

# Therapeutic Substitution

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# Therapeutic Equivalence-Related Terms

- Approved Drug Products with Therapeutic Equivalence
  - “Orange Book”
- Pharmaceutical equivalents
  - Same active ingredient, same dosage form, route of administration, same strength or concentration
  - May differ in shape, scoring, packaging, excipients
    - Eg. Chlordiazepoxide hydrochloride (Librium) 5 mg capsules

# Therapeutic Equivalence-Related Terms

- Pharmaceutical alternatives
  - Same therapeutic moiety but different salts, esters or complexes
    - Tetracycline hydrochloride 250 mg capsule vs. tetracycline phosphate complex 250 mg capsule
    - Extended release vs. immediate release products with the same active ingredient

# Therapeutic Equivalence-Related Terms

- Therapeutic equivalents
  - Pharmaceutical equivalents and expected to have the same clinical effect and safety profile
- Therapeutically equivalent products are
  - Approved as safe and effect
  - Pharmaceutical equivalent
    - Identical amounts of the same drug, same dosage form, route of administration
    - Meet compendial standards (USP) for strength, quality, purity and identity

# Therapeutic Equivalence-Related Terms (Cont.)

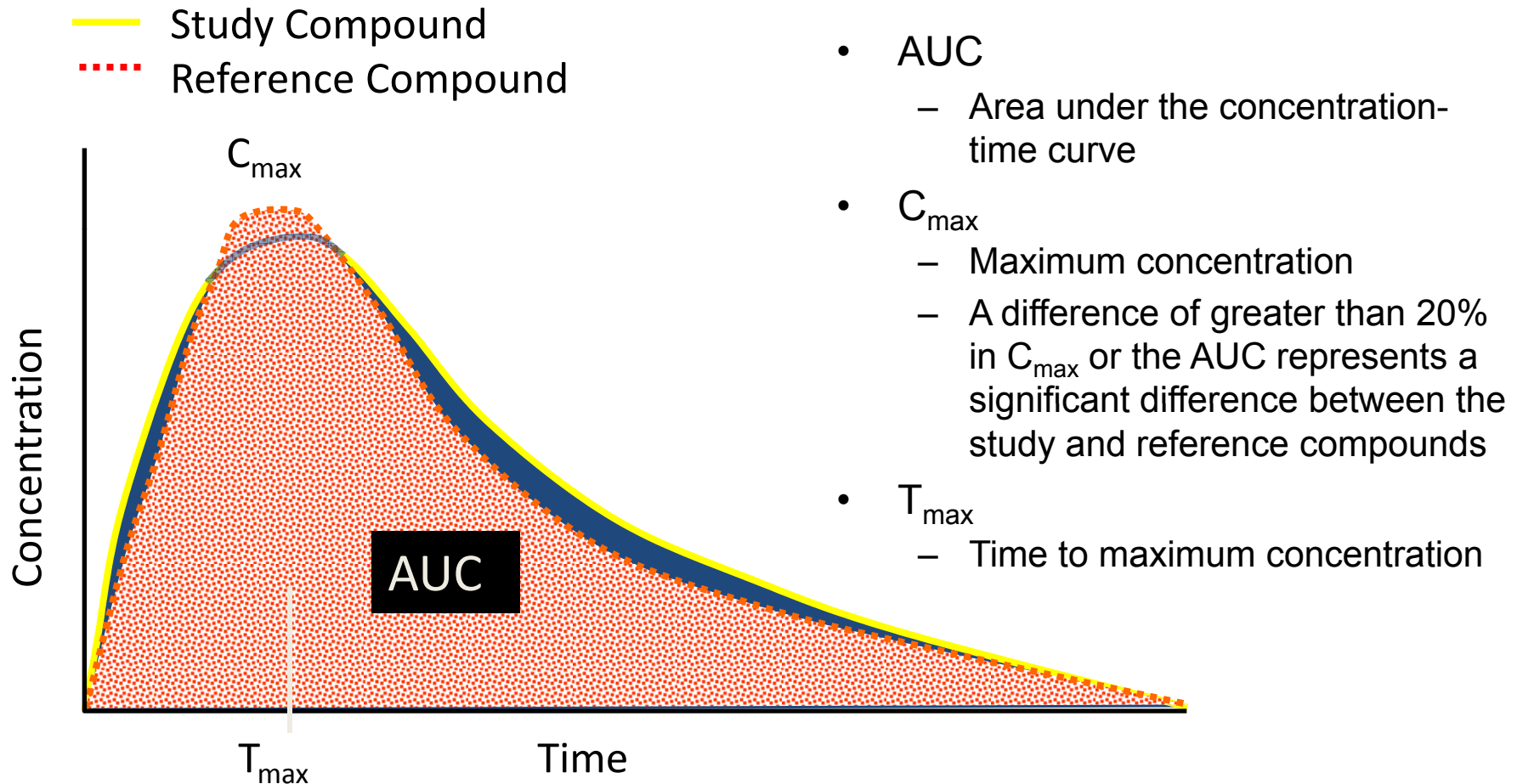
- Bioequivalent
  - Do not present bioequivalence problem and meet appropriate bioequivalence standards
- Adequately labeled
- Manufactured in compliance with GMP regulations
- Therapeutic equivalence does not encompass two different ingredients that are used to treat the same condition
  - Eg. Ibuprofen vs. naproxen

# Bioavailability

- Rate and extent active moiety is absorbed from a drug product
  - Parameters of bioavailability
    - $C_{max}$  – peak blood concentration
    - $T_{max}$  – time of the peak blood concentration
    - AUC – area under the concentration time curve
- For two drugs to be declared bioequivalent mean and confidence interval must be in the range of 80-125% of the reference product
- Bioequivalent products are “AB” rated
  - “BX” means the products are not equivalent

# Pharmacokinetic Studies

## Key Measurements

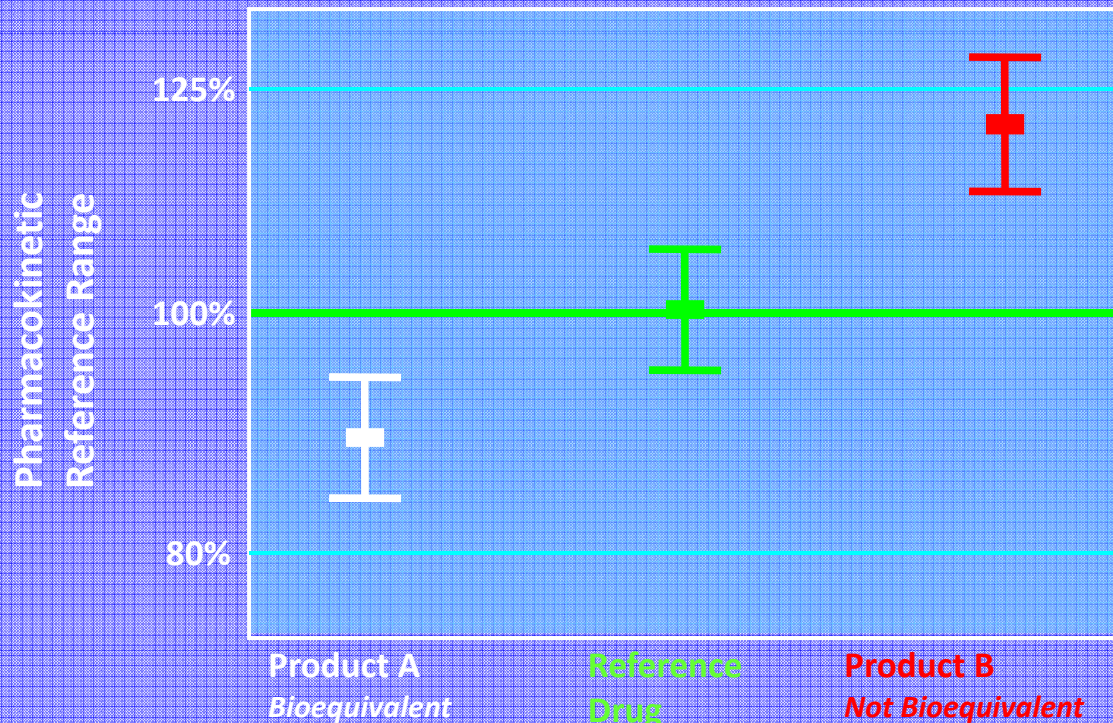


*Approved Drug Products With Therapeutic Equivalence Evaluations*. 23<sup>rd</sup> ed. 2003. FDA/CDER Web site. Available at: [http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm#Therapeutic Equivalence-Related Terms](http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm#Therapeutic%20Equivalence-Related%20Terms). Accessed

September 29, 2003.

# Levothyroxine Bioequivalence

AUC and Cmax 90% confidence intervals of the study drug must be within 80 to 125% of a reference compound

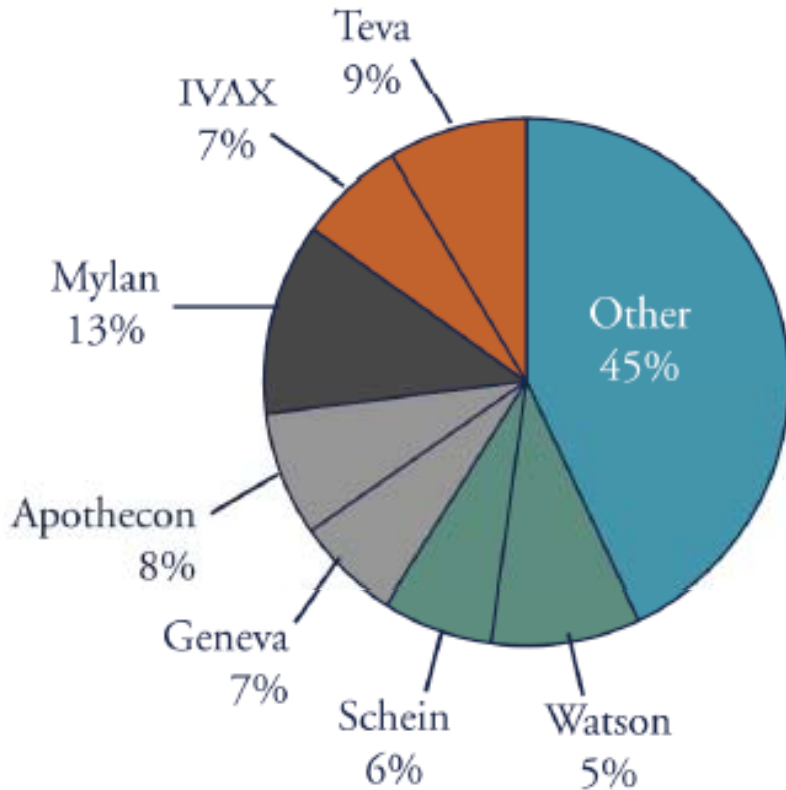




# Levothyroxine Bioequivalence Thyroxine Product Status

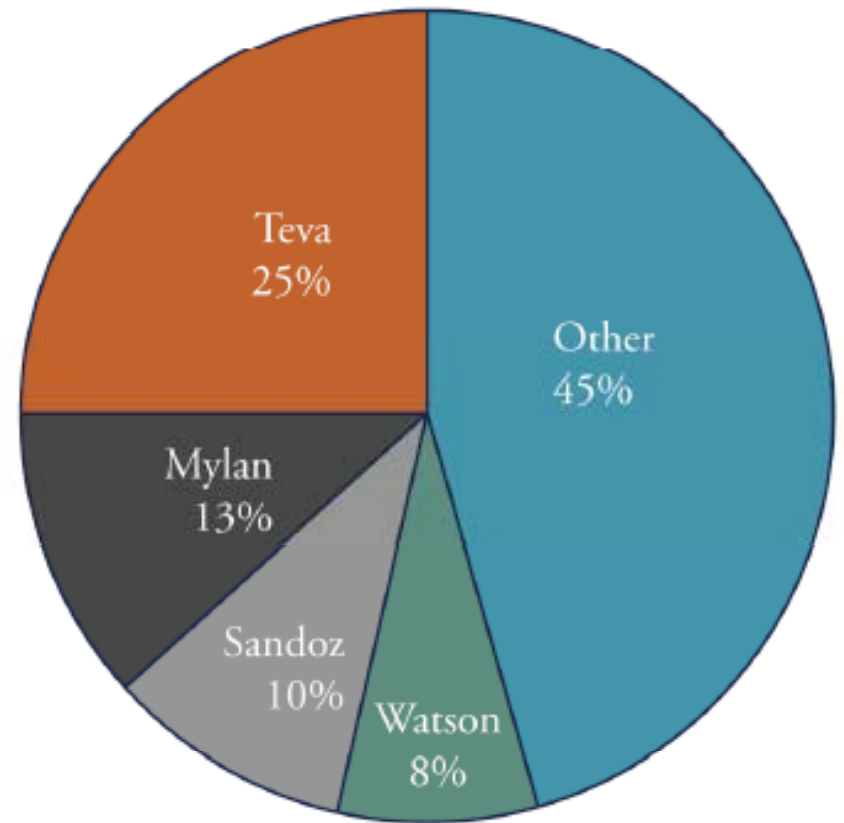
	Synthroid	Levoxyl	Levothroid	Unithroid	LT4- Sandoz	LT4- Mylan	Novothyrox	Levolet
<b>Synthroid</b> (Abbott)	-----	BX	BX	BX	<b>AB2</b>	<b>AB2</b>	BX	BX
<b>Levoxyl</b> (Jones)	BX	-----	BX	<b>AB 3</b>	<b>AB3</b>	<b>AB3</b>	BX	BX
Levothroid (Forest: Formerly Lloyd Thyrotabs)	BX	BX	-----	BX	BX	BX	BX	BX
<b>Unithroid<sup>1</sup></b> (Stevens)	BX	<b>AB1</b>	BX	-----	BX	<b>AB1</b>	BX	BX
LT4-Sandoz	<b>AB2</b>	<b>AB3</b>	BX	BX	-----	<b>BX</b>	BX	BX
LT4-Mylan	<b>AB2</b>	<b>AB3</b>	BX	<b>AB1</b>	<b>BX</b>	-----	BX	-----
Novothyrox (Genpharm)	BX	BX	BX	BX	BX	BX	-----	BX
Levolet (Vintage)	BX	BX	BX	BX	BX	BX	BX	-----

## U.S. TOTAL GENERIC RX MARKET SHARE, 1998 VS. 2008



1998

Total US Sales: \$10B



2008

Total US Sales: \$33B

# Generic Substitution

- Substitution of therapeutically equivalent products
  - Amoxicillin by Smith for amoxicillin by Jones
- Generic substitution is commonly done in inpatient and outpatient (community) pharmacies
- Law varies from state to state
- “Medically necessary” “Do not substitute”

# Generic Substitution in Texas

- All of the following conditions are met
  - Generic product costs the patient less
  - Patient does not refuse substitution
  - Prescriber does not prohibit substitution
- Pharmacist may substitute a generically equivalent drug unless
  - “Brand Necessary” or “Brand Medically Necessary” written by hand

# Why Generic Substitution

- Generics are usually less expensive
- Substitution is not a problem if the drug is NOT a “Narrow Therapeutic Index” (NTI) drug
  - Levothyroxine
  - Lithium
  - Warfarin
  - Phenytoin
  - Digoxin
- Prescription co-pay should be considered

# 2010 Prescription Discount Plans

Updated January 2010

*not all-inclusive; only contains most common medications*

		Target		Wal-Mart/Sam's		K-Mart	Rite Aid		Walgreens		CVS	Kerr Drug	
		\$4	\$10	\$4	\$10	Free program membership	Free program membership	\$20 individual, \$35 family membership	\$10 individual membership	\$13		\$5 family	
		30 days	90 days	30 days	90 days	prices listed	30 days	90 days	30 days	90 days	90 days	90 days	
Cardiac/Hypertension	Combination products	Amiloride/HCTZ 5/50mg	30	90	30	90	90 for \$10	30	90	30	90	90	90
		Atenolol/Chlorthalidon 50/25, 100/25mg	30	90	30	90	90 for \$10	30	90	30	90	90	90
		Benazepril/HCTZ 5/6.25mg	--	--	--	--	90 for \$15	--	--	--	--	90	--
		10/12.5, 20/12.5mg	--	--	--	--	90 for \$15	--	--	30	90	90	90
		20/25mg	--	--	--	--	90 for \$15	--	--	--	--	90	90
		Bisoprolol/HCTZ 2.5/6.25, 5/6.25, 10/6.25mg	30	90	30	90	90 for \$10	30	90	30	90	90	90
		Enalapril/HCTZ 5/12.5mg	30	90	30	90	90 for \$10	30	90	60	180	90	180
		10/25mg	--	--	--	--	90 for \$10	30	90	30	90	90	90
		Lisinopril/HCTZ 10/12.5, 20/12.5, 20/25mg	30	90	30	90	90 for \$10	30	90	30	90	90	90
		Propranolol/HCTZ 40/25, 80/25mg	--	--	--	--	90 for \$15	--	--	--	--	180	--
	Spirolactone/HCTZ 25/25mg	--	--	--	--	--	30	90	30	90	--	90	
	Triamterene/HCTZ cap 37.5/25mg	30	90	30	90	90 for \$10	30	90	30	90	90	90	
	50/25mg	--	--	--	--	--	30	90	--	--	--	--	
	Triamterene/HCTZ 37.5/25, 75/50mg	30	90	30	90	90 for \$10	30	90	30	90	90	90	
	ACE inhibitors	Benazepril 5, 10, 20, 40mg	30	90	30	90	90 for \$10	30	90	30	90	90	90
		Enalapril 2.5, 5, 10, 20mg	30	90	30	90	180 for \$10	30	90	60	180	90	180
		Fosinopril 10, 20mg	--	--	--	--	--	--	--	30	90	90	--
		40mg	--	--	--	--	--	--	--	30	90	90	--
		Lisinopril 2.5, 5, 10, 20mg	30	90	30	90	90 for \$10	30	90	30	90	90	90
		30, 40mg	--	--	--	--	90 for \$10	30	90	30	90	90	90
Quinapril 5, 10mg		--	--	--	--	90 for \$15	--	--	30	90	90	90	
20mg		--	--	--	--	90 for \$15	--	--	30	90	90	90	
40mg		--	--	--	--	90 for \$15	--	--	30	90	90	90	
Trandolapril 1, 2, 4mg		--	--	--	--	--	--	--	30	90	--	90	
CCBs	Amlodipine 2.5mg	--	--	--	--	90 for \$15	30	90	--	--	--	90	
	5, 10mg	--	--	--	--	90 for \$15	30	90	--	--	--	90	
	Nicardipine caps 20, 30mg	--	--	--	--	180 for \$15	--	--	--	--	--	--	
	Cartia XT caps 120mg	--	--	--	--	--	--	--	--	--	90	--	
	Diltiazem 30, 60, 90mg	60	180	60	180	180 for \$10	60	180	60	180	180	180	
	120mg	30	90	30	90	90 for \$10	30	90	30	90	90	90	
	Diltiazem ER caps 24hr 120, 180, 240mg	--	--	--	--	--	--	--	30	90	--	--	
	Verapamil 40mg	--	--	--	--	--	60	180	--	--	--	--	
	80, 120mg	30	90	30	90	90 for \$10	60	180	30	90	90	90	
	Verapamil ER 180mg	--	--	--	--	--	--	--	30	90	90	90	
240mg	--	--	--	--	--	--	--	30	90	90	90		

# Therapeutic Substitution

- Substitution of one drug for another within the same class
  - Enalapril for lisinopril (ACEI to ACEI)
    - Same potency
- Substitution of one drug for a drug from a different class with similar pharmacologic effect
  - Enalapril for amlodipine (ACEI to CCB)
    - Both lower blood pressure
    - Roughly similar potency but different mechanism of action

# Therapeutic Substitution

- Setting where therapeutic substitution is likely to occur
  - Hospital protocols
  - Federal facilities
  - Collaborative drug management
    - Inpatient or outpatient settings
    - Protocol between a prescriber and a pharmacist
- Unlikely to occur between PCP and community pharmacies (independent or chain)



# Therapeutic Substitution

- PBM plans routinely try to implement therapeutic substitution
  - Often driven by contractual arrangements
  - Frequent calls/fax to physicians to influence prescribing
  - Use of co-pays for prescriptions to increase the use of preferred drugs
    - Formulary vs non-formulary
    - Preferred vs non-preferred

# AMA Policy on Therapeutic Substitution

The AMA adopted policy H-125.991, “Drug Formularies and Therapeutic Interchange,” opposing therapeutic substitution which is “the act of dispensing a therapeutic alternate for the drug product prescribed without prior authorization of the prescriber.” Similarly, the AMA adopted H-125.993, “Legislation Prohibiting Therapeutic Substitution,” which opposes “the establishment of a system at the federal or state level premised on therapeutic interchangeability of prescription drugs and formularies, since it will inevitably interfere with the ability of the patient's physician to assure that the medication prescribed is dispensed to the patient.”

# American Society of Health-System Pharmacists

## Principles of a Sound Drug Formulary System

### Role of the Pharmacy and Therapeutics Committee

Implements generic substitution and therapeutic interchange programs that authorize exchange of therapeutic alternatives based upon written guidelines or protocols within a formulary system. (Note: Therapeutic substitution, the dispensing of therapeutic alternates without the prescriber's approval, is illegal and should not be allowed—see Glossary.)

Endorsed by ASHP BOD June 4, 2000

# American Pharmacists Association

## APhA Adopted Resolutions

### **1996.14 - Patient Care Protocols**

APhA-ASP supports pharmacist therapeutic substitution under appropriate patient care protocols.

# Possible Consequences of Therapeutic Substitution

- Under/over treatment
  - Substitution of simvastatin for Lipitor®
- Adverse effects improved/worsened
- Adverse effects different
- Lower or higher cost of prescription
  - Consider co-pays
  - Big box generics
  - Medicaid limit of 3 Rx per month