

Clinical Discussion of Specific Populations

Su-Young Choi, Pharm.D., Ph.D
Office of Clinical Pharmacology, Division 4
Office of Translational Sciences
Center for Drug Evaluation & Research

FDA Clinical Investigator Training Course
November 14, 2018



Disclaimer

- The opinions contained in this presentation are my own and do not necessarily represent the views of the FDA.

Specific Populations

- Women
- Pregnant/lactating women
- Pediatrics
- Geriatrics
- Patients with organ dysfunction

One Size Does Not Fit All



Study Subject Demographics

Demographic Factor	Phase 1 subjects	Phase 3 patients	Real-life patients
Age	Usually 18-65	Higher % of older patients (>65 yr)	Can be more variable/ heterogeneous
Pregnancy	Excluded	Excluded	
Race/ethnicity	Not diverse	↑ diversity but still many studies are not well diversified	
Renal/Hepatic Function	Normal	Often have at least minor degrees of impairment	

Women

- Women appear to be more sensitive to QT interval prolongation following anti-arrhythmic drug administration.
- Disease progression can also manifest differently between men and women (e.g., multiple sclerosis).
- Women tend to have a lower body weight, higher percentage body fat, and lower plasma volumes than men. Differences in body composition also influence the absorption and distribution of drugs.

Ambien[®] (zolpidem tartrate) in Women

- Sleeping aid, approved in the U.S. in 1992
- FDA Med Watch Safety Alert (2013)¹

“Lower Doses Recommended for Sleep Drugs— Especially for Women

- **Risk:** New data show that blood levels in some people who take zolpidem may be high enough in the morning after use to impair activities that require alertness, including driving. This risk is highest for people who take products containing extended-release zolpidem. Women are especially vulnerable because zolpidem is cleared from the body more slowly in women than in men

¹<http://www.fda.gov/forconsumers/consumerupdates/ucm340655.htm#2>

Pregnant Women

- Percentage of pregnant women on prescription medications
 - Estimates vary (30-90%)
 - Use of medication is recommended for certain diseases
 - Example - all pregnant women living with HIV should receive antiretroviral drugs, initiated as early in pregnancy as possible, to prevent perinatal transmission regardless of plasma HIV RNA copy number or CD4 T lymphocyte count
- Pregnant women are often excluded in premarketing clinical trials
- Ethically justifiable to include pregnant women (45 CFR subpart B) in clinical trials
 - Should be justified based on benefit vs. risk assessments
 - Nonclinical studies (including pregnant animals) have been completed
 - Clinical studies have been conducted (including nonpregnant individuals)

Pregnant Women

- Drug concentrations, responses to drug therapy, and disease progression can be altered during pregnancy
- Physiological changes during pregnancy
 - Changes in body weight and body fat composition, increase in blood volume, altered gastrointestinal motility, increase in glomerular filtration rate
- An approved dose for nonpregnant patients may not be optimal for pregnant patients
 - Example – Darunavir/cobicistat (Prezcobix®), an HIV drug
 - Use of darunavir/cobicistat is not recommended during pregnancy because of substantially lower drug concentrations in pregnant women as compared to non-pregnant patients → potentially result in loss of efficacy and development of viral resistance.

Lactating Mothers

- Drugs can be transferred to infants from mothers by breastfeeding
 - It can result in unintended exposures of drugs to infants
 - Infants may not eliminate drugs efficiently or may be more susceptible to the drug's side effects
- Example
 - A case report of the death of a breastfed infant whose mother took codeine
 - The women had a genetic makeup that allowed rapid conversion from codeine to morphine
 - The baby received a lethal dose of morphine through breastfeeding
 - FDA issued a public health advisory in 2007
 - Use of codeine by some breastfeeding mothers may lead to life-threatening side effects in nursing babies. When prescribing codeine for a nursing mother, doctors should prescribe the lowest dose for the shortest amount of time to relieve pain or cough.

When to conduct a Clinical Lactation Study?

- Clinical lactation studies are useful in the following situations:
 - A drug is known/expected to be used by women of reproductive age
 - A new indication is being sought for an approved drug and there is evidence of use or anticipated use of the drug by lactating women
 - Marketed medications that are commonly used by women of reproductive age (e.g., antidepressants, antihypertensives, anti-infectives, diabetic and pain medications)

Clinical Study Design Considerations for Lactating Women

- Mother-Infant Pair Design
 - Determine the PK of the drug in lactating women
 - Determine the amount of drug transferred into breast milk
 - Show effects of drug on milk production and composition
 - Assess drug exposure and PD in the breast-fed child
- Lactating Women Only Designs
 - Plasma and milk
 - Milk only
- Other Design Considerations
 - Longitudinal or multiple arm design
 - Study participants, controls, sample size, etc

Pediatrics



- Definition of pediatric patient
 - Labeling regulations for prescription drug: 0 to 16 years old
 - Clinical trials: children refers to persons who have not attained the legal age for consent
- Children are not small adults!
 - Dynamic developmental physiology
 - Drugs may be handled differently
 - Absorption, distribution, metabolism, and excretion are different as compared to adults
 - Certain adverse events may be more concerning for children
 - Example – drugs inhibiting bone growth
 - Longer life expectancy

Pediatrics

- Lack of pediatric use information poses significant risks for children
- However, conducting a clinical trial in pediatric patients is challenging
 - Ethically, scientifically, and clinically challenging
- Various approaches to stimulate pediatric clinical trials have been put in place over the past 20 years such as BPCA and PREA.

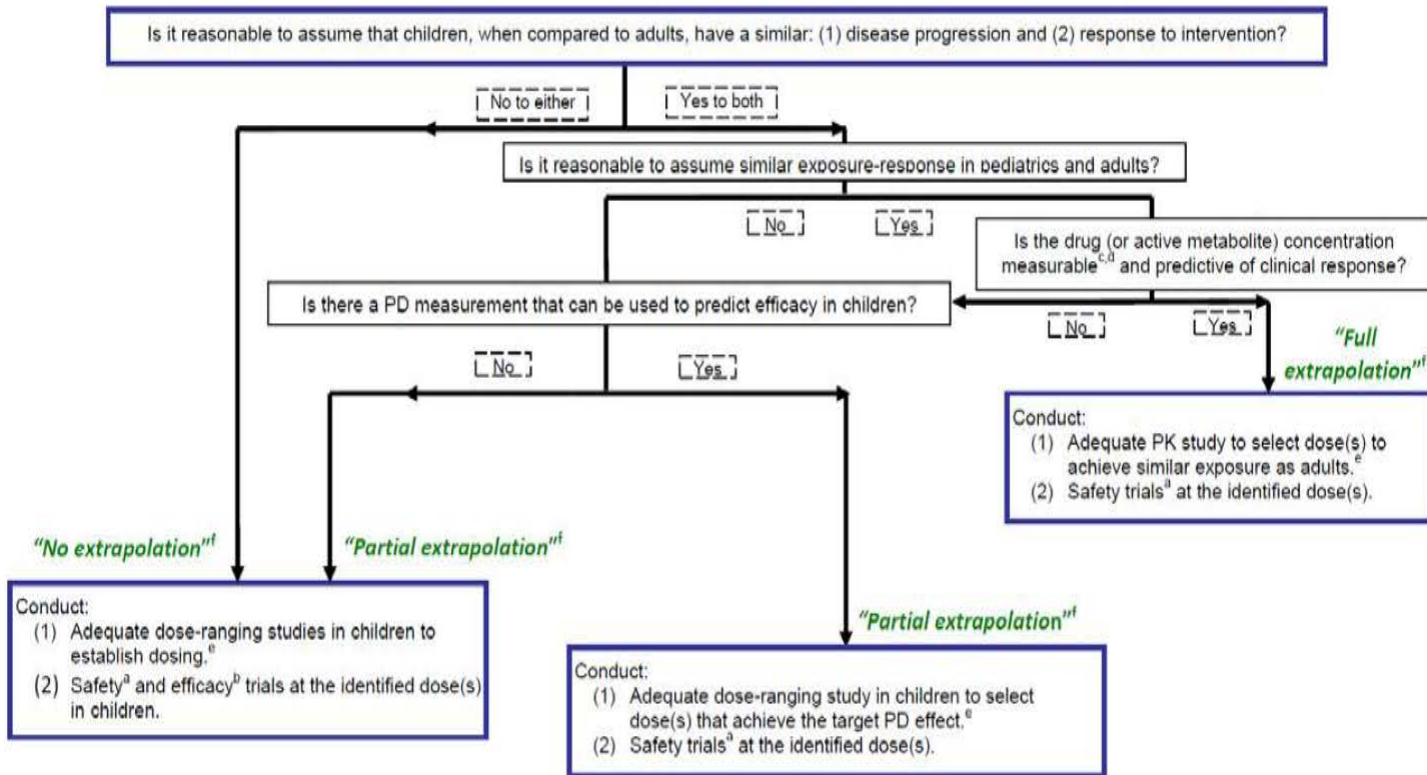
PREA and PBCA

- Pediatric Research Equity Act (PREA)
 - Requires companies to assess safety and effectiveness of new drugs in pediatric patients
 - Exemption, waiver, or deferral are available under certain circumstances.
- Best Pharmaceuticals for Children Act (BPCA)
 - Provides a financial incentive (additional 6 month exclusivity) to companies to voluntarily conduct pediatric studies

Approaches to Pediatric Studies

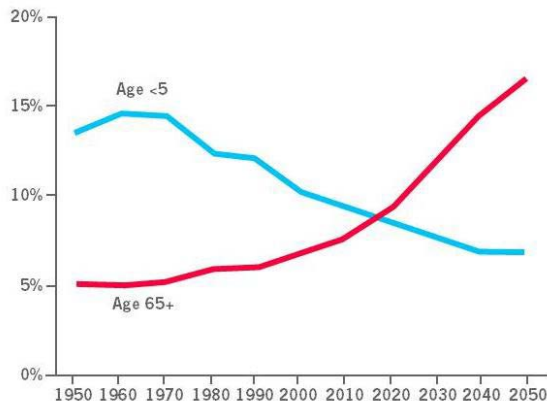
- Depending on what we know about disease progression, response to intervention, and exposure-response relationship...
 - PK only approach (i.e. full extrapolation)
 - Conducting a PK study to select dose to achieve similar drug exposures as adults + safety assessments
 - PK/PD approach (i.e. partial extrapolation)
 - Conducting an adequate dose-ranging study to select doses that achieve the target PD effect + safety assessments
 - PK/efficacy approach (i.e. no extrapolation)
 - Conducting and adequate dose ranging studies to establish efficacy/safety

Pediatric Study Decision Tree



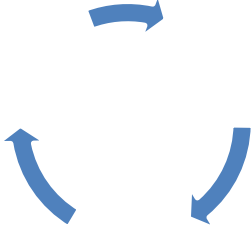
Geriatric Population

- Many age cutoffs to delineate this group, but most in need of special considerations are > 70 years
- Often times, a limited number of subjects are enrolled in Phase 3 trials (i.e., under-representation of the patient population)



Source: United Nations. World Population Prospects

Major Organ Functions in Geriatric Population

- Renal Function
 - Declines with age
 - Higher systemic exposure of drugs
 - Host Defense
 - Diminished cell-mediated immunity
 - ADME
 - Altered absorption due to gut motility
 - Liver function
 - Higher systemic exposure
 - CNS Function
 - Declines with age
 - Physical effects (balance, hearing)
 - Psychological effects
- 

May result in altered drug concentrations and altered sensitivity to drugs

Organ Impairment

- Kidney and Liver → the two major organs responsible for drug elimination from the body
- Subjects with impaired kidney or liver function → may have higher drug exposures and require different dosing regimens
- Example
 - Lamivudine (an antiviral drug that is renally eliminated)
 - Drug concentrations are significantly higher in subjects with renal impairment as compared to subjects with normal renal function. Therefore, doses should be reduced based on renal function

Creatinine Clearance (mL/min)	Recommended Dosage of EPIVIR
≥50	150 mg twice daily or 300 mg once daily
30-49	150 mg once daily
15-29	150 mg first dose, then 100 mg once daily
5-14	150 mg first dose, then 50 mg once daily
<5	50 mg first dose, then 25 mg once daily



Scientific Advances in Specific Population Research

- Application of modeling and simulation
 - Inform design/conduct of clinical studies
 - Improve drug development efficiency
- Advances in PK sampling (e.g. dried blood spots)
 - Reduce invasiveness and blood volume (robust PK studies)
- As science grows so will our understanding of benefit/risk of a medication in specific populations



U.S. FOOD & DRUG
ADMINISTRATION