Phase I: Types of Studies

1. Dose escalation tolerance
    a. Surveillance for expected and unexpected but lethal toxicities
    b. Define acceptable maximally tolerated dose
    c. Starting dose relative to NOAEL or LD10 in animal studies
    d. Escalation up to 2X per step dependent upon disease severity
    e. 3-6 per cohort

2. Pharmacokinetics
    a. Vd, Cl, k (t1/2)
    b. Characterize dose and time dependencies or non-linearities
        i. First order versus mixed order?; autoinduction?
    c. Compare single and multiple doses
        i. PK curve, up to 12 time points,
        ii. Blood and urine assayed for drug
        iii. Compartmental or non-compartmental models

3. Bioavailability
    a. Only important if 2 formulations available
    b. IV and oral PK curve; calculated AUC IV: AUC PO ratio = F

4. Radiotracer
    a. Mass balance, elimination, elimination
    b. Only needed if most of drug not accounted for in blood and urine
    c. May be helpful with significant first pass metabolism
        i. Compare parent/metabolite ratio by different routes

5. Delivery systems
    a. Start studies with system likely to have best bioavailability (F)
    b. Food effect?
    c. Methods: PK paired analysis of individuals receiving both dosage forms or with/without food

6. Special populations
    a. Dysfunction with elimination systems
    b. Disease which alters distribution
    c. Genetically determined drug metabolism
    d. Methods: PK/AE comparison to historic controls

7. Drug interactions
    a. Expectations of common use with other drugs for same therapeutic category
    b. Expectations of uncommon use but theoretical reason for dangerous interaction
    c. Method: steady-state PK curves Drug A, Drug A + Drug B, Drug B

8. Suitability of animal model
    a. Above study types generate data to evaluate suitability of animal extrapolation
    b. Cmax, Cmin, Css, AUC, protein binding, plasma: rbc ratio
    c. Did animals get comparable concentration to predict toxicity?
    d. Examine factors that change concentration at target site
    e. Metabolite in man, not seen in animals?