Bioavailability and bioequivalence

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Subject: Biopharmaceutics & Pharmacokinetics (BP 604T)
Topic: Bioavailability and Bioequivalence

Objectives

- Discussthe pharmacokineticprocesses that determine absolute bioavailability
- Discuss the basic FDA requirements for approval of ANDAs submitted by generic drug manufacturers
- Discuss the basic study methods for bioequivalence
  - Study design
  - Statistical analysis

Bioavailability (F)

- "Rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action"
- AUC (total amount of unchanged drug that reaches the systemic circulation) is used to calculate F

$$\text{absolute } F = \frac{\left(\text{Dose}_{IV} \times \text{AUC}_{oral,\infty}\right)}{\left(\text{Dose}_{oral} \times \text{AUC}_{IV,\infty}\right)}$$

Factors that affect F

- Physical or formulation properties (molecular weight, polarity, dissolution rate, stability in gastric acid)
- Gastric emptying rate
- Metabolism in intestinal wall (CYP3A4)
- Drug efflux from intestinal wall (Pgp)
- Hepatic first pass metabolism

Bioequivalence

- "Absence of a significant difference in the rate and extent to which the active ingredient or active moiety in *pharmaceutical equivalents or pharmaceutical alternatives* becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designedstudy"

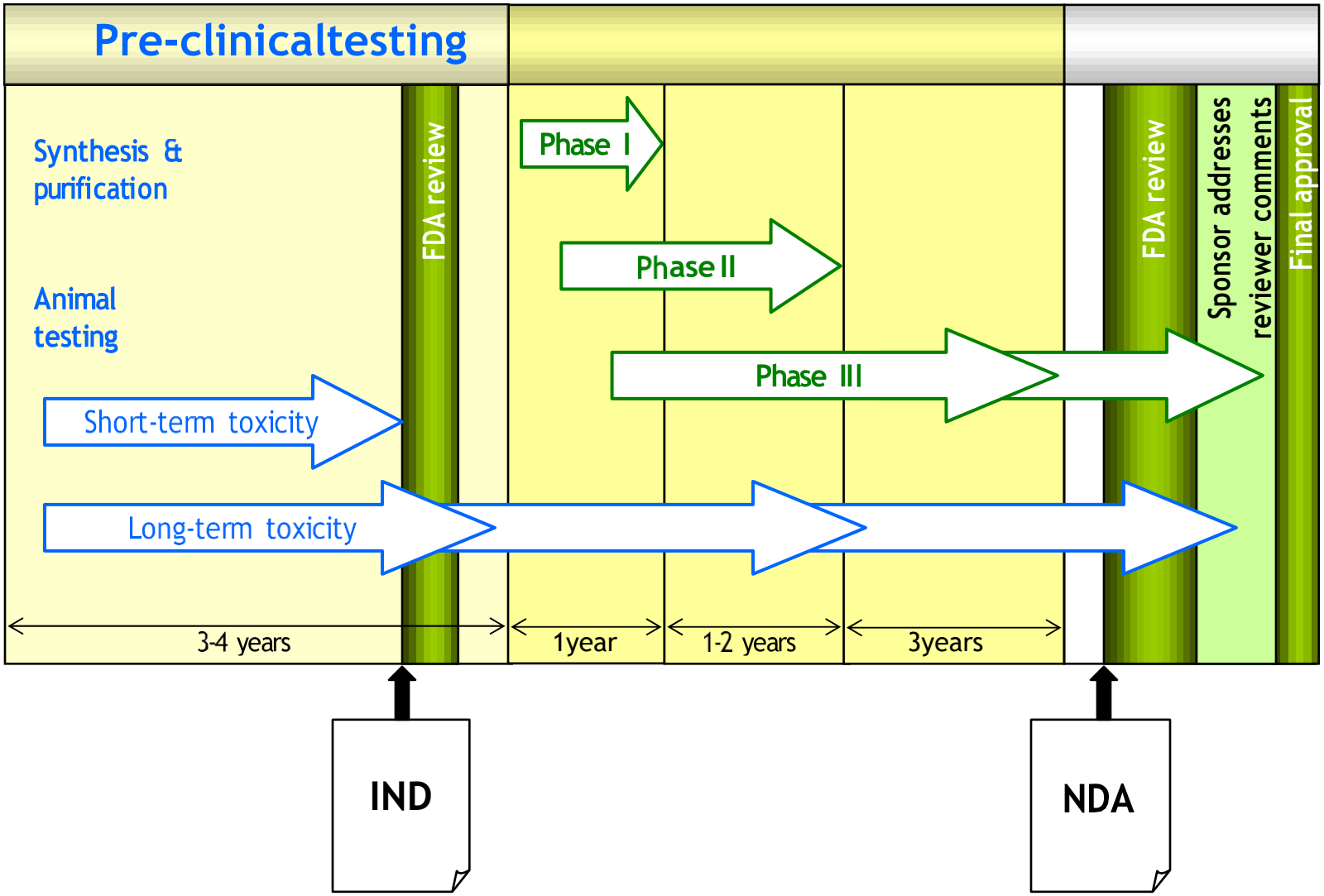
Definitions

- Pharmaceutical alternatives
  - Same activeingredient
  - May differ in salt, ester, dosage form or strength
  - *Example: different dosage forms or strengths within a single manufacturers' product line*
- Pharmaceutical equivalents
  - Sameactiveingredient, dosageform and strength
  - Same USP standards (strength, quality, purity, identity)
  - May differ in shape, color, excipients, release mechanism, packaging, labeling and expiration date
  - *Example: brand name and generic version of a drug*

Therapeutic equivalents

- Defined by the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act)
  - Permits pharmaceutical equivalents to be considered "therapeutically equivalent" (will have the same clinical effect and safety profile)
  - Allows generic manufacturers to gain FDA approval via ANDA *(abbreviated NDA)* submission
  - ANDAs do not include pre-clinical data or proof of safety / efficacy; *only have to prove bioequivalence*

Normal drug approval process



Investigational new drug (IND)

- Under the Federal Food, Drug & Cosmetic Act no drug can be distributed across state lines prior to final FDA approval
  - IND grants an exemption to the sponsor in order to conduct clinical trials
  - Three types: Investigator IND, Emergency Use IND, Treatment IND
  - Must include: (1) animal pharmacology/toxicology; (2) manufacturing information; (3) detailed clinical testing plan (protocols/investigator qualifications)

NDA

- Submitted after clinical testing; must include:
  - "Substantial evidence" of safety and efficacy (results of both animal and human testing)
  - Proposed labeling, package insert
  - Proof of adequate "Good Manufacturing Practices" to maintain USP standards for drug identity, strength, quality, and purity
  - Duration of FDA review
    - Regular review must be completed within 12 months
    - Fast-track review is completed within 6 months

ANDA (generic drugs)

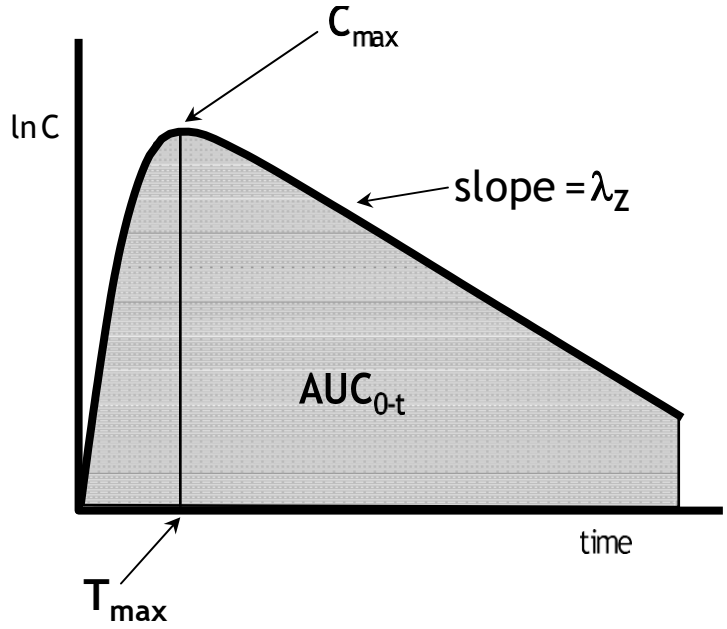
- Activeingredient was alreadyapproved under the original sponsor NDA
  - Genericmanufactureronlyrequired to demonstrate bioequivalence (Phase I)
  - Typically 24-36 healthy volunteers in a double-blind, randomized, crossover trial (or trials)
    - Single-dose fasting
    - Steady-state fasting
    - Single-dose fed/fasting

Study design

- Randomized, two-sequence, two-period crossover
  - Treatment sequence is randomized
    - Every subjects gets both treatments
    - Half get generic drug first, half get brand drug first (minimizes the sequence effect)
  - Crossover design
    - Each subject serves as his/her own control (minimizes intersubject variability)
    - Fewer subjects required to achieve adequate statistical power
  - Treatment periods separated by a washout
    - At least 5 drug half-lives
    - Minimizes the carryover (residual) effect

Sampling of biologic specimens

- Blood (plasma) samples are recommended
  - 12-18 samples (including predose) in each subject, spanning at least 3 drug elimination half-lives
  - Samplings should be spaced to allow accurate estimation of C_{max} and λ_z
  - Minimum of 3-4 samples during terminal log-linear phase to accurately estimate λ_z



Requiredstudies

- Oralsolutions,elixirs,syrups,tinctures
  - Bioequivalence studies are generally waived
- Oralsuspensions andimmediate-release solid oral dosage forms
  - Single-dose fasting (highest strength)
- Extended-release solid oral dosage forms
  - Single-dose fasting (all strengths)
  - Multiple-dose steady-state (highest strength)
  - Single-dose fed/fasting (highest strength)

Single-dose fasting

- PK parameters to be submitted
  - Subject, period, sequence, treatment
  - Plasma concentrations and time points
  - Measures of systemic exposure (reflect rate and extent of absorption):
    - Early exposure - partial AUC (truncated at population median T_{max} value)
    - Peak exposure - C_{max}
    - Total exposure - AUC_{0-t} , AUC_{∞}
  - Also report T_{max}, λ_Z, $t_{½}$
- Statistical analysis of AUC_{0-t} , AUC_{∞}, and C_{max}

Multiple-dose (steady-state)

- PK parameters to be submitted:
  - Subject, period, sequence, treatment
  - Plasma concentrations and time points
  - Total systemic exposure – $AUC_{0-\tau}$ (τ = dosing interval)
  - Also report
    - C_{max}
    - T_{max}
    - C_{min}
    - $C_{avg,ss}$ ($AUC_{0-\tau}/\tau$)
    - DF_{ss} (degree of fluctuation, or $[C_{max} - C_{min}]/C_{avg,ss}$)
    - Swing ($[C_{max} - C_{min}]/C_{min}$)
- Statistical analysis of $AUC_{0-\tau}$ and C_{max}

Single-dose fed/fasting

- PK parameters to be submitted
  - Subject, period, sequence, treatment
  - Plasma concentrations and time points
  - Measures of systemic exposure (reflect rate and extent of absorption):
    - Early exposure - partial AUC (truncated at population median T_{max} value)
    - Peak exposure - C_{max}
    - Total exposure - AUC_{0-t} , AUC_{∞}
  - Also report T_{max}, λ_Z, $t_{½}$
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Demonstrating bioequivalence

- Statisticalcomparison of genericto brand C_{max} and AUC using ANOVA
  - Evaluates potential confounding effect of 4 factors:
    - Sequence (treatment order)
    - Period
    - Subject
    - Treatment (formulation)
  - C_{max} and AUC arelog-transformed prior to analysis
    - ANOVA is based on the assumption of normal distribution of data
    - Mostpharmacokinetic parameters haveaskeweddistribution(log transformation normalizes the distribution)

Thank you