Science and Generic Drugs

John R Peters, MD
Deputy Director
Office of Generic Drugs
Definition

Science, noun:

1. A branch of knowledge or study dealing with a body of facts or truths systematically arranged and showing the operation of general laws.

2. Systematic knowledge of the physical or material world gained through observations and experimentation

3. A disciplined questioning of observations
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.
“Why?” Never Goes Away

The Scientific Method as an Ongoing Process

1. Make Observations
   - What do I see in nature?
   - This can be from one’s own experiences, thoughts, or reading.

2. Think of Interesting Questions
   - Why does that pattern occur?

3. Formulate Hypotheses
   - What are the general causes of the phenomenon I am wondering about?

4. Develop Testable Predictions
   - If my hypothesis is correct, then I expect a, b, c, ... ...

5. Gather Data to Test Predictions
   - Relevant data can come from the literature, new observations, or formal experiments. Thorough testing requires replication to verify results.

6. Refine, Alter, Expand, or Reject Hypotheses

7. Develop General Theories
   - General theories must be consistent with most or all available data and with other current theories.

Theodore Garland, “The Scientific Method as an Ongoing Process”, 2015, University of California
Complex Drugs

Complex Formulations

Complex Drug-Device Combinations

Complex Route of Delivery

Complex Generics

Complex Active Ingredients

Non-biologics complex drugs (NBCD)

Biological complex drugs (Biosimilars)
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
Identity of Generic Drugs

- Chemistry
- Pharmaceutical Equivalence
- Bioequivalence
- Clinical Relevance
Equivalence is a Judgment not a Fact

Biases
- Heuristics
- Extrapolation from experience
- Confirmation bias
  - Attentional bias
  - Authority bias
  - Bandwagon Effect
  - Hindsight bias
  - Expectation bias
  - Status quo bias

Facts
- Important
- Unimportant
  - Relevant
  - Irrelevant

Judgment

Assumptions
- Foundational Assumptions of Science:
  - Rational universe
  - Accessibility of universe
  - Cause and Effect
  - External Objectivity
  - Inclusiveness (unified universe)
- Correct and Accurate Data
- No hidden variables

Articles of Faith
- Unshakeable Belief not requiring proof
- Unquestionable, foundational beliefs
  - “Facts” accepted as true a priori
- Dogma: authoritative, uncritically accepted belief
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 administrated 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
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”?
Questions?

Thinking is difficult, that's why most people judge.
Carl Jung

YOU ARE WHAT YOU REPEATEDLY DO. EXCELLENCE IS NOT AN EVENT, IT IS A HABIT.

I would rather have questions that can't be answered than answers which can't be questioned.
~ Richard Feynman