Topical Bioequivalence Update

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Current State of Topical Bioequivalence

- Demonstration of bioequivalence requires clinical studies
- Exceptions
  - Topical solutions
  - Corticosteroids
    - (Skin blanching pharmacodynamics)

Example Bioequivalence Studies

- Topical anti-fungals
  - Test, reference, placebo arms in patients
  - 90% confidence interval on test – reference cure rate
  - Estimated CV's ~100%

N	%Cure Test	%Cure Ref	90%CI
728	50%	48%	[-12,+16]
453	46%	40%	[-8,+20]
447	29%	27%	[-9,+13]

Is There a Problem?

- Barriers to product improvement and generic drugs
  - Need to demonstrate BE after formulation change or in product development
- Clinical endpoints have high variability
  - Inefficient detection of formulation differences
- Unnecessary human testing

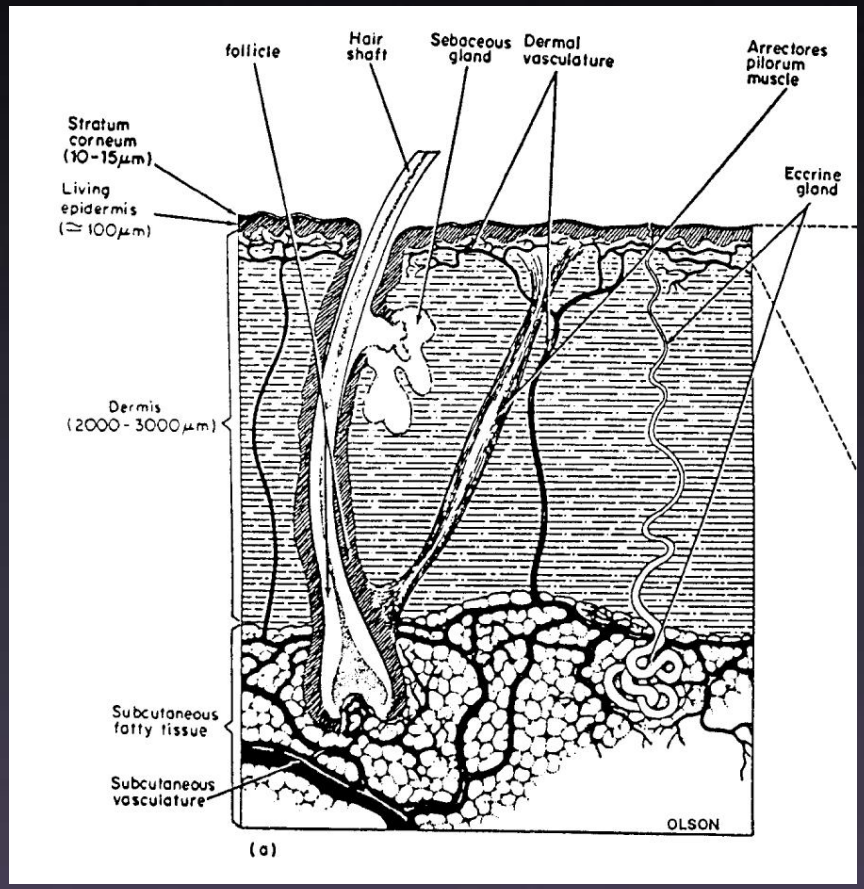
Goals

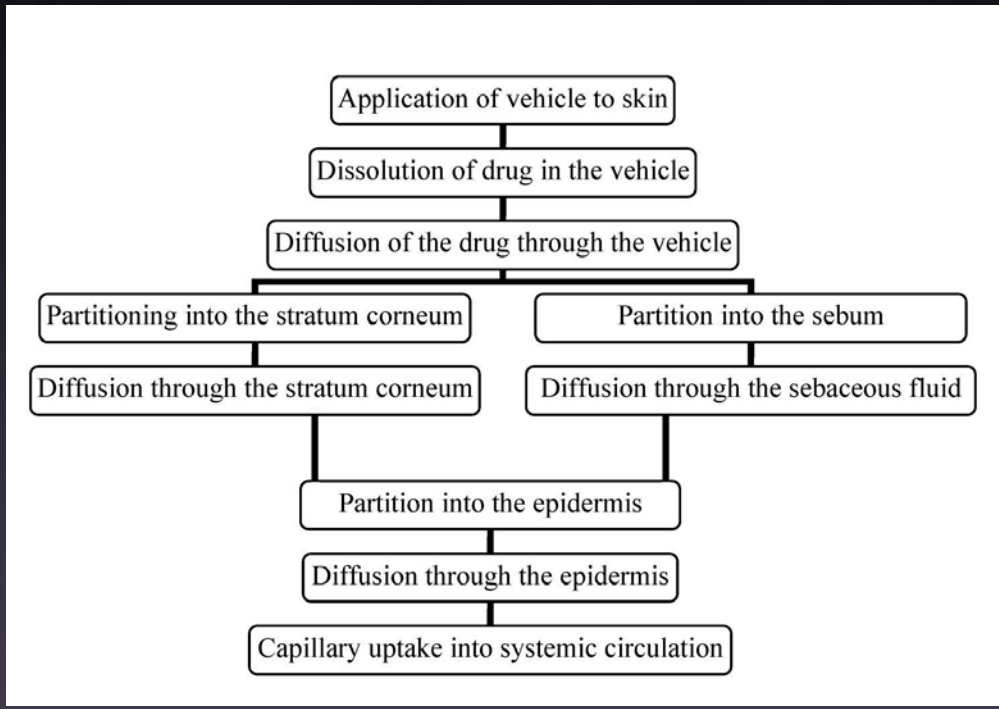
- Identify when clinical studies are not necessary to demonstrate bioequivalence of topical products
- Provide alternative methods that assure product quality

Topical Bioequivalence

- Bioequivalence strategy
  - Mechanistic understanding of key parameters that affect bioavailability
  - Identification of in vivo and in vitro tests
  - Classification of formulation similarity
- Proposed decision tree based on site of action (stratum corneum)
- External research projects

Topical Absorption Process

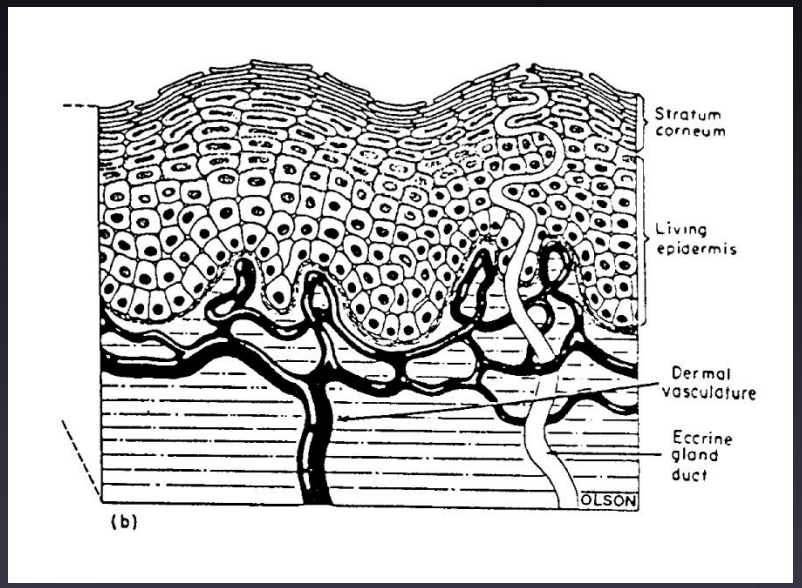




G. L. Flynn, *Cutaneous and Transdermal Delivery: Processes and Systems of Delivery*, Modern Pharmaceutics .Dekker, New York, third edition, 1996.

Bioequivalence

- Is about the formulation
  - Clinical effectiveness has already been established
- Defined as no significant difference in rate and extent of absorption
  - Rate at which drug can leave the formulation
  - Rate at which drug can cross the SC



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Key Aspects of Absorption

- The stratum corneum permeability is the limiting resistance

$$P = \frac{DK}{h}$$

$$J = PAC_{veh} = \left(\frac{DS_{mem}A}{h}\right)\left(\frac{C_{veh}}{S_{veh}}\right)$$

- Thermodynamic activity of the drug in the formulation is the driving force for absorption
- Formulation additives can alter barrier properties of the skin (permeability)

Causes of Inequivalence
(for equal drug content)

- Application
  - Different spreading on the skin
- In the formulation
  - Drug does not leave formulation
  - Thermodynamic activity is different (suspension v. dissolved drug)
- Across the stratum corneum
  - Formulations have different effects on stratum corneum
  - One formulation prefers follicular pathway

In Vitro Tests

- Diffusion Cell
  - Measures diffusion through the formulation and fraction of free drug
  - Not predictive of bioavailability (does not measure limiting resistance) but sensitive to formulation differences
  - Safety: Drug release in absence of SC
- Rheology
  - Determines how vehicle spreads on the skin
  - Dosage form classification
  - Pharmaceutical equivalence (patient experience)

In Vitro Tests (Suspensions)

- Dissolution (for suspension formulations)
- Particle size
  - Identify particle sizes that could preferentially transport via follicles

In Vivo Tests

- Skin Stripping
  - Can measure D,K in the SC independently[1]
- Microdialysis
  - Measures concentration that has reached the dermis
  - Recently used for evaluations of BE[2]
  - Not appropriate for drugs that target stratum corneum
- **In vivo tests quantify the effect of formulation on the stratum corneum**

1 A. Bungie. Presentation to FDA advisory committee for pharmaceutical science, October 2003.

2 Eva Benfeldt, Unpublished Data

Future Directions

- First focus on products that target SC
- Classify product similarity
  - Q1: Same components
  - Q2: Same components in same amount
  - Q3: Same components in same amount with the same arrangement of matter (microstructure)
- Select appropriate in vivo and in vitro tests

Q3 Identical Products

- Q3 identical products are bioequivalent
  - Example: Topical solutions
- For formulations more complex than solutions direct demonstration of Q3 equivalence is a challenge
  - Particle size

Q1 and Q2 Identical

- Is the rheology the same?
  - Adhesion to the skin
- Is the solubility of the drug in the formulation the same?
- Are excipients released at same rate?
- Is particle size the same? (suspensions)
  - Dissolution
  - Follicular transport

Q1 and Q2 Identical

- Require equivalence in
  - Rheology
  - In vitro release (diffusion cell)
- Are in vitro tests sufficient to ensure BE?
  - All concerns are potential Q3 differences due to the manufacturing process
  - In vitro tests are the best evaluation method for manufacturing quality

Q1 Identical

- Excipients' effect on skin barrier properties can be concentration dependent
- Thermodynamic activity could differ
- All tests for Q1 and Q2 similar products plus,
- In vivo test required if composition differences in excipients could potentially alter either skin permeability or the solubility of drug in the formulation

Q1 Differences

- All tests for Q1 and Q2 similar products
- In vivo test required to demonstrate that new excipients do not alter permeability

Decision Tree (Targeting SC)

- If Q1 and Q2 equivalent
  - in vitro testing
  - in vivo testing waived based on in vitro results
- If Q1 equivalent but Q2 difference
  - in vitro testing
  - in vivo tests if Q2 difference is potentially significant
- if Q1 and Q2 differ
  - in vitro testing
  - in vivo tests required to demonstrate no formulation effect on absorption

Research Projects

- In vivo skin stripping (Colorado School of Mines)
  - Reduce variability
  - Measure thickness removed via TEWL
  - Measure D (effect of formulation on SC) and K (effect of formulation on partition)
- In vitro characterization (Kentucky)
  - Prepare Q1 and Q2 formulations with known manufacturing differences
  - Measure rheology and in vitro release