

# Sex differences during translational research and clinical drug development: Practical issues

Douglas Feltner, M.D.  
VP, Head of Translational Medicine,  
Pharmacotherapeutics Research Division,  
Pfizer Inc.

Views presented are my own, and not necessarily  
those of Pfizer Inc.

# General Concepts and Practical Issues

- The molecules we work on in drug development are drug candidates, not drugs.
  - We develop information on safety and efficacy of drug candidates with cost and time being important constraints.
  - The drug candidate becomes a drug when we have an approved product label (prescribing information) and approval to market the product.
  - It can cost as much as 1 billion dollars to go from idea to marketed product for one drug.

# Overview of Key Concepts

- Sex differences in animal safety (toxicology) findings
- Need for embryo-fetal development studies in rats and rabbits prior to exposure of fertile women
- Animal behavioral models of efficacy/pharmacology are generally done in male rodents
- Recruitment rate in clinical studies is always a concern

# Toxicology Background

- In animal toxicology studies, rodent and non-rodent animal species are exposed to drug concentrations far in excess of the projected efficacious concentration to identify safety issues that might be of concern in humans.
- Both sexes on animals are included in the IND toxicology studies used to support exposing humans
- Animal toxicology data are used to set a human exposure limit —a drug candidate concentration that we will not exceed in humans.

## Key questions:

- Is the animal toxicology finding reversible and monitorable?
  - E.g. tissue necrosis or cellular hyperproliferation is generally not reversible and monitorable; sedation or changes in HR, BP, QT interval are reversible and monitorable.
- Is there a therapeutic index?
  - Compare plasma concentration for animal safety findings vs projected efficacious concentration

# Toxicology Findings: Sex Differences do Occur

- Not infrequently, animal safety findings differ between males and females
  - The same finding may occur at different exposures in male and female animals
  - A unique safety finding may occur only in male or female animals—sometimes in reproductive organs, sometimes in other organ systems
  - Safety findings may occur at the same exposure in male and female animals, but the associated doses may be quite different due to differences in bioavailability, distribution, metabolism or elimination

# Toxicology Findings: Sex Differences

- Translatability of irreversible, non-monitorable animal safety findings with no projected therapeutic index:
  - usually unknown, because the drug candidate generally will be stopped (an alternative candidate may be advanced if one exists).
  - Safety findings of this type in either sex will generally stop development of a drug candidate for both sexes
- Translatability of reversible, monitorable safety findings is often known.
  - This can provide a bridge for moving to humans despite the higher risk of failure if there is no apparent TI
- Male/female differences in animal safety findings that are reversible and monitorable, and/or have an acceptable therapeutic index are generally not of significant concern in progressing to human exposures

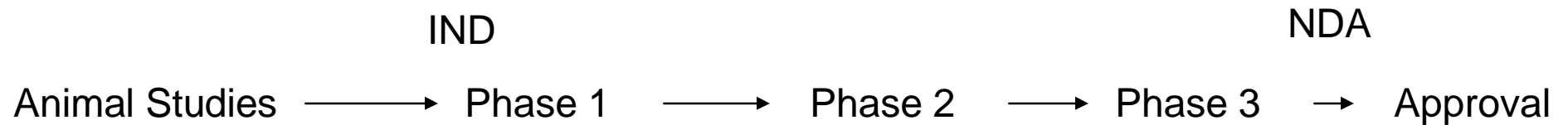
## 14-Day Regulatory Toxicology Study in Rats for an antidepressant drug candidate

Dose (mg/kg)	C <sub>max</sub> (ng/mL) Day 14 M/F	AUC <sub>(0-24)</sub> (ng·hr/mL) Day 14 M/F	TI* (Based on AUC) M/F	Observations
15	71 / 32	654 / 139	1-1.5x / <1x	NOAEL
50	675 / 175	9850 / 2100	16-23x / 3.5-5x	<ul style="list-style-type: none"> <li>• Muscle degeneration/necrosis (females)</li> </ul>
150	1470 / 667	25500 / 7010	43-59x / 12-17x	<ul style="list-style-type: none"> <li>• Myocardial necrosis in males;</li> <li>• Skeletal muscle degeneration/necrosis in males and females</li> </ul>

# Translating Efficacy (or Pharmacology) Data

- Most neuroscience animal behavior assays are done in male rats (or mice)
  - Reduce variability (and thus sample size ) for signal detection
  - Male/female efficacy differences are generally not explored in animals
- Successfully matching novel targets to the right patients is a major problem for neuroscience discovery
  - Activity in animal models too often does not translate to efficacy in a patient population
  - Would studying both male and female animals help with this problem?

# Phases of Drug Development



Phase 1: Initial small studies in healthy volunteers to determine PK, initial safety and tolerability; mechanistic activity; MTD

Phase 2: Phase 2a—determine whether drug candidate has efficacy in patients; initial safety information in patients

Phase 2b— confirm efficacy , expand safety information; refine dose for phase 3

Phase 3- Larger efficacy/safety studies in patients to demonstrate safety/efficacy at Dose expected to be in the label; all clinical studies needed to provide prescribing info

# Reproductive Toxicology

- IND toxicology is completed prior to doing reproductive toxicology
  - Therefore, reproductive toxicology won't be available at the start of phase 1
- Reproductive toxicology (RT) generally consists of a package of four types of studies
  - Embryo-fetal development in rats and rabbits (maternal and fetal toxicity)
    - Completed prior to exposing women of childbearing potential
  - Female fertility and early embryonic development study; Male fertility study
    - Completed prior to phase 3 clinical trials
  - Pre- and postnatal developmental toxicity study
    - Completed prior to New Drug Application
- Embryo-fetal development studies are usually completed shortly prior to phase 2a, in order to allow for adequate patient recruitment and to have a more representative population, but depends on indication
  - Depression/anxiety disorders-yes; schizophrenia-usually; Alzheimer's disease-no

# M:F Inclusion in Clinical Trials

- Typical M/F subject ratios in Phase 1 First-in-Human and Multiple Dose Tolerance studies
  - Embryo-fetal toxicology not yet done
  - Males predominate
  - Women of non-child bearing potential can participate
  - Inclusion/exclusion guidance provided in protocol on including women of non-childbearing potential
    - Postmenopausal (2 yrs), hysterectomy, tubal ligation, oophorectomy
- After embryo-fetal developmental toxicology is done, M:F ratio is whatever is recruited, which would be typical for the disease being studied, except actual recruitment may have slightly more males than the epidemiology would predict
  - Reason(s) unknown (Barriers to participation?)
  - Pregnant/lactating women still excluded; appropriate contraception required

# Assessment of M/F differences In humans

- Phase 1 (Healthy Volunteer) Studies
  - Differences in tolerability related to M/F exposure differences and sometimes to unexplained differences occasionally occur
  - Careful PK characterization allows for understanding M/F differences in exposure by dose; but small sample size and HV population give limited information on differences in tolerability, no information on efficacy

# Phase 1: Safety and Tolerability Difference Example

<u>Dose</u>	<u>Male</u>	<u>Female</u>
50 MG BID	Tolerated	Tolerated
100 MG BID	Tolerated	MTD
150 MG BID	Tolerated	Abd. Pain, Nausea
250 MG BID	MTD	--

MTD = Maximum Tolerated Dose;

# Assessment of M/F differences In Phase 2/3

- Phase 2/3
  - Drug-Drug Interaction effects of concurrent medications (hormone replacement; breast CA drugs; BPH or prostate/testicular CA drugs) need to be considered and sometimes studied
  - Assess M/F efficacy by study—baseline covariate in ANCOVA model; start of Population PK modeling;
- New Drug Application (NDA) submission:
  - Typically gender effect on exposure examined in population PK analysis across studies;
  - PKPD model built as data accumulates; efficacy and common adverse events are related to exposure or dose by gender; findings used to support dosing recommendation

# Label Example

- Information on gender differences can end up in the drug label
- Zoloft® (sertraline) for PTSD:
  - “Post-hoc exploratory analyses revealed a significant difference between ZOLOFT and placebo on the CAPS ... in women, ... but essentially no effect in the relatively smaller number of men in these studies. The clinical significance of this apparent gender interaction is unknown at this time.”

# Duloxetine Gender Difference in PK Example

- From the FDA clinical pharmacology review:

## **Is there an effect of gender on duloxetine pharmacokinetics?**

Women have higher exposures than men and exposures are on average 2 fold higher. This greater exposure cannot be explained simply on the basis of weight, nor can it be normalized to body size or mass, but is probably largely due to lower expression of CYP1A2 in women, with a possible contribution from the higher protein binding (lower free fraction) in women. In several phase I studies women had a higher incidence of adverse effects compared with men.

- From the drug label (Prescribing information)

## **Special Populations**

Gender — Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

### **Special populations:**

*Gender:* pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximately 50% lower in females). Based upon the overlap in the range of clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

# Accutane Prescribing Information

**ACCUTANE®**  
(isotretinoin capsules)

R<sub>x</sub> only

**CAUSES BIRTH  
DEFECTS**



**DO NOT GET  
PREGNANT**

## **CONTRAINDICATIONS AND WARNINGS**

Accutane must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking Accutane in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. There are no accurate means of determining whether an exposed fetus has been affected.