Challenges in Generic Drug Safety and Surveillance

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Outline

1. An example
2. Generic Drug Differences from New Drugs
3. Generic Drug Safety Challenges
4. Another example

Clonidine Transdermal System

Clonidine Transdermal System USP (0.1 mg/day, 0.2 mg/day or 0.3 mg/day)

Indicated for the treatment of hypertension

- 89 reports lack of adhesion and efficacy
- MedWatch reports = large size of the generic patch.

For 0.3 mg/day:

Brand = 10.5 cm^2

2cm X 5cm

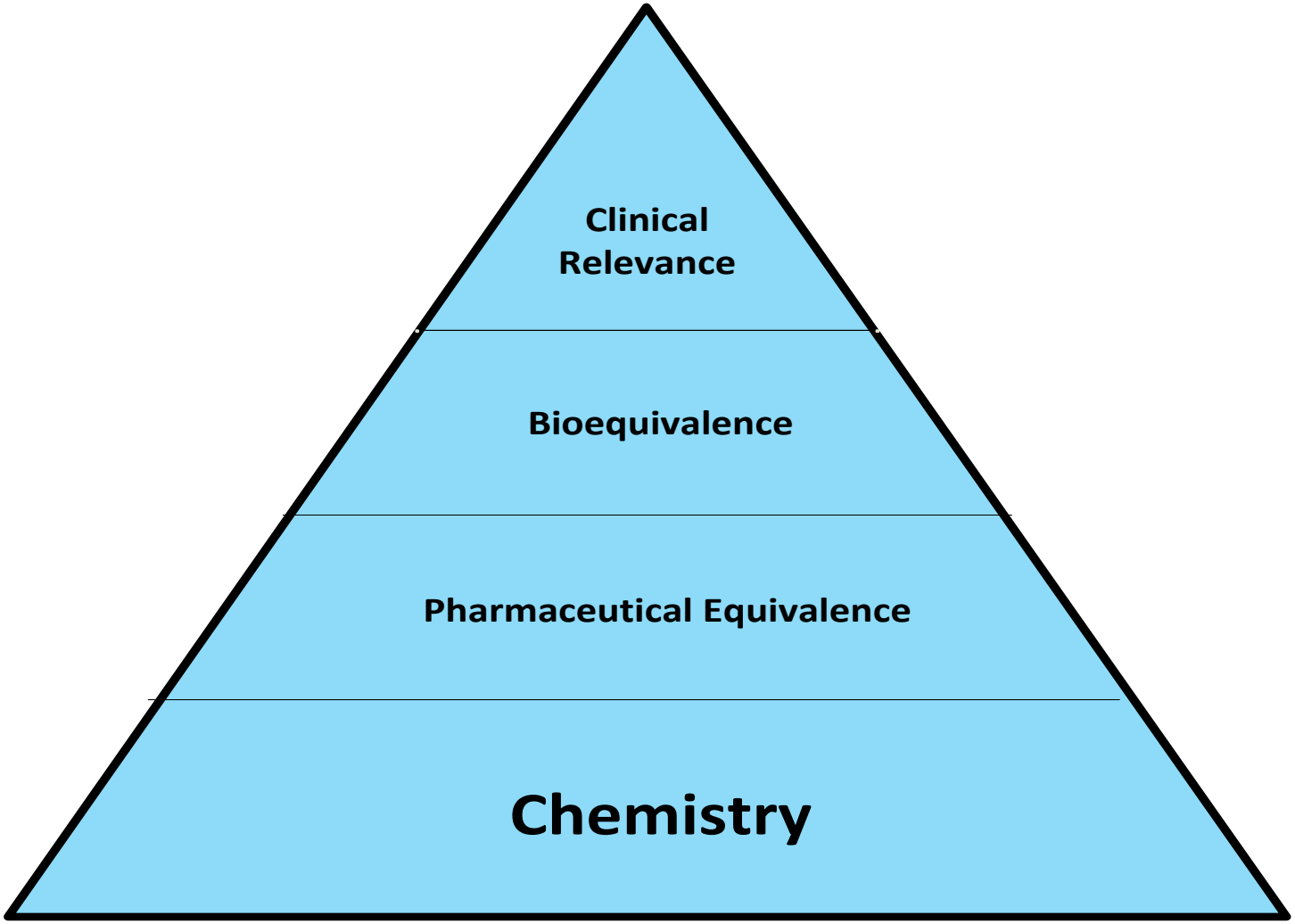
Generic = 32.4 cm^2

3cm X 10cm

Clonidine Transdermal System

- FDA inspection = significant manufacturing problems
- A warning letter was issued to the generic manufacturer on May 21, 2010.
- Generic applicant voluntarily removed the generic patch in March 2011.

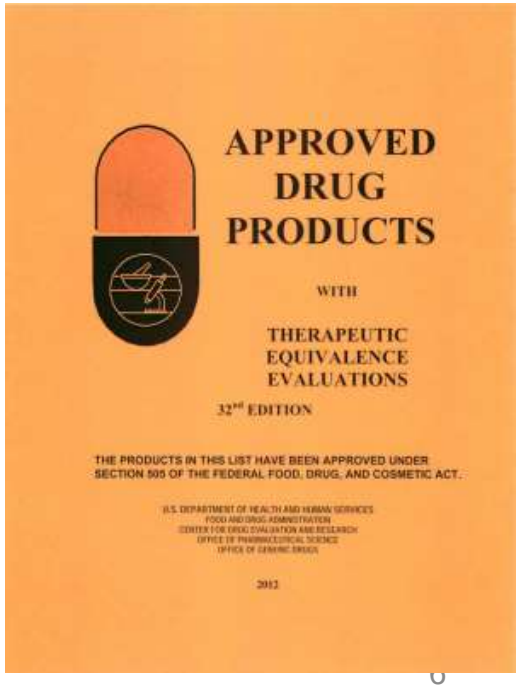
Foundation for Identity of Generic Drugs



Pharmaceutical Equivalence (PE)

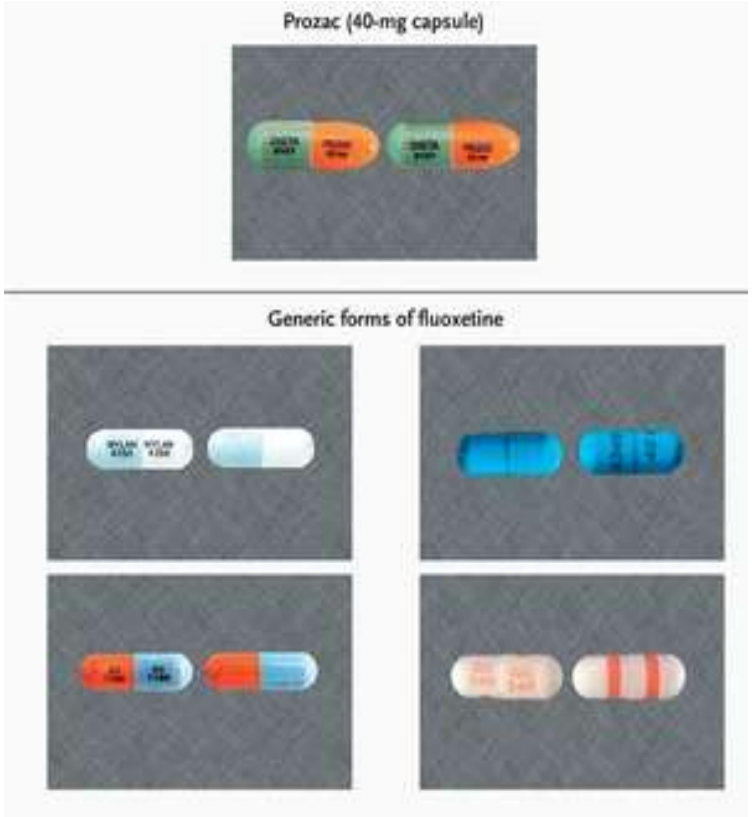
Pharmaceutical equivalence means the *same*:

- Active ingredient(s)
- Dosage form,
- Route of administration
- Strength, quality, purity, and identity



Allowable Differences

Generic Drugs can sometimes differ in:



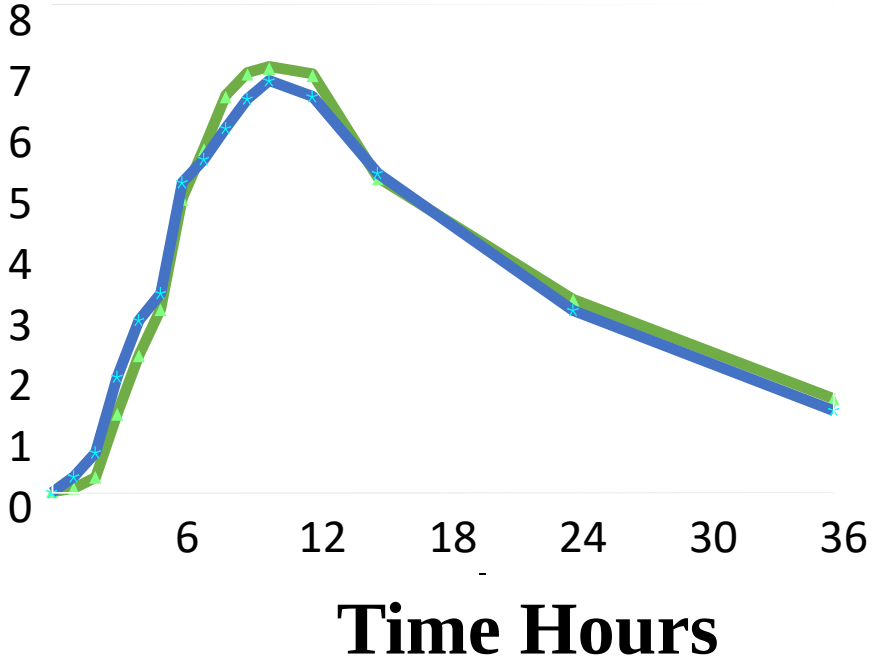
- Shape
- Scoring configuration
- Release mechanisms
- Packaging
- Excipients
- Expiration time
- Labeling (within certain limits)

Bioequivalence (BE)

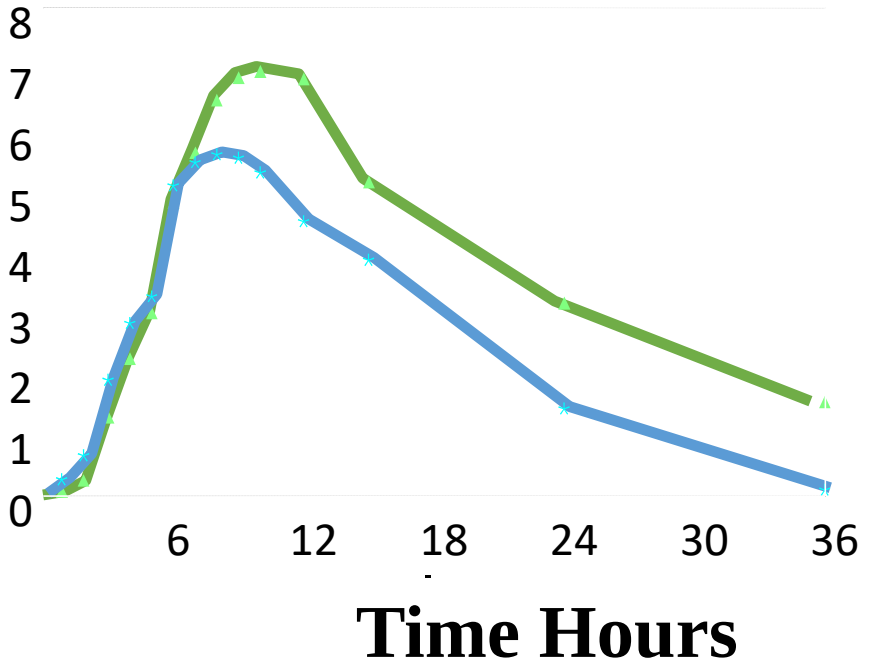
- Generic and brand drug should deliver the same amount of the active drug at the same rate

- A BE and PE generic drug will perform **in the same way** as the brand drug in vivo.

Bioequivalent



Inequivalent



Test/Generic

Reference/RLD

NDA vs. ANDA Requirements

Brand Name Drug NDA Requirements	Generic Drug ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal Studies 7. Clinical Studies 8. Bioavailability	6. Bioequivalence

Clinical Relevance

- A generic drug that is both PE and BE must also act **in the same clinically relevant way.**
- The same clinical effect and safety profile when administered to patients under conditions specified in labeling.
  - **Duration of use**
  - **Indication**
  - **Target population**

Why worry about generic drug safety?

Unexpected safety considerations and concerns over time

- Generic drug use is more widespread
- Patients are switched from a brand to a generic
- Patients are switched from one generic to another generic

Postmarketing Surveillance of Generic Drugs

Examples include:

- Reports of generic drug adverse events
- Quality problems
- Patient perceptions of generic drug inferiority
- Suspected contamination
- Concern for difference in safety profile

Quality Issues and Complaints

- Tablets breaking apart
- Scored tablets breaking unevenly or crumbling when split
- Tablets sticking in the throat
- Unusual odor, taste, smell, or texture
- Precipitates in oral liquids and injectables
- **Patches not sticking**
- Container/closure issues
- Device issues
- Dropper issues with ophthalmologic products
- **Large size tablet/capsule**

Potential Postmarketing Safety Signal Sources

- Contacts from the public directly communicated to FDA
- MedWatch reports submitted to FDA
- Internal FDA databases
- Reports from other regulatory agencies
- Manufacturer reports
- Scientific literature

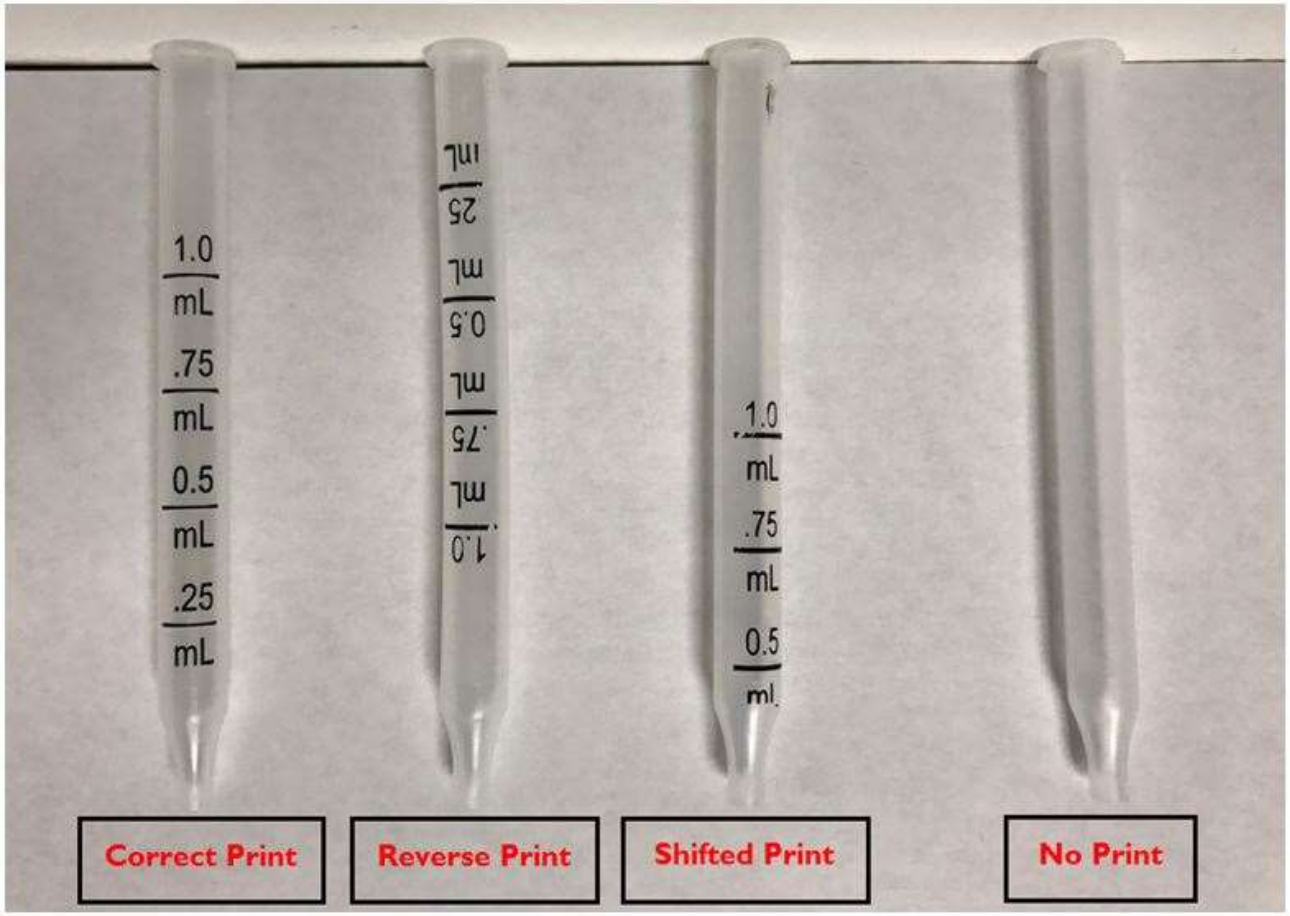
One more example before I go

Lorazepam Oral Concentrate

- Lorazepam Oral Concentrate USP, 2 mg/mL, 30 mL bottle.
- Indicated for the treatment of anxiety.
- This liquid is used with a calibrated dropper.
- Mostly used in children and in those with trouble swallowing tablets.

Lorazepam Oral Concentrate

The company recalled the 13 affected lots on August 14, 2017.



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THANK
YOU