

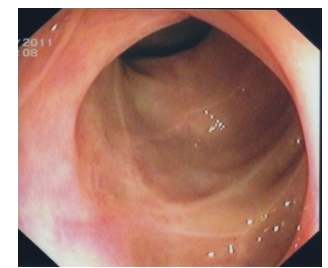
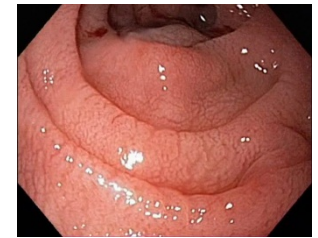
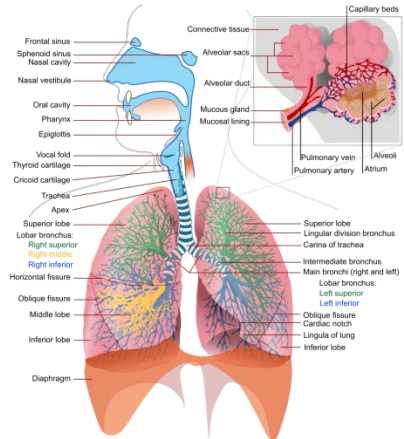
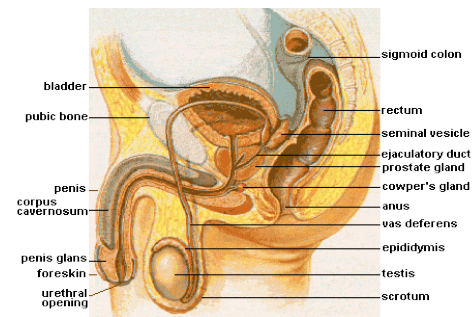
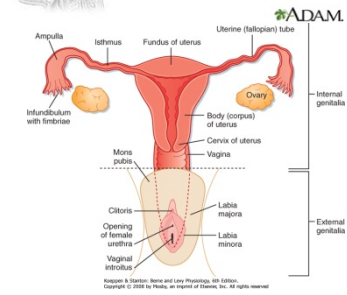
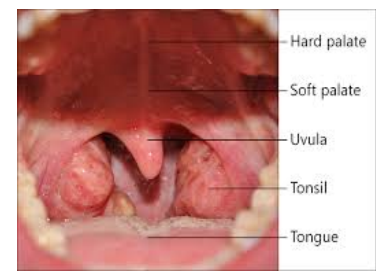
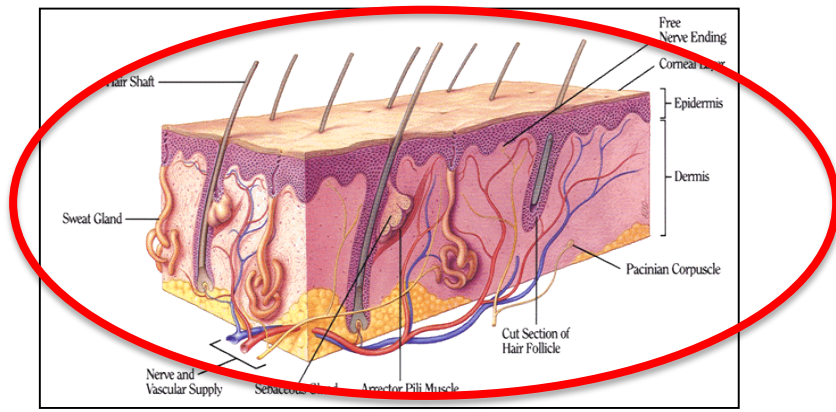
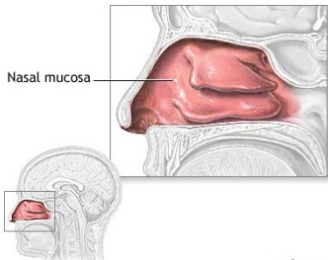
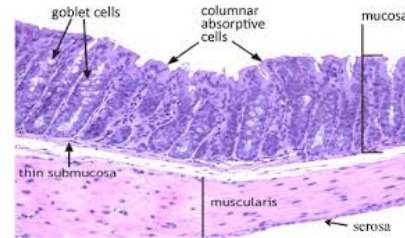
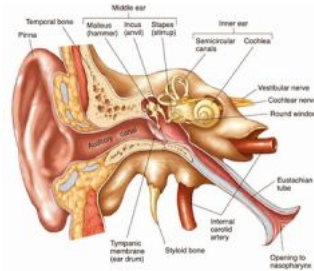
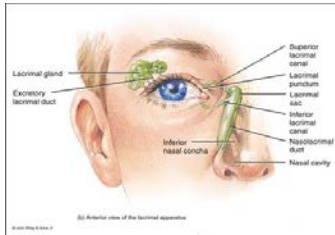
# Demonstrating Dermatological Bioequivalence

## Beyond the in vivo Clinical Endpoint Bioequivalence Study

John R Peters, MD  
Deputy Director,  
Office of Generic Drugs  
Center for Drug Evaluation and Research



# Topical Drug Products



# History of Generics

**1670—“A SHORT VIEW OF THE FRAUDS, and ABUSES Committed by APOTHECARIES; As well in Relation to PATIENTS, as PHYSICIANS: AND Of the only Remedy thereof by PHYSICIANS making their own MEDICINES.”, Christopher Merrett**

- They use Medicines quite contrary to the prescription
- They falsify the grand Compositions
- 'Tis very common for them to load Medicines with Honey, and other cheaper ingredients, and to leave out in whole or in part, those of greater value
- ...if such Simples are prescribed they know not, they fetch from the Herb-women what they give them, true or false; for many of these Women give to very many Plants false names
- [They] buy of the whole-sale men, who affirm of one another, especially of such who gain great Estates in short time, that they cannot sell their Medicines honestly made at so low a rate as they do
- they sometimes fail in their Cures...especially since the Apothecary may as easily falsify, and to greater profit in the one, then in the other
  - ..use of bad or decayed Drugs
  - ...more frauds may be committed by the Apothecaries, then by any other Trade, and by supposition that gain will tempt most men to dishonest actions, especially where they may act undiscovered

**Physicians have clearly not trusted generic drugs for quite some time**

# Generic Drugs are Substitutable

- **OPQ:** Pharmaceutical Quality
- **OND:** Safety and Efficacy
- **OGD:** Identity

Bioequivalence is not a gold standard but rather a fundamental principle that generic drugs must be the same as the innovator in all significant respects; *substitutability depends on similarity in all ways that are agreed upon as mattering to the therapeutic response*

The trick is in identifying what is of critical importance to the therapeutic response. To establish Identity requires clear and concrete understanding of critical elements identified in the development of the Reference Listed Drug

# Innovator vs Generic

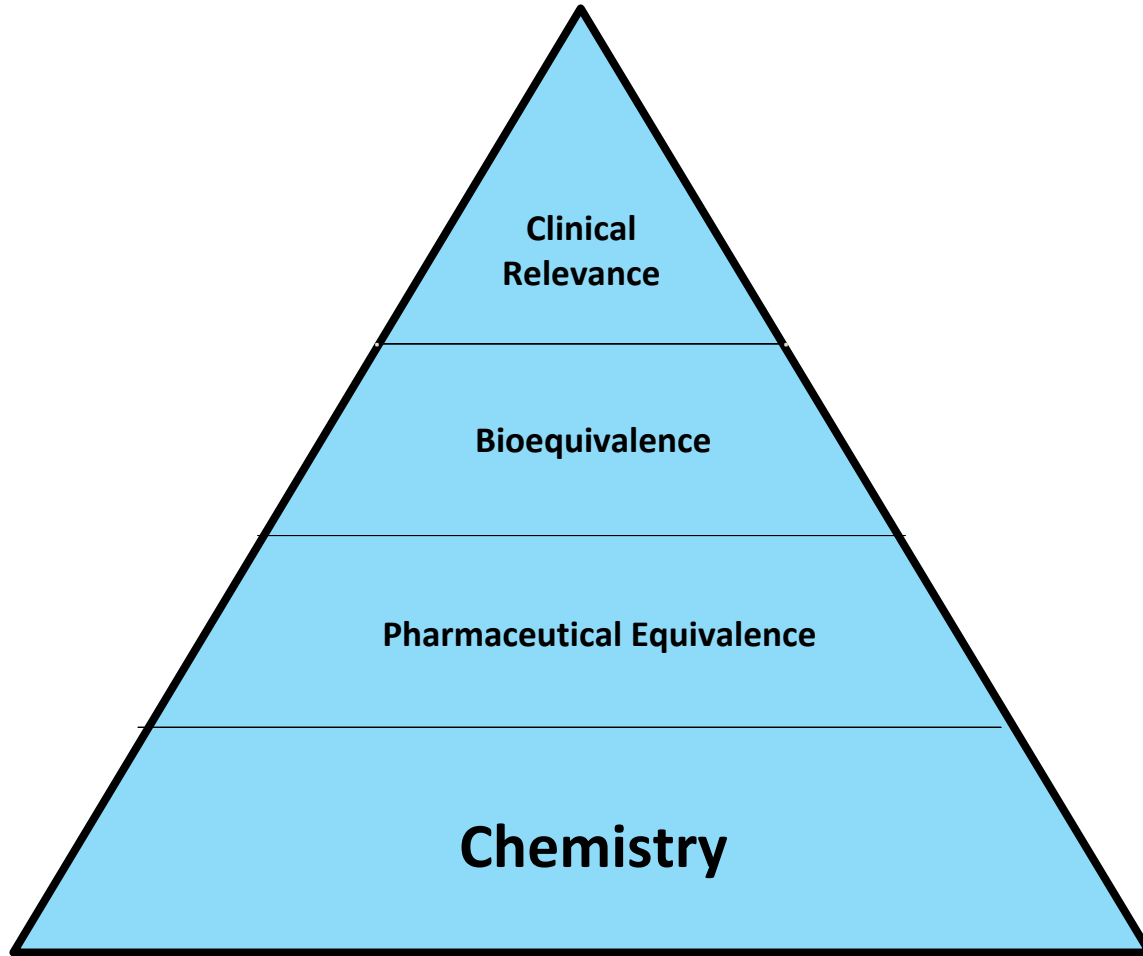
For an innovator drug product the criteria for approval are demonstration of Efficacy and Safety

For a generic drug approval the criterion is demonstration of a “shared identity” with the reference product. Shared identity means Efficacy and Safety can be inferred.

Generic drug approval is really a forensic process.



# Identity of Generic Drugs



# Pharmaceutical Equivalence: Sometimes it is not enough

- Pharmaceutical equivalence by itself does not necessarily imply therapeutic equivalence
- Therapeutic equivalence is inferred when:
  - Pharmaceutically equivalent
  - Bioequivalent
  - Clinically Relevant (to the indication, target population, and treatment regimen)
  - Same safety and efficacy profiles after administration of same dose



# Critical Elements of Identity



## No Significant Differences from the RLD

- **CHEMISTRY:** The physiological effects of the active pharmaceutical ingredient (API) is the basis for development of the drug
- **PHARMACEUTICAL EQUIVALENCE:** the foundation of generic equivalence is a formulation developed as a means of delivering the API
  - Same active ingredient(s)
  - Same strength
  - Same dosage form
  - Same route of administration
- **Bioequivalence:** supports true pharmaceutical equivalence
  - absence of a significant difference in the rate and extent of absorption after administration
  - available at the site of drug action when administered at the same molar dose under similar conditions
- **Clinical Relevance:** supports therapeutic equivalence in the context of the intended target population and for the same duration of therapy

# Scientific Method

A method of research in which a problem is identified, relevant data are gathered, a hypothesis is formulated, and the hypothesis is empirically tested.

Scientists question “authorities” and “facts”

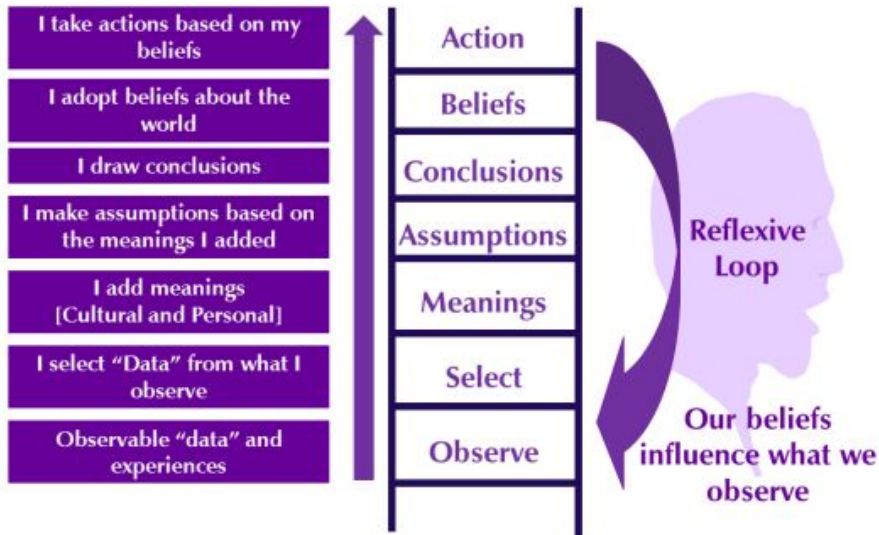
Scientists always ask “Why”

Science is an iterative process of observation, hypothesis generation, and testing of the hypothesis

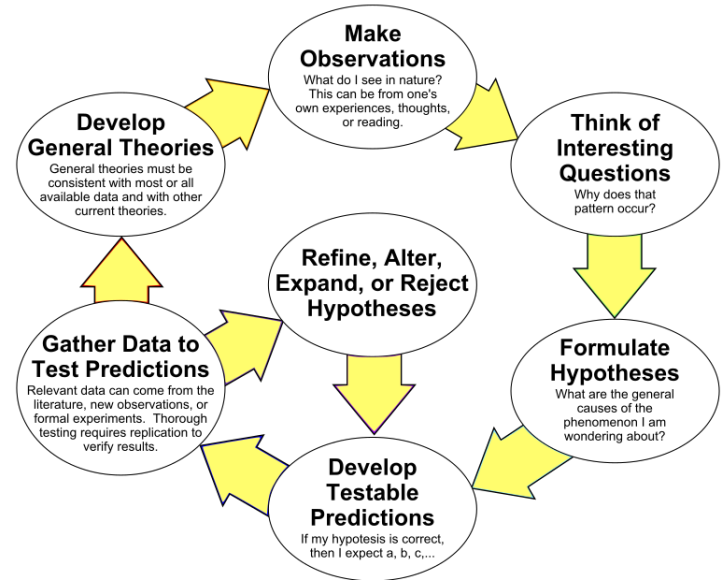
# INFERENCE/JUDGMENT

**Inference** is the act or process of deriving logical conclusions from premises known or assumed to be true. Alternatively, inference may be defined as the non-logical, but rational means, through observation of patterns of facts, to indirectly see new meanings and contexts for understanding.

## The Ladder of Inference

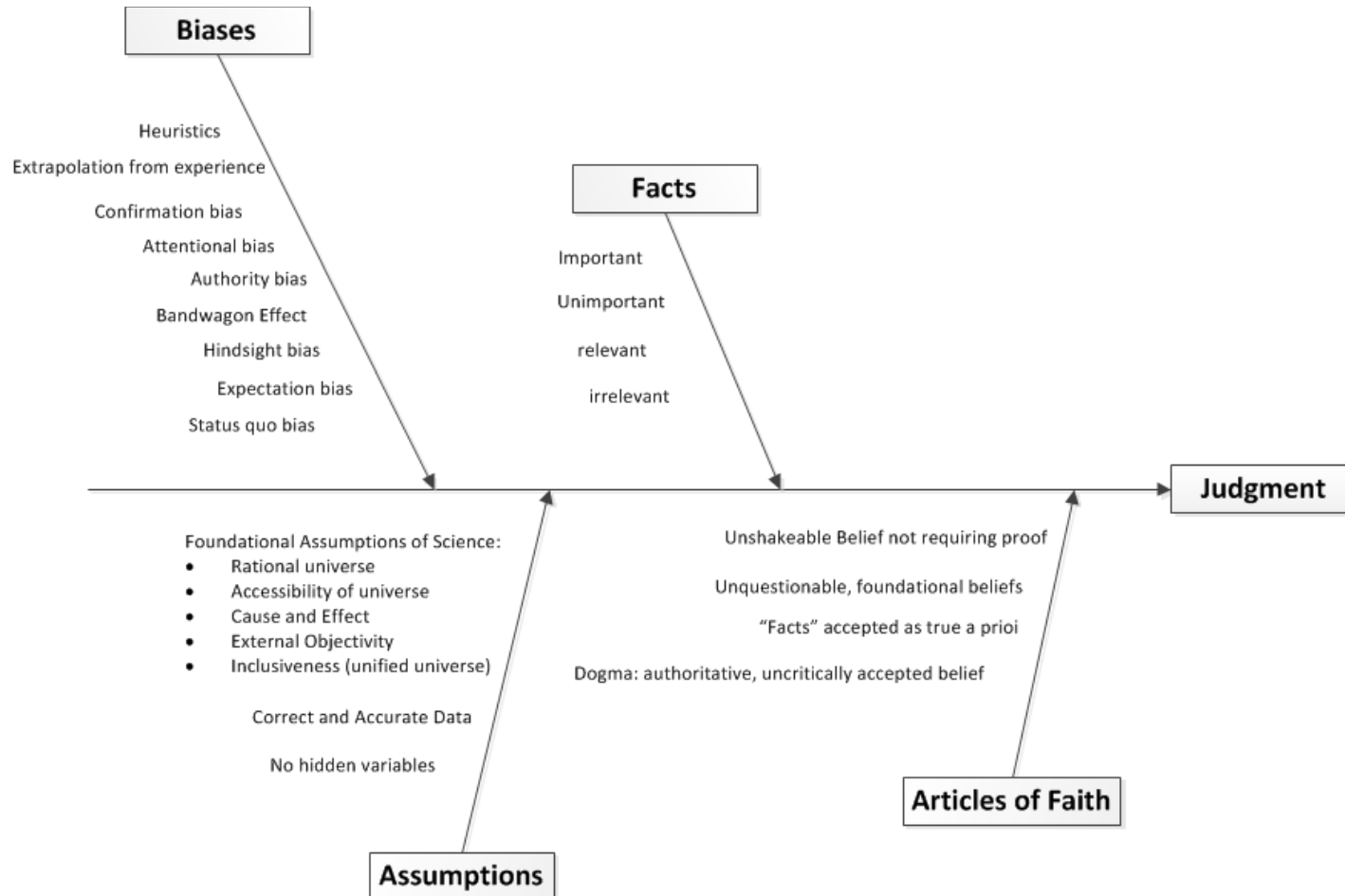


## The Scientific Method as an Ongoing Process



Theodore Garland, "The Scientific Method as an Ongoing Process", 2015, University of California

# Equivalence is a Judgment not a Fact



# Clinical Endpoint BE Study



- For an **NDA** drug **Safety and Efficacy** must be established. **This requires a randomized clinical trial.**
- For an **ANDA** drug **Bioequivalence** must be demonstrated in a **Pharmaceutically Equivalent Product.**
- There are 4 options to do this:
  - in vivo pharmacokinetic study
  - in vivo pharmacodynamic study
  - in vivo clinical endpoint bioequivalence study
  - in vitro methodology

**The Clinical Endpoint BE study is the poorest of the 3 in vivo options for establishing BE.**

# Clinical Endpoint Bioequivalence

Typically  $PE + BE = TE$

A clinical endpoint bioequivalence trial is **not**:

- a study of safety or efficacy
- a non-inferiority trial

It is a quantitative comparison of a clinical (therapeutic) effect. Comparison of therapeutic effect (**not** efficacy) allows for the inference that the test and reference products are bioequivalent

**In this case  $PE + TE$  infers  $BE$**

# Critical Review Elements for Generics



- **Chemistry**
  - Drug Product
  - Dose Form
  - Specifications
  - Impurities
  - Formulation
- **Bioequivalence**
  - Pharmacokinetics
  - Pharmacodynamics
  - In vitro Characterization
  - Statistics
  - Formulation
  - Impurities
  - Clinical Intent of Product Design
    - Clinical Use
    - Target Populations
    - Specific Indications
    - Chronicity of Use
- **Inspections**
  - Facility
  - Bioanalytic
  - Clinical
- **Labeling**
- **Legal/Regulatory**
  - Federal Food, Drug, and Cosmetics Act
  - Hatch-Waxman Amendment
  - Code of Federal Regulations
  - FDAAA
  - FDASIA
  - Precedent
  - Citizen Petitions

# Why?

A technician will use the tools of science to measure and collect data for analysis. Data collected and analyzed will be based on the defined critical elements of identity.

## **A scientist will ask “Why” and “What”?**

Why are these elements important?

What are my possible biases, beliefs, and articles of faith that lead me to label these elements as critical?

Why are these and no others used to define “significant difference”?

What modern and innovative approaches can we use to provide better assurance of equivalence than the clinical endpoint BE study?



# Question Are What We Do

