Risk and Benefit Assessments for Optimal Dose Selection Based on Exposure Response

2003 FDA/Industry Statistics Workshop

Peter I. Lee, PhD
Associate Director, Pharmacometrics
OCPB, CDER, FDA

Disclaimers

- No official support or endorsement of this presentation by the FDA is intended or should be inferred.
- My remarks today do not necessarily reflect the official views of FDA.
- All examples in this presentation are masked.

What is the "Right Dose" ?

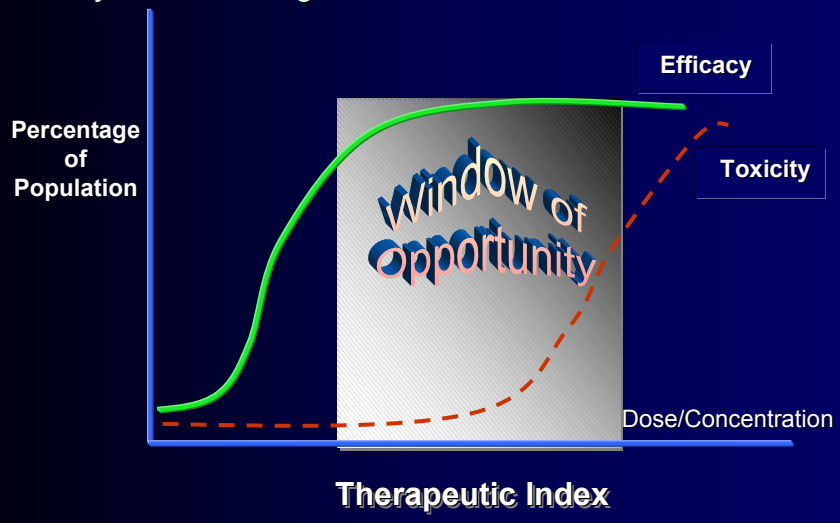
- OCPB/FDA Mission Statement, 2000 Retreat:
  - Right Dose, Right Drug, Right Time
- Hierarchy of "Right Dose" (Right Patient)
  - Population based
  - Special population
  - Individualization
- Risk/benefit ratio

Common Limiting Factors to "Dose Optimization" (other than risk/benefit)

- Formulation
- Preclinical Pharmacology & Toxicology
- Phase I maximum tolerance dose (MTD)
- Patient convenience (i.e. regimen)
- Efficacy of other competitors
- Statistical power of E/S trials

Key Information for Dose Optimization

- Objective: To do good without harm



Selecting 'Right Doses' with Exposure-Response (ER Guidance, April 2003)

- Support dose adjustment in 'special populations'
  - Standardized approach proposed at CPSC
  - OCPB GRP MaPP
- Optimize dose selection
- Support efficacious and safe doses (entire population)
  - NDA examples
  - More efficient review and drug development

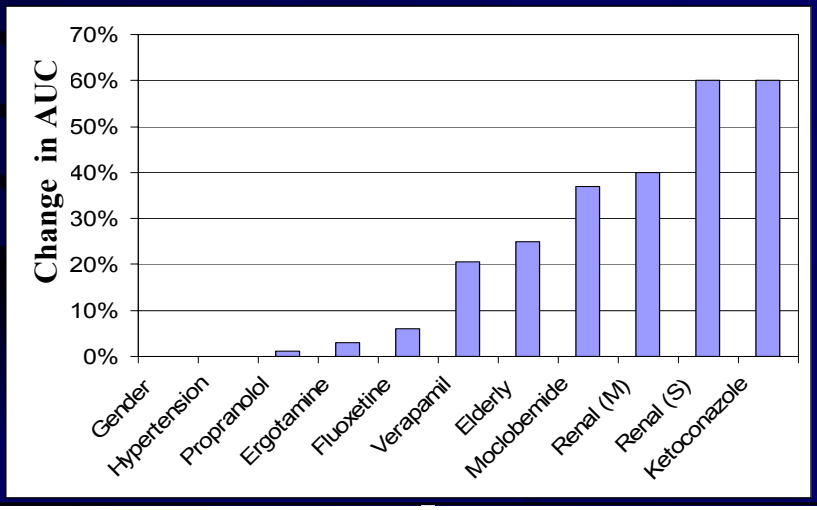
The First Topic

- Support dose adjustment in special populations
  - Standardized approach proposed at CPSC
  - OCPB GRP MaPP
- Optimal dose selection
- Support efficacy and safety
  - More efficient review and drug development
  - NDA examples

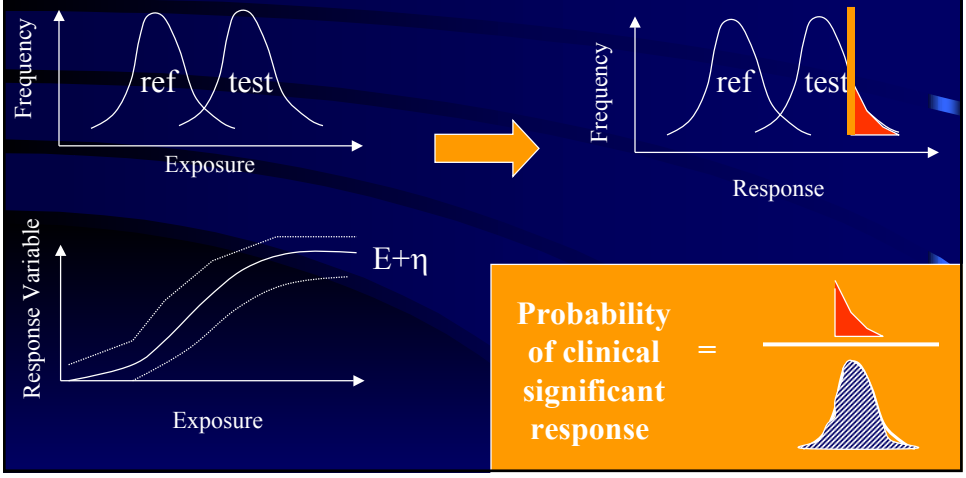
Quantitative Risk Analysis Using ER for Determining Dose Adjustments in Special Populations

- NDAs may contain up to 20 or more special population and DDI studies.
- Intrinsic/extrinsic factors result in increases or decreases in drug exposure due to change in pharmacokinetics.
- Need a consistent approach to determine dosing adjustment in special populations.

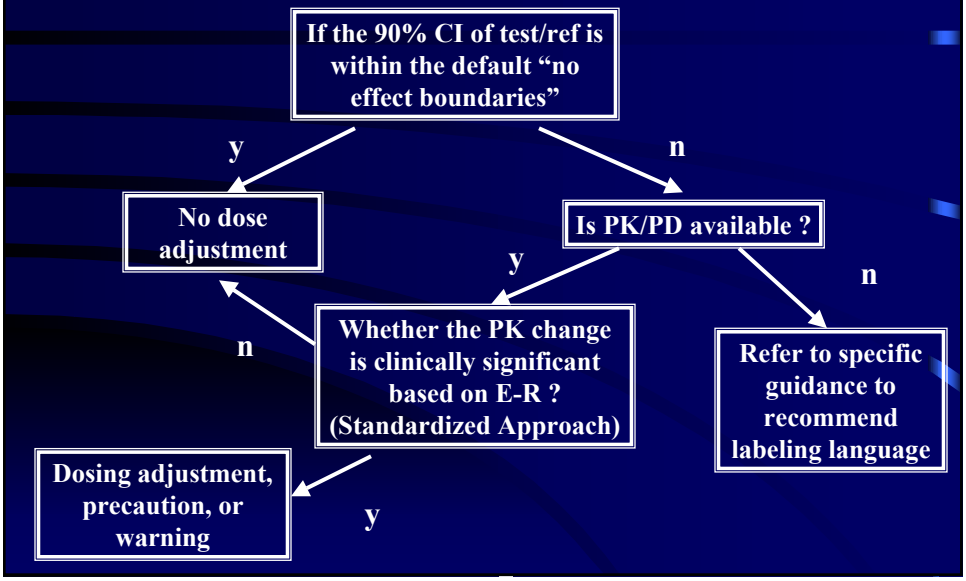
An Example of Changes in Drug Exposure in different populations: What is the right dose ?



A Standardized Approach: Estimating the Probability of Response (CPSC)



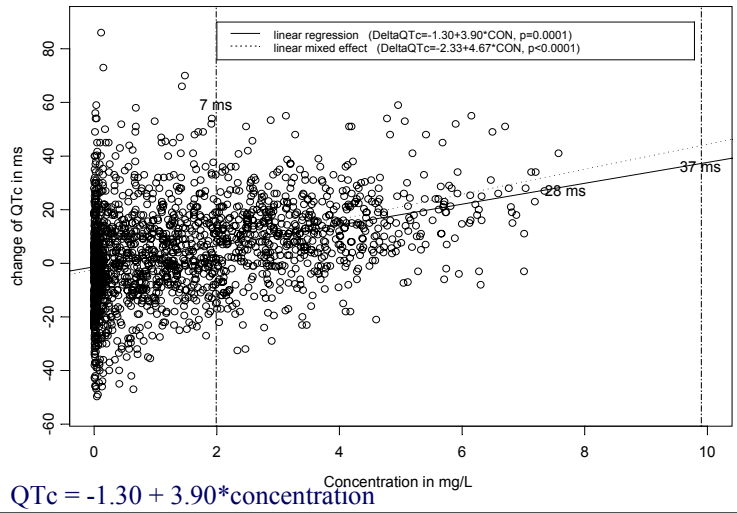
Decision Tree for Dosing Adjustment Recommendations (CPSC Advisory Mtg)



Example: Anti-infective Drug A

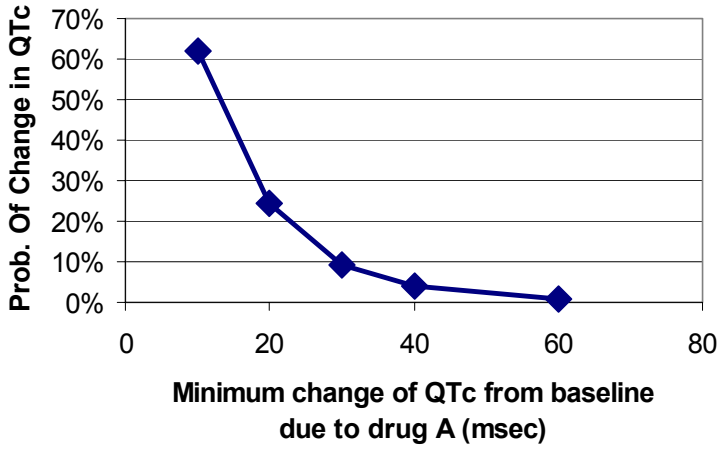
- Intrinsic factors
  - Special populations
    - 100% increase in elderly
    - 40% increase in mild/severe renal impairment
- Extrinsic factors
  - Drug-drug interactions
    - Ketoconazole causes 95% increase in AUC

Delta QTc vs Concentration by Linear and Linear Mixed-Effects Model

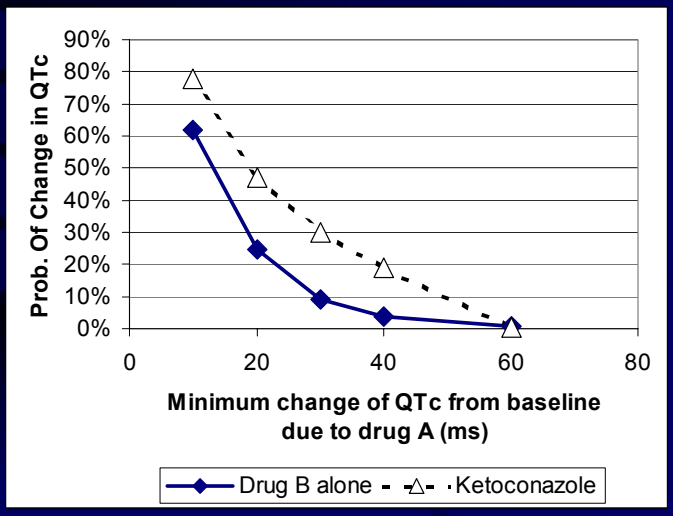


QTc = -1.30 + 3.90*concentration

'Probability' of QTc Change in the Elderly due to Plasma Concentration of Drug A Alone at Clinical Dose



‘Probability’ of QTc Change in Elderly due to Drug B and Ketoconazole Interaction



The Second Topic

- Support dose adjustment in special populations
  - Standardized approach proposed at CPSC
  - OCPB GRP MaPP
- Optimal dose selection
- Support efficacious and safe doses (entire population)
  - NDA examples
  - More efficient review and drug development

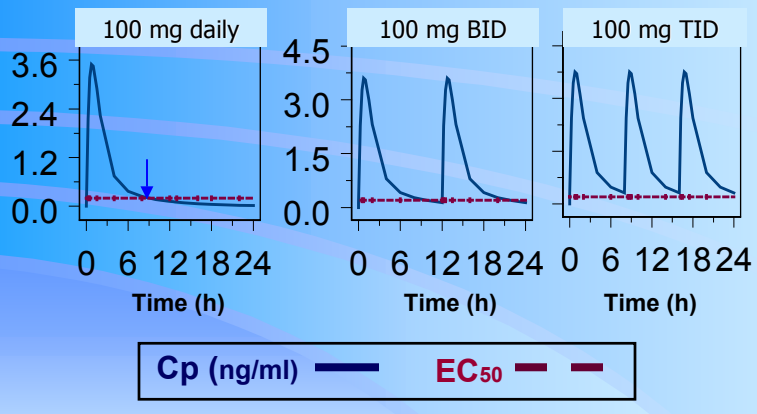
How Does ER Support E/S ?

- A common reason for FDA "non-approvable" or "approvable" decisions: sub-optimal doses that cause toxicity or lack efficacy
  - ER can help optimize the dose regimen selected in the phase III clinical trials.
  - Support optimal dose selection in typical patients and special populations to balance risk and benefit of drug therapies.
- ER can help reducing review time and cycles.
  - Provide evidence for efficacy and safety and/or obviate the need for lengthy and costly clinical trials.
- CTS applying ER can help design clinical trials

Risk of No Benefit - Drug B

- Cardio-vascular Division
- Short pharmacokinetics half-life and immediate response
- But, the sponsor proposed a QD regimen
- A simulation based on conc-response model (built on phase II data) showed effectiveness only in the first half of the QD regimen

Simulation of Dosing Regimens: Time Above EC_{50}



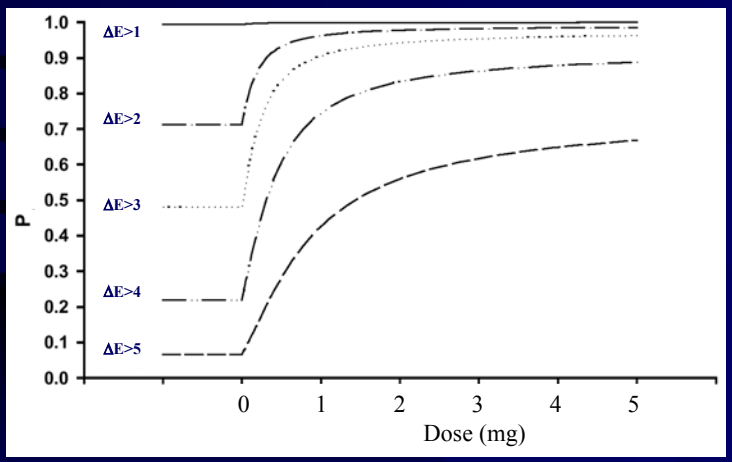
FDA Reviewer's Recommendations

- "There are inadequate data on dose response". Before approval, "It will be necessary to explore the appropriate inter-dosing interval, … such as BID …"
- 'Lesson' learned: Early meetings between the sponsor and FDA to discuss the exposure-response data and dose selection would have avoided conducting efficacy/safety trials at an ineffective drug regimen.

Optimal Dose Selection - Drug C

- Division of Reproductive/Urologic
- One dose (4 mg) was proposed in the initial NDA
- Unexpected AE observed in a significant number of patients of the phase III trials
- Based on a PK/PD analysis, two low (1, 2 mg) doses were only slightly less effective than the proposed dose

Dose Response (Efficacy) Relationship



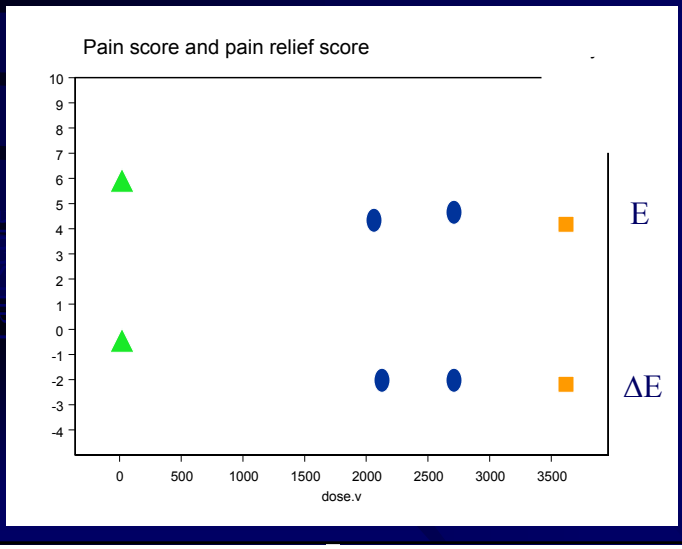
FDA Reviewer's Recommendations

- A PK/PD analysis showed that a lower dose (2 mg) was only slightly less effective than the proposed dose
- The ED50 of two primary endpoints were 0.6 mg
- The two lower doses (1 & 2 mg, rather than the initially proposed 4 mg) were approvable
- Additional data on the lower doses, such as CMC, were needed for the final approval.

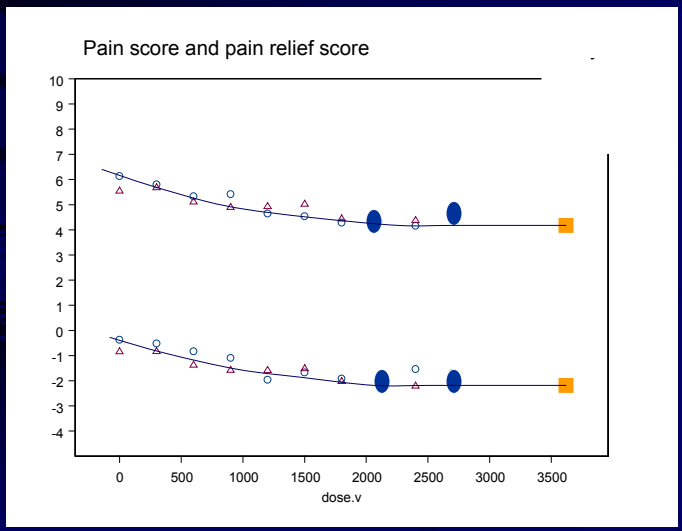
Confirmatory Evidence - Drug D

- Div. of Anesthetic/Critical Care/Addiction
- Two phase III studies were conducted at three different doses
- The review Division were considering the need of additional 'duplicate' studies to support the efficacy.
- The FDA reviewer conducted exposure-response modeling to bridge the effectiveness at the three doses

Three Different Doses from Two Pivotal Trials



Cross-validation of Efficacy Between the Two Pivotal Trials



FDA Reviewer's Recommendations

- Exposure-response modeling bridged the effectiveness at the two doses
- No additional confirmatory clinical studies were needed for approval
- Approved: "Pharmacokinetic/ pharmacodynamic modeling provided confirmatory evidence of efficacy across all doses"

Conclusions

- ER can facilitate the dose selection process (both drug development and regulatory review)
  - minimize uncertainty and reduce the review cycle
    - justify dose selection
    - support efficacy and safety
    - more complete NDA package
  - sometime reduce the need for large clinical trials
  - optimize phase III study designs
- Early interactions between sponsors and FDA during drug developments on dose selection strategy may be critical

Mission and Vision

"The Right Dose of the Right Drug at the Right Time for the Right Patient"