperlipidemia</td>
<td>Anp4a, Soat1, Hmgcr</td>
<td>liver, lung, brainstem</td>
</tr>
<tr>
<td>78</td>
<td>$209m</td>
<td>AcipHex</td>
<td>Rabeprazole</td>
<td>Gastritis, GERD, Esophagitis</td>
<td>Atp4a</td>
<td>liver</td>
</tr>
<tr>
<td>90</td>
<td>$189m</td>
<td>Lunesta</td>
<td>Eszopiclone</td>
<td>Insomnia</td>
<td>Tspo, Gabra3</td>
<td>kidney, lung, adrenal gland</td>
</tr>
<tr>
<td>98</td>
<td>$173m</td>
<td>Prilosec</td>
<td>Omeprazole</td>
<td>Gastritis, GERD, Esophagitis</td>
<td>Atp4a</td>
<td>liver</td>
</tr>
<tr>
<td>99</td>
<td>$171m</td>
<td>FocaLin XR</td>
<td>Desmethylphenidate</td>
<td>Attention deficit hyperactivity disorder</td>
<td>Slc6a4</td>
<td>kidney, adrenal gland</td>
</tr>
</tbody>
</table>

**Table 1:** Drugs from the top-100 best-selling drugs list that target circadian genes AND have half-life < 6h. For full table, see Dataset S1. Rank and sales are based on USA 2013 Q1 data from Drugs.com.

Zhang and Lahens et al. PNAS 2014
Time dependent hypotensive effect of low dose aspirin

Hermeida group  Chronobiol Int 2013 Mar;30(1-2):260-79
Time dependent hypotensive effect of low dose aspirin in mice on HSD

Wang et al 2016
A circadian gene expression atlas in mammals: Implications for biology and medicine

Ray Zhang, Nicholas F. Lahens, Heather L. Ballance, Michael E. Hughes, and John B. Hogenesch

*Department of Pharmacology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104; and \(^{2}\)Department of Biology, University of Missouri, St. Louis, MO 63121

Edited by Joseph S. Takahashi, Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX, and approved September 19, 2014 (received for review May 13, 2014)

mir22

UGUCAGAAGUGG--ACCGUCGAA

Ptgs1 (COX-1)
The Host Clock Influences the Intestinal Microbiome

Bacteroidetes

Firmicutes

B/F Ratio

$p=0.00749$

$p=0.01718$

$p=0.01069$
Bi-directional Interaction between NSAIDs and the Microbiome

Abx: Neomycin and Vancomycin

T₁/₂ and Vₘ have significantly different variance

N=6/group

Mann-Whitney test

Data: mean and SEM

Liang et al Elife 2015
Drug-Drug Interactions
COX-1 acetylation reflects aspirin exposure
Differential interaction with other NSAIDs

Interaction by mixed, but not COX-2 selective inhibitors to undermine antiplatelet effects of aspirin

- Li X et al. PNAS. 2014 ;111(47):16830
ImPRECISION

• Comparison of celecoxib vs ibuprofen vs naproxen in patients with CVD (PRECISION and SCOT)
• Not powered for separate analysis of those on and off aspirin
• Mistaken advice to avoid interaction
• No biochemical documentation of aspirin status
• Ibuprofen and naproxen but not celecoxib may interact to undermine the platelet inhibitory effects of low dose aspirin
Off Target Effects
Overview

- Methods development
  - Quantify drug protein interactions
  - Associate interactions to indications
- Apply to NSAIDs

*Drug protein interactions*
- Functional targets
- Unintended binding to other proteins

Diagram:
- Druggability
- Promiscuity
- Dose
- High risk off-targets
PocketFEATURE: predict promiscuity
Selection of the drug concentration in hASMC

hASMC

In vivo

Emanuela Ricciotti
Celecoxib reduces neointimal hyperplasia after vascular injury

COX-2 independent effects might modulate celecoxib’s effect on restenosis
# KEGG pathway analysis

**No IL-1 β**

<table>
<thead>
<tr>
<th>Pathway</th>
<th>P-value</th>
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<tbody>
<tr>
<td>focal adhesion</td>
<td>8.20E-06</td>
</tr>
<tr>
<td>aminoacyl tRNA biosynthesis</td>
<td>0.00078</td>
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<tr>
<td>erbB signaling pathway</td>
<td>0.00143</td>
</tr>
<tr>
<td>mapk signaling pathway</td>
<td>0.00268</td>
</tr>
<tr>
<td>renal cell carcinoma</td>
<td>0.00340</td>
</tr>
<tr>
<td>adherens junction</td>
<td>0.00460</td>
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<tr>
<td>colorectal cancer</td>
<td>0.00389</td>
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<tr>
<td>notch signaling pathway</td>
<td>0.00897</td>
</tr>
<tr>
<td>regulation of actin cytoskeleton</td>
<td>0.01036</td>
</tr>
</tbody>
</table>

http://amp.pharm.mssm.edu/Enrichr/#new
Parsing Multiple Sources of Variance

• Stratification for the big ones – gender, age, concomitant medications
• Stratification (or at least information) on time of dosing which can be a big one
• **HPS** to identify other potential signatures of efficacy, likely or emerging risk
• Diversified approaches to modelling
• In most cases, even comprehensive understanding of the genome will contribute only partial insight into variance
Involvement of bacterial de-conjugation

- Indomethacin undergoes enterohepatic circulation which requires gut bacteria
  - Indomethacin is glucuronidated in liver
  - Glucuronidated indomethacin is excreted to the small intestine via biliary excretion
  - Bacterial $\beta$-glucuronidase catalyzed the de-conjugation
    - Parent drug is reabsorbed
Biologic Variability to Drug Response: Sex Differences in Clinical Trials
WHICH SUBGROUPS MATTER?

David J. Greenblatt, M. D
Tufts University School of Medicine
Boston MA
Pre-emptive

Target population

NOT animal models, in vitro models
Age

Gender

Body habitus

Race (ethnicity)
ALTERED MEDICATION RESPONSE IN THE ELDERLY

**Dynamic:**

Altered response (efficacy and/or side effects) at any given plasma/brain concentration

**Kinetic:**

Reduced clearance causing higher plasma/brain concentrations

Zolpidem, 5 mg p. o.
Cotreau MM. Clin Pharmacokin 2005; 44: 33-60

CYP3A substrate drugs
**gender** (jĕn'dər) *n.* 1. *Gram.* **a.** A set of two or more categories, as masculine, feminine, and neuter, into which words are divided according to sex, animation, psychological associations, or some other characteristic, and that determine agreement with or the selection of modifiers, referents, or grammatical forms. **b.** One category of such a set. **c.** The classification of a word or grammatical form in such a category. **d.** The distinguishing form or forms used. 2. *Classification of sex.* — *tr. v.* -dered, -der-ing, -ders. *Archaic.* To engender. [ME gendre < OFr., kind < Lat. genus.]

**sex** (sĕks) *n.* 1. **a.** The property or quality by which organisms are classified according to their reproductive functions. **b.** Either of two divisions, designated male and female, of this classification. 2. Males or females collectively. 3. The condition or character of being male or female; the physiological, functional, and psychological differences that distinguish the male and the female. 4. The sexual urge or instinct as it manifests itself in behavior. 5. Sexual intercourse. 6. The genitalia. — *tr. v.* sexed, sex-ing, sex-es. To determine the sex of (young chickens). [ME < Lat. sexus.]

Zolpidem, 5 mg p. o.
10 January 2013:

Followed by: Farkas RH, Unger EF, Temple R: Zolpidem and driving impairment – identifying persons at risk.
Is there a clinical signal that women are at risk?
NHANES DATA

MEAN WEIGHT (pounds): 130, 140, 150, 160, 170, 180, 190, 200, 190, 168

YEAR
MEAN WEIGHT (pounds)
130
140
150
160
170
180
190
200
190
168

MALE
FEMALE
Editorial

The Seventy-Kilogram Fantasy

Clinical Pharmacology in Drug Development
2(2) 101-102
© The Author(s) 2013
DOI: 10.1002/cpdd.33
Hanley MJ. Clin Pharmacokin 2010; 49: 71-87
\[ t_{1/2} = \frac{0.693 \times V_d}{\text{Clearance}} \]

Drug distribution

Drug elimination
CLORAZEPATE, 15 mg p.o.
(Abernethy: J Pharm Sci 1982; 71:942-944)

MALE, 23 yr, 175 kg (2.26 x IBW)
$t_{1/2}=12.9$ days

MALE, 26 yr, 64 kg (0.93 x IBW)
$t_{1/2}=34.7$ hours
LIMITATIONS OF ANIMAL MODELS

• Different CYP isoforms

• Rodent CYP3A inducible by testosterone

• Different clearance/extraction of substrates
<table>
<thead>
<tr>
<th></th>
<th>CYP3A</th>
<th>CYP2D</th>
<th>CYP2C</th>
<th>CYP1A</th>
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<td>6</td>
<td>8, 9, 19</td>
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<td>Rat</td>
<td>1, 2</td>
<td>1</td>
<td>6, 7, 11</td>
<td>1, 2</td>
</tr>
<tr>
<td>Dog</td>
<td>12, 26</td>
<td>15</td>
<td>21, 41</td>
<td>1, 2</td>
</tr>
<tr>
<td>Monkey</td>
<td>8</td>
<td>17</td>
<td>40, 43</td>
<td>1, 2</td>
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</tbody>
</table>
Biologic Variability to Drug Response: Sex Differences in Clinical Trials
Regulatory Perspective on Subgroup Analysis
Identifying Variability in Response to Drugs

Robert Temple, MD
Deputy Center Director For Clinical Science
Center for Drug Evaluation and Research
Food and Drug Administration

Duke Margolis
Biologic Variability to Drug Response
May 16, 2016
Variability in Response

For reasons that, at least in hindsight, seem obvious, FDA has a long-standing interest in differences among individuals and groups in responses to drug treatment. Such differences, after all, go to the heart of showing that a drug is safe and effective (and in whom).

Presumably, such differences will always result from PK or PD differences. We can, nowadays, virtually always test for and recognize the former fairly easily, but PD differences are often much more difficult, as the mechanism of action of many drugs is not fully known or easily measured or easily translated to clinical outcomes (safety and effectiveness). Individual characteristics that might lead to differential responses therefore might not be anticipated.

A consequence of the uncertainty is that you need to look at important population subgroups within a study to examine both effectiveness and safety, even if no difference is suggested by PK or recognized PD differences.
Because, on a population basis, differences in response among demographic subgroups would have major implications, we have long urged both inclusion and analysis of population subgroups, i.e., age, sex, and race.
The regulation on content of an NDA [21 CFR 314.50] has, since 1998, included a requirement that the integrated summaries of effectiveness and safety include presentation by gender, age, and race and note any needed modifications of dose or dose interval for specific groups.

Guidances long ago discussed at length inclusion of the elderly and both genders

   ICH guidance 1994; Q&A 2010
Long-standing Interest

Guidance and regulations thus have called for broad inclusion of population subgroups and analysis of demographic differences, but they have not specified inclusion expectations or requirements, which has at times been criticized.

- The gender inclusion figures in 1993 proposed gender guidance and subsequent analyses show reasonable participation of both sexes, with lower female participation in cardiovascular drug studies, higher participation in depression and arthritis studies.
- ICH elderly guidance amended in 2010 to urge greater inclusion of people > 75 (previous guidance specified elderly at > 65, plainly not reasonable today, if it ever was).
- Black participation was around 10-12% but has declined as more trials are conducted outside the US.
Broader Interests

In this age of “individualized” treatment, we plainly want to identify demographic and any other subgroup differences, both anticipated and unexpected.

So it is critical to look at a wide range of subgroups. Note that differences can be caused by pharmacokinetic differences (easily detected by blood levels and anticipated from studies of metabolism, clearance, and drug-drug interactions) or pharmacodynamic (differences in response to the same blood levels, more difficult to detect) These can be seen in:

- Demographic subgroups
- Genetically or pathophysiologically defined subgroups
- Other subgroups not easily identified
PK Variability

Nowadays we know a great deal more than we once did about the PK of any new drug, including

- Metabolism & PK of parent and metabolites, as well as the pharmacologic effects of the metabolites.
- Effects of renal and hepatic impairment
- PK consequences of enzyme deficiencies (CYP450 2D6, 2C19, etc) and effects of drug-drug interactions that inhibit or induce metabolic enzymes (fluoxetine, a 2-CYP450 2D6 inhibitor, increases tricyclic levels by 5-fold).
- We know that parent and metabolite can differ significantly, since the terfenadine experience; parent prolonged QT, but was present at low levels; active metabolite (fexofenadine) did not. Became important when CYP450 3A4 metabolism was blocked (ketoconazole).

And we adjust doses accordingly, for reduced renal function (often relevant to elderly), concomitant Rx, missing metabolic enzymes (where it is critical), sometimes body size.
PK/PD

As a general matter, relatively small PK differences, e.g., because of small differences in body size or renal function, would not be expected to be critical, but that depends on the steepness of the C/R relationship and where patients are on it. For drugs on the flat part (plateau) of the curve, small PK differences will not matter.

But for drugs with important toxicity (generally not given on the plateau of the D/R curve), such as cytotoxic oncology drugs, we often dose by weight and adjust for excretory function. For really difficult drugs, both toxic and variable in blood levels, we can even (although rarely) adjust for blood levels.

Less dramatic examples, but pertinent, include two drugs, zolpidem and amlodipine, with reduced doses recommended in women.
PK/PD

1. Zolpidem

Higher blood levels after a 10 mg dose would be expected in women who, on average, are smaller, but initial studies showed no difference in safety of effectiveness.

But a better (more sensitive) PD marker revealed a critical difference. Driving studies showed that the higher morning blood levels more often seen in women would impair driving performance. This led to a lower recommended dose (5 mg vs 10 mg).
2. Amlodipine

Amlodipine, a widely used (in hypertension) dihydropyridine calcium channel blocker, causes dose-related fluid retention (edema), troubling enough to interfere with treatment, as well as other symptoms. There was a clear male/female difference in the principal adverse effects seen in trials.
PK/PD (cont)

• For the NOACs, or at least dabigatran and edoxaban, we have extremely good data relating trough blood levels to the two critical endpoints when NOACs are used to treat AF
  – thromboembolic stroke
  – serious bleeding

We knew that blood levels (translated into INR) corresponded to stroke rates and both intracranial and overall bleeding for warfarin. There is a “sweet spot” of INR 2-3, that optimizes stroke effect without too much bleeding. So the highly variable PK is really managed by assessing a relevant PD effect, i.e., INR.
PK/PD (cont)

- NOACs (cont)

For dabigatran we saw, as for warfarin, that there was a threshold level for optimal stroke effect, about 75-150 ng/ml, with relatively little bleeding. This was clear from the clinical trial RE-LY, where the small difference between the 150 mg and 110 mg doses had a marked effect (28% reduction) on stroke rate because it put almost everyone into a high enough concentration range. On the other hand, some people on 150 mg had blood levels greater than needed for optimal stroke reduction, at a cost of bleeding. And there is not yet any equivalent of an INR. It seems possible that measuring trough dabigatran levels could allow appropriate adjustment.
PK/PD (cont)

NOAC’s (cont)

The most recent NOAC, edoxaban, revealed substantial differences in effect with dose but, in addition, with differences in renal function, with stroke rates greater than warfarin if CrCl was > 95 ml/min. The drug was not approved for the patients with CrCl > 95 ml/min. Moreover, the best results on ischemic stroke were in patients with mild renal impairment (CrCl 50-80), who had higher blood levels. The controlled trial thus showed a striking relationship between renal function and outcome.

These findings reflected the steep C/R curves for stroke and bleeding, making relatively small differences important.
Optimal management of NOACs has been widely discussed. Possibilities have included use of a blood level measurement and adjustment of dose for renal function.
PD Variability

There have been recognized PD (mechanistic) bases for differential response for decades. An obvious one is sensitivity of bacteria to different antibiotics.

A classic case is the greater responsiveness of high renin hypertension (most common in whites) than low renin hypertension (most common in blacks) to drugs that inhibit the renin-angiotensin system (beta blockers, ACEIs, ARBs). Not well understood, interestingly, is the greater frequency of angioedema in blacks with ACEI’s.
The first rule of everything is
You’re almost never quite smart enough

There are therefore cases of population differences where the differences surprise us. They are presumably PD-related, but not for reasons we know (at least not yet). A few illustrations:

- Angioedema appears to be more common in blacks than whites but the increase in risk of angioedema from ACEIs is also greater in blacks. Reichman, et al recently reported this for the Medicare population.
- Alosetron, a drug for diarrhea – predominant IBS appeared to be effective only in women and was approved only for women.
PD, But Not Fully Understood

• Ticagrelor

In the PLATO study of ticagrelor, early analyses showed an effect on CV mortality and non-fatal MI, in all regions but the US. A huge array of covariates were examined but only one mattered. The US/OUS difference was shown to result from the use of higher aspirin doses in the US in about 50% of patients vs 7% elsewhere and ticagrelor’s effect was reduced in people receiving higher dose aspirin. Corrected for ASA dose, results were similar in the US and elsewhere. The reason for the aspirin effect is not known, but the case illustrates how important it can be to examine subsets for possible differences.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Treatment Effect</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Primary Endpoint (100%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Geographic region</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>US (8%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Outside US (92%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>ASA by median dose</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>&gt;=300 (5%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>&gt;100 &lt;300 (6%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>&lt;=100 (83%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Planned Treatment Approach</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Invasive treatment (72%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Medical treatment (28%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Early PCI (&lt;24 hours after randomization)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>No (50%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Yes (50%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Patients undergoing CABG after randomization</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>No (90%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Yes (10%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Diabetes History</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>No (75%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Yes (25%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Prior TIA/Stroke</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>No (94%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Yes (6%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa Inhibitor</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>No (73%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Yes (27%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Age Group</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>&lt;65 years (57%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>&gt;65 years (43%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>&lt;75 years (85%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>&gt;75 years (15%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Male (72%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Female (28%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Race</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Caucasian (92%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Black (1%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Asian (6%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Other (1%)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
</tbody>
</table>

Source: Alison Blaus et al. Circulation. 2015;132:1425-1432

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PD, But Not Fully Understood

- BiDil

Two early VA studies in CHF strongly suggested that there was a response (a strong one) to BiDil only in self-identified blacks and a smaller effect in whites.
There actually was reasonably persuasive evidence that the effect of BiDil in whites was small, at best. There were two previous studies, V-HeFT 1 and 2, that pretty convincingly showed, at best, a much smaller effect in whites.

<table>
<thead>
<tr>
<th></th>
<th>Overall (459)</th>
<th>Blacks (128)</th>
<th>Whites (324)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BiDil</td>
<td>Plbo</td>
<td>BiDil</td>
</tr>
<tr>
<td>Annualized mortality</td>
<td>9.7%</td>
<td>17.3%</td>
<td>16.9%</td>
</tr>
<tr>
<td>RR</td>
<td>0.73</td>
<td>0.34</td>
<td>0.75</td>
</tr>
<tr>
<td>P</td>
<td>0.09</td>
<td>0.004</td>
<td>0.11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Overall (804)</th>
<th>Blacks (215)</th>
<th>Whites (574)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BiDil</td>
<td>Enal</td>
<td>BiDil</td>
</tr>
<tr>
<td>Annualized mortality</td>
<td>12.9%</td>
<td>12.8%</td>
<td>14.9%</td>
</tr>
<tr>
<td>RR</td>
<td>1.23</td>
<td>0.95</td>
<td>1.48</td>
</tr>
<tr>
<td>P</td>
<td>0.08</td>
<td>0.83</td>
<td>0.009</td>
</tr>
</tbody>
</table>
PD, But Not Fully Understood

We therefore allowed a trial in ONLY self-identified blacks, with quite spectacular results.

<table>
<thead>
<tr>
<th></th>
<th>BiDil</th>
<th>Placebo</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=518</td>
<td>N=532</td>
<td></td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>6.2%</td>
<td>10.2%</td>
<td>43% (p=0.012)</td>
</tr>
<tr>
<td>First CHF Hosp’n</td>
<td>16.4%</td>
<td>24.4%</td>
<td>39% (p=0.001)</td>
</tr>
</tbody>
</table>

As noted, we don’t know why BiDil is more effective in blacks, but it clearly seems to be the case.
Conclusion

Experience has shown many subset differences, including many that were not anticipated. Our vast increase in PK information, together with the concentration-response (C/R), modeling information we almost always have, given the routine collection population PK data, enhances our ability to anticipate and detect these. As the workshop materials indicate, these findings do not usually arise from subset analyses of RCTs (although the C/R data comes from such trials and can be detected in PK studies. But not all subgroup findings are predictable and analyses of controlled trials will continue to represent a major source of data to find (or not find) subgroup differences. All such analyses need cautious examination, as there is great multiplicity involved, but they should still be carried out and considered (and then studied, if possible).
Biologic Variability to Drug Response: Sex Differences in Clinical Trials
When To Be Concerned With Sex As A Subgroup

Rita F. Redberg, MD, MSc, FACC, FAHA
Professor of Medicine
Director, Women’s Cardiovascular Services
University of California, San Francisco
Advisor, Women’s Heart Alliance
Disclosures

• Member, FDA Circulatory System Devices Panel
• Editor, JAMA Internal Medicine
• Member, Medicare Payment Advisory Committee
“Most biomedical and clinical research has been based on the assumption that the male can serve as representative of the species. This has been in spite of increasing awareness … [that] women and men differ in their susceptibility to and risk for many medical conditions, and they respond differently to drugs and other interventions. The close of the previous decade saw 8 out of 10 prescription drugs withdrawn from the U.S. market because they cause statistically greater health risks for women.”

— Viviana Simone, Science (June 2005)
Sex and Gender

- Animal models show sex differences; gender difference unique to humans

When should sex be a primary consideration in clinical trial design?

• Assume risks and benefits differ by sex until proven otherwise
• Start with randomized controlled trials
  – Both sexes in proportion to the disease population
• Sex-specific analyses
Heart Disease Differs in Men and Women

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>% Women (mean)</th>
<th>% Women Among Those With Disease</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Artery Disease</td>
<td>29%</td>
<td>46%</td>
<td>AHA</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>23%</td>
<td>52%</td>
<td>ADHERE</td>
</tr>
<tr>
<td>Sudden Cardiac Death</td>
<td>17%</td>
<td>23%</td>
<td>AVID registry</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>39%</td>
<td>55%</td>
<td>AHA</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47%</td>
<td>53%</td>
<td>AHA</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>27%</td>
<td>53%</td>
<td>AHA</td>
</tr>
</tbody>
</table>

AHA indicates American Heart Association; ADHERE, Acute Decompensated Heart Failure National Registry; NHFP, National Heart Failure Project (patients >65 years old); Seattle/King EMS, Retrospective cohort study of all out-of-hospital arrests in Seattle and King County, WA, since 1970s.
Evidence from Research

• Heart disease differs in men and women

• Without sex-specific data efficacy and safety of drugs and devices cannot be determined

• Nonbinding recommendations are not followed consistently enough
Heart Disease

• Women present with similar symptoms to men
• Medical treatment delayed
• Risks and benefits of drugs and procedures differ
  – Bleeding risk higher in women
• Thus, higher mortality after MI with lower health-related quality of life for women
Why Differences? Theories

• Biological differences impact action of drugs: body weight and composition, gastrointestinal tract factors, liver metabolism, and renal function

• Differences affect pharmacokinetics and pharmacodynamics of drugs including drug absorption, distribution, metabolism and elimination
  – Pharmacodynamic differences particularly with cardiac and psychotropic drugs

• Pregnancy, menopause and menstruation may have profound drug effects in humans

Sex Matters for Safety & Efficacy

• Only 51 (41%) of studies had an analysis to address gender bias
• 25% found a difference in safety or effectiveness by sex
• No increase over time in the enrollment of women

Different Treatment Risks

• Aspirin effectiveness similar in men and women
  – But: Evidence of higher risk of GI bleeding

• Women have higher risk of bleeding complications with invasive procedures

• Benefits of Dual Antiplatelet Therapy less in women as compared to men

• Clopidogrel treatment: odds ratio for bleeding higher among women than men
Factors Impacting Bleeding

• Sex differences in bleeding are impacted by an overlapping set of factors

Womenheart Summit 2015 - Strengthen and Enforce Existing Policies

• Hold the NIH, FDA, AHRQ, CDC and private funders accountable for enforcing current policies

• Strengthen NIH and FDA policies to ensure that study results are transparent, available, and include results by sex.

• Enforce FDA regulations to insure that CVD sex-specific data and information on sex differences are required as a condition of approval
Thank You!
Biologic Variability to Drug Response: Sex Differences in Clinical Trials

Session 1b: Determining which subgroups matter

Virginia M. Miller, MBA, PhD
FDA/DUKE
May, 2016
Human karyotype

Female

Male
Every cell has a sex
Hormones

Cholesterol

↑ Testosterone  ↓ Testosterone

↑ Estrogen  ↓ Estrogen

Aromatase
Sex Biasing Factors Across the Life Span
Sex Matters in Physiology and Pathophysiology (and drug development)

Because

Sex specific chromosomes and hormones

There are

Sex differences in response to drugs
Gender influences

- Life style
- Access to care
- Employment
- Drug costs
- Culture
- Geographical location/Urbanization

Biological influences

- Sex
  - Race (species or strain)
  - Age
  - Hormonal status
  - Pregnancy
  - Co-existing conditions

Health, Disease, Treatment, Outcomes
Sex should be a primary analysis
43 year-old woman with newly diagnosed type 2 diabetes

Parents immigrated from Mexico. Mother and maternal grandmother with type 2 diabetes. Mother had a MI at age 45

PCOS diagnosed during infertility evaluation

Gestational diabetes during pregnancy

No follow-up testing until recently when she was told she had diabetes by blood tests
Doctor, What Diabetes Treatment is Best for Me? How do I prevent Heart Disease?

• PCOS
• Personal history of gestational diabetes
• Mexican Hispanic-American
• Family history of diabetes
• Obesity
Sex Differences in Coronary Heart Disease (CHD) with T2D

- 3-fold excess fatal CHD risk in women with T2D compared with nondiabetic women
  - Women with DM (HR=14.74; 95% CI, 6.16–35.27)
  - Men with DM (HR=3.77; 95% CI, 2.52–5.65).

Juutilainen et al., 2004
Survival Post-MI in Diabetic and Nondiabetic Men and Women

Adapted from Sprafka JM et al Diabetes Care 1991;14:537-543.
Heart Disease

• Current recommendations for prevention, diagnostic testing, and medical and surgical treatments of coronary heart disease in women are extrapolated from studies conducted predominantly in men.

• Underrepresentation of women in trials of cardiovascular clinical procedures and therapies and, when women are enrolled, inadequate provision of sex-specific analyses limit ability to define specific benefits and risks experienced by women.
Women with T2D:
27% greater risk of stroke compared to men
Stroke

- Diabetes increases the risk of stroke in women even more than men
- More detailed prospective data are needed on:
  - Relationship between DM and stroke types in women and men,
  - As well as on the effects of DM duration or control on stroke incidence
Peripheral Artery Disease

- Relatively little is known about sex differences in the diagnosis, symptoms, and treatments of DM in combination with PAD
- Women fare worse than men.
- More studies needed to evaluate the sex differences in prevalence of coexisting DM and PAD
Treatments for Claudication:
Cilostazol- Pooled Data on Absolute Claudication Distance

CLZ 100 mg bid vs Placebo

Subgroup
- Male
- Female
- < 65 Years Old
- ≥ 65 Years Old
- Caucasian
- Non-Caucasian
- Non-Smoker
- Smoker
## Subgroup analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity/race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Basic Assumption

Results obtained from experiments using only one sex or material that is unidentified by sex can be applied to both sexes (general population).
Doctor, What Diabetes Treatment is Best for Me? How do I prevent Heart Disease?

- PCOS
- Personal history of gestational diabetes
- Mexican Hispanic - American
- Family history of diabetes
- Obesity

Drug X is effective to prevent stroke and MI in women; and for her daughter with PCOS and gestational diabetes, drug xx will reduce development of diabetes.
Women with type 2 Diabetes: Biological Difference vs Disparities in Treatment?

- Not well understood
- Probably both contribute
- Much more research is needed to evaluate these questions.
Medication and Risk for Cardiovascular Disease

• Women with type 2 diabetes and heart disease have poorer control of both diseases, receive less intensive medical treatment than do men
  • may help explain why death due to heart disease has decreased among men but not women with type 2 diabetes

Gouni-Berthold June 2008

• Many more women will qualify for treatment with statins using newer guidelines
  • all individuals > 40 years with diabetes
“Sex” is a biological construct referring to differences defined by sex chromosomes (XX, XY) and the presence of functional reproductive organs and sex steroids.

“Gender” is a cultural construct referring to behaviors thought to be specified by psychosocial expectations that accrue on the basis of perceived or assigned sex. Wizemann TM, Pardue ML: Exploring the Biological Contributions to Human Health: Does Sex Matter? Board on Health Sciences Policy: Institute of Medicine; 2001.Washington, DC

The Canadian Institute of Health Research defines gender as the socially constructed roles, behaviors, expressions and identities of an individual. Gender influences how people perceive themselves and each other, how they act and interact, and the distribution of power and resources in society (http://www.cihr-irsc.gc.ca/e/47830.html). Gender, as defined by the Gendered Innovations group, is the constellation of socio-cultural processes that interact with and influence human biology (https://genderedinnovations.stanford.edu/what-is-gendered-innovations.html).
Impact of Experimental Design
The effects of the selective poly-ADP ribose polymerase (PARP-1) inhibitor PJ-34 in wild-type (WT) mice of both genders. Treatment with PJ-34 at ischemic onset reduced total infarction in male mice compared with saline-treated controls (* P<0.001). A significant increase in ischemic damage was seen in PJ-34-treated females compared with control (‘ P<0.001).
Biologic Variability to Drug Response: Sex Differences in Clinical Trials
Biologic Variability to Drug Response: Sex Differences in Clinical Trials

Issam Zineh, PharmD, MPH, FCP, FCCP
Office of Clinical Pharmacology
Office of Translational Sciences | CDER | US FDA
May 16, 2016
Critical Path of Informed Decision Making

Development
- Safety
- Efficacy
- Quality

Review
- Benefit
- Risk

Action
- Access
  - Never
  - Ever
  - Yes

Access

Use
- For Whom
- In Whom
- How
The Ultimate Goal

• Anticipating, accounting for, and predicting variability in drug response (safety, efficacy, PK, PD)
  – Anticipating > Accounting > Predicting

• Known (and unknown) sources of variability → key drivers of uncertainty
  – Fundamental to de-risking decisions (drug development, regulatory, clinical)
  – Done routinely (at least for PK*)

• Goal: Knowledge → rational (if not optimal) use of pharmacotherapy in specific patients or subsets

• How this is done
  – Prospective maneuvers based on biological priors (rare for sex)
  – Evaluation in small, dedicated clinical studies (conditioned on a priori understanding of mechanism; rare for sex, common for other IEFs)
  – Population evaluation in large sample set (subgroup analyses on primary endpoints, popPK; common)

* This is extensively done, but clearly a one-dimensional exercise [addresses only one proximal source of variability]
Clinical Pharmacology in Drug Development and Evaluation

Pre-Clinical Phase I Phase II Phase III Phase IV

IND EOP1 EOP2 NDA SNDA

- Chemical, MOA, Safety Characteristics
- Develop Bioanalytical Method
- In vitro metabolism, transporter, & DDI
- In vitro protein binding, cellular/tissue distribution
- Relevant animal/POC
- Target, mechanistic, &/or physiologic biomarker identification
- First in human Dose-ranging studies Early PK/PD
- Early Food-Effect
- Mass Balance
- Food - Effect
- In vivo DDI Extrinsic factors
- Renal/Hepatic Dx Intrinsic factors
- PK/PD & E-R/E-S in target population (TP)
- Dose optimization Mitigation strategies in the TP
- BA/BE
- QTc study
- Genomics
- Pharmacostatistical Modeling & Simulation

Discovery Learn Confirm

“Dedicated” IEF Studies

Advantages
- Feasible
- Reduce noise
- Worst-case scenario
- Empirical
- Well-established
- Can be incorporated into real time development
- Decision support

Limitations
- Small, limited phenotype information
- Highly contrived
- Not systems-oriented
- Often not incorporated into real time development
- Not a nimble “lifecycle” management strategy
“Dedicated” IEF Studies

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- Not a nimble “lifecycle” management strategy
Pharmacokinetic Modeling & Simulation

Mechanistic (Predictive) vs. Explanatory (Empirical)

- Intrinsinc/extrinsic factors:
  - Extrinsic: Drug-drug interactions, Environment, Age, Race, Disease, Pregnancy, Genetics, Others
  - Intrinsic: Medical practice, Regulatory, Alcohol use

- PBPK model components:
  - System component (drug-independent): Lung, Skin, Intestines
  - Drug-dependent component: ADME, PK, PD, MOA
    - Metabolism, Active transport, Passive diffusion, Protein binding, Drug-drug interactions, Receptor binding

- PBPK model:
  - Predict, learn, confirm
  - Individual or combined effects on human physiology

- Clearance distribution
  - Congestive heart failure, The elderly, Healthy males, Healthy females, Smokers, Children
Questions/Issues that Could Inform (Complicate) Recommendations

• What constitutes meaningful difference
  – 2007-2010*
  – 52/69 NMEs had sex-based PK info
  – 73% no sex-differences in PK: 4 reported $\Delta <20\%$; 10 reported $\Delta > 20\%$ (1 $\Delta >40\%$
  – No differences in dosing recommendations (flat E/R; explained by other factors)

• Sex differences in context of other IEFs

• Within-sex differences vs. between-sex differences
  – Data on between-sex differences (e.g., in ADME processes) are not robust
  – Data on between-sex differences on patho-biological processes scant
  – Data on within-sex differences (e.g., pre-, peri-, post-menopausal) also suggestive

* Courtesy Lei Zhang, OCP | FDA
Summary

• Sex as a source of variability should always be considered
• Can be planned for by clinical trial design or by population-based evaluative methods
• The approach likely based on biological priors
• Data interpretation and clinical recommendations multi-factorial
Biologic Variability to Drug Response: Sex Differences in Clinical Trials Workshop

Ruthie Davi, Ph.D.
May 16, 2016
Effectiveness data shall be presented by gender, age, and racial subgroup [21 CFR 314.50 (d)(5)(v)].


FDA Clinical and Statistical Review Templates include sections dedicated to evaluation by age, sex, and race.

FDA Drug Snapshots can be a mechanism to make information more readily available and transparent.
Clear description of product efficacy by subgroup

Focus on transparency

Descriptive statistics

Existing data

www.fda.gov/drugtrialssnapshot
Drug Snapshot Statistical Review

Examines treatment effects overall, within, and across subgroups

• What are the benefits of this drug?
• Were there any differences in how well the drug worked in clinical trials among sex, race, and age groups?

Utilizes the primary efficacy endpoint and analysis

• Incorporate a test for the subgroup-by-treatment interaction
• Appropriately adjust for study when combining studies

Applicant involvement

• Information request
• Integrated Summary of Efficacy
### Statistical Points of Interest

**Should studies with differing populations or doses be combined or analyzed individually?**

- Increased power in subgroups
- Difference in subgroup effects across clinical settings could be missed
- Differences in design and need for appropriate meta-analyses

**Tests for treatment-by-subgroup interaction**

- What does insignificance mean?
- Is it worth considering estimates in subgroups if study is underpowered?

**Multiplicity**

- Consequences of type I error are different
- Consistency in differences in treatment effect across studies
Were there any differences in how well the drug worked in clinical trials among sex, race, and age groups?

The figure below summarizes the primary efficacy endpoint, the mean percent change in LDL-C from baseline to week 24, by sex, age, race, and ethnicity. Data are provided combining the five placebo-controlled trials to allow for the largest possible sample sizes in each subgroup and since comparisons of the treatment effect across subgroups were consistent across trials. Statistical tests assessing whether the treatment effect varied across subgroups are provided.

Figure 4: Difference (95% Confidence Interval) in Average Percent LDL-C Change at Week 24 (Pravulent minus placebo): Trials 1 to 5 Combined (N=3499)

- Sex
  - Males
  - Females

- Age
  - Below 65 years
  - 65 years and above

- Race
  - White
  - Black or African American
  - Asian
  - American Indian or Alaska Native
  - Other

- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino

P-value for statistical test measuring whether the treatment effect differs across subgroups (i.e., p-value for test of treatment-by-subgroup interaction) for studies 1 to 5 combined: Sex: 0.001, Age: 0.14, Race: 0.25, Ethnicity: 0.02

Source: FDA Statistical Review and Evaluation for Drug Snapshot
Existing clinical development programs are sometimes sufficient to understand efficacy results by sex
• Strategically focus resources to development plans that need it.

Even when they are not we should provide descriptive analyses of the data
• Confidence intervals reflect the uncertainty
• Combining studies (meta-analyses) is helpful
• Tests for treatment-by-subgroup interactions are needed
Duke-FDA Biologic Variability Workshop
Impact of Sex Identity on Trial Design & Execution

Rick Sax, M.D.
May 16, 2016

Connect insights
Better outcomes
Superior delivery

Improve your probability of success™
Approaches to sub-group analysis and potential impact

A  Historical Clinical Trial Data
   - US Census + Epi data
     - Does not account for statistical significant of outcomes.
   - Effect size + US Census + Epi data
     - Know outcome could result in smaller sample sizes if trial successful.

B  Clinical Trial Design Stage
   - Assume uniform effect
     - Subgroup population distribution would not impact outcomes.
   - Assume heterogeneity in subgroups
     - Large sample sizes required to have sufficient power to show differences in the subgroups.
   - Unknown Heterogeneity
     - Sample sizes unclear due to a number of potential heterogeneities to test for. Would need complex trial design.

Recommendation

Mirror demographics according to subgroup populations unless prospectively known heterogeneity or If potential effect identified after the fact, address post-market
Impact of sex identity on trial enrollment to meet a U.S. population target

<table>
<thead>
<tr>
<th>Existing Trial Population</th>
<th>Increase in Enrollment Duration (months)</th>
<th>US Target Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 DM</td>
<td>Female: ↑ 1-15 months</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>Alz. Dis.</td>
<td>Female: ↑ 3-5 months</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>CVD</td>
<td>Female: ↑ 4-7 months</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
</tr>
</tbody>
</table>

Each subgroup was modeled separately and thus optimized independent of one another.

Targeting 90% of US Census proportion for a given demographic subgroup.

Enrollment durations reported are based on median enrollment duration upon running 100 simulations per scenario.
Moving from existing trial populations to powering for statistical significance among all subgroups dramatically delays access to new medications.

Impact on Trial Enrollment Duration Based on Subgroup Representation

*Based on Quintiles’ analysis of historic type 2 diabetes mellitus trials simulated through Infosario Design and modeling techniques. Similar trends were found for multiple sclerosis, Alzheimer's disease, and cardiovascular disease.
## Corollaries and unintended consequences of requiring demographic subgroup matching to disease prevalence

### Key Learnings

- Targeting 100% subgroup population matching **markedly** increased enrollment duration*
- Constraining sites to specific targets could have unintended consequences, such as excluding eligible patients from participating in a trial on the basis of demographic characteristics
- Site-level enrollment-rate data is required to effectively model and match subgroups
- Enrollment duration will be longer if existing site list is constrained vs. prospectively optimized
- Start-up and other trial-specific conditions can significantly impact enrollment durations, resulting in high variances

### Conclusions

- Aim to enroll a representative sample of the intended population balancing unmet medical need, scientific rationale, disease-specific information, and practical considerations
- Avoid site-specific quotas and use innovative drug development approaches to generate evidence about meaningful variability in response to medicines
- Develop clear definition of objectives for study populations and use modeling techniques based on site-specific enrollment rates to prospectively address subgroup demographic needs when scientifically warranted

*Target Audience is Sponsor

**Target Audience is FDA**
How to make inference for treatment difference of a relatively small subgroup in clinical trials?

T. Hasegawa (Shionogi), L. Tian (Stanford), B. Claggett (Harvard), J. Schindler (Merck) and L.J. Wei (Harvard U.)
Data from a comparative trial for a specific subgroup

- The general goal for a clinical study is to explore/confirm the overall treatment efficacy/risk for a rather general patient population
- The size of the study was generally determined for such overall comparison (feasible within a reasonable time frame)
- Not enough information for a small subgroup
How to borrow information from male subset to female subset?

• Sex is a very broad “marker” for patients

• Using patient’s baseline covariables, genetic factors, biomarkers (except for sex) to build a “prediction” model for the binary outcome at Month 12 (having event or not)

• Using data from males for this model building
Baseline covariates

1. Age [years]
2. Left ventricular ejection fraction [%]
3. Body Surface Area
4. eGFR (kidney function) adjusted for Body Surface Area
5. Systolic blood pressure [mmHg]
6. NYHA functional class – IV
7. Body-mass index [kg/m²]
8. Never smoker
9. Current smoker
10. Heart rate [beats/min]
11. History of related illness – Hypertension
12. History of related illness – Diabetes mellitus
13. Cause of heart failure – Ischemic
14. Atrial fibrillation
What is the key concept behind?

• If we can collect “enough” genetic factors or biomarkers for patients, we may be able to estimate the variation due to females supplemented with data from males

• Different from biological mechanism of action

• Application to multi-regional studies (global trials), for example, how to make inference for Rx effectiveness for Japanese patients
Other methods for making inferences about Rx efficacy for females

• Combining data from multiple studies to estimate effect for females

• Cross Design Synthesis - Integration of evidence from observational and experimental (RCT) studies to confirm female response rate.
Biologic Variability to Drug Response: Sex Differences in Clinical Trials