Quality assurance of generic drugs in infectious disease practice

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Disclosure on Conflict of Interest

- Medical Director, Otsuka Pharmaceuticals Philippines, Inc.

- Speaker: GSK Vaccines Philippines, MSD Vaccines, Natrapharm-Patriot, Abbot Philippines, Astellas Pharmaceuticals

- Advisory Board: MSD Vaccines

The global change

- US FDA and ICH guidelines
- Health Canada's Guideline on Preparation of Drug Identification Number (DIN) Submission
- WHO document (1999): "Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability"
- Note for Guidance on the Investigation of Bioavailability and Bioequivalence, Committee for Proprietary Medicinal Products (CPMP), 26 July 2001 (CPMP/EWP/QWP/98)
- Pan-American Network on Regulatory Harmonization: Bioavailability and Bioequivalence Working Group 2004
- ASEAN BA/BE Harmonization Guideline 2009/2010

Generics are pharmaceutical products that contain well-established drugs

- They are:
  - Intended to be interchangeable with the original product
  - Usually manufactured without a license from the original manufacturer
  - Marketed after the expiry of patent or other exclusivity rights
  - Marketed either under a non-proprietary name (INN or other approved name) or other brand names ("branded generics")

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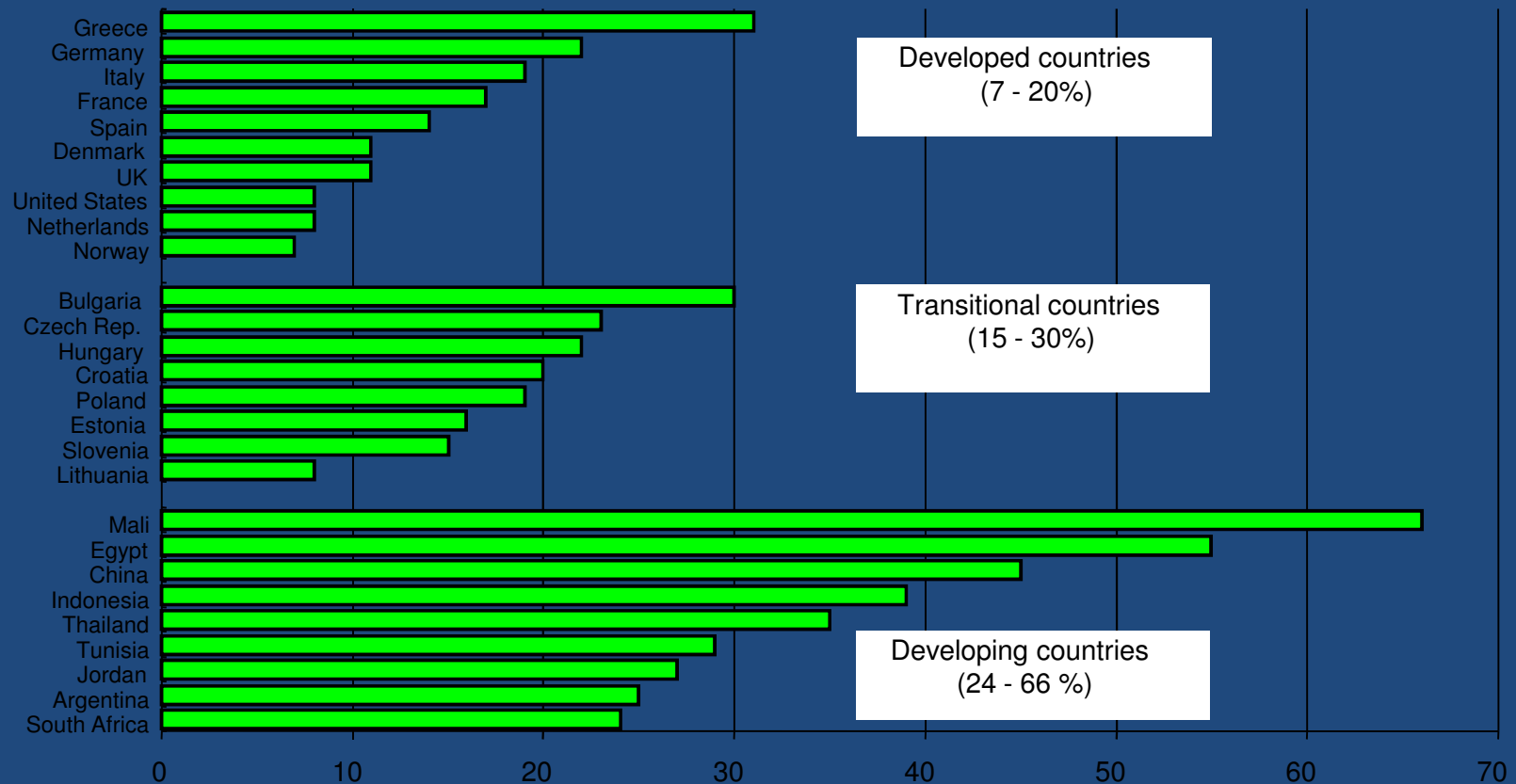
The worldwide role of generic pharmaceuticals

- PUBLIC HEALTH NEED

- NATIONAL STRATEGIES

- SOCIAL RESPONSIBILITY
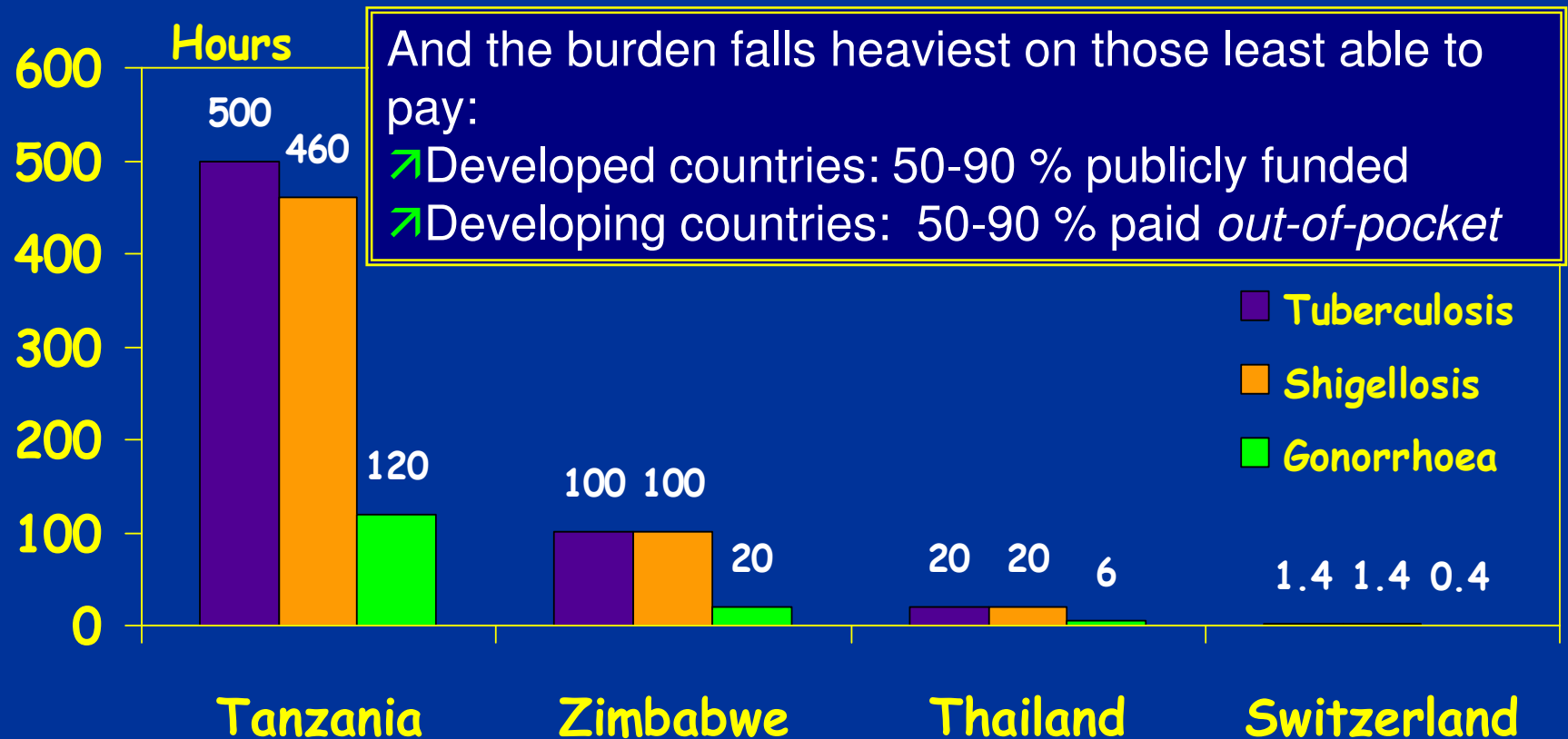
Public health need

In poor countries drugs are largest household and second largest public expenditure for health

Pharmaceutical spending, as % of total health spending

Developed countries
(7 - 20%)

Transitional countries
(15 - 30%)

Developing countries
(24 - 66 %)

The cost of medicine is substantial - number of working hours to pay full treatment course

Hours

And the burden falls heaviest on those least able to pay:
↗ Developed countries: 50-90 % publicly funded
↗ Developing countries: 50-90 % paid *out-of-pocket*

Legend:
- ■ Tuberculosis
- ■ Shigellosis
- ■ Gonorrhoea

Chart data (working hours):

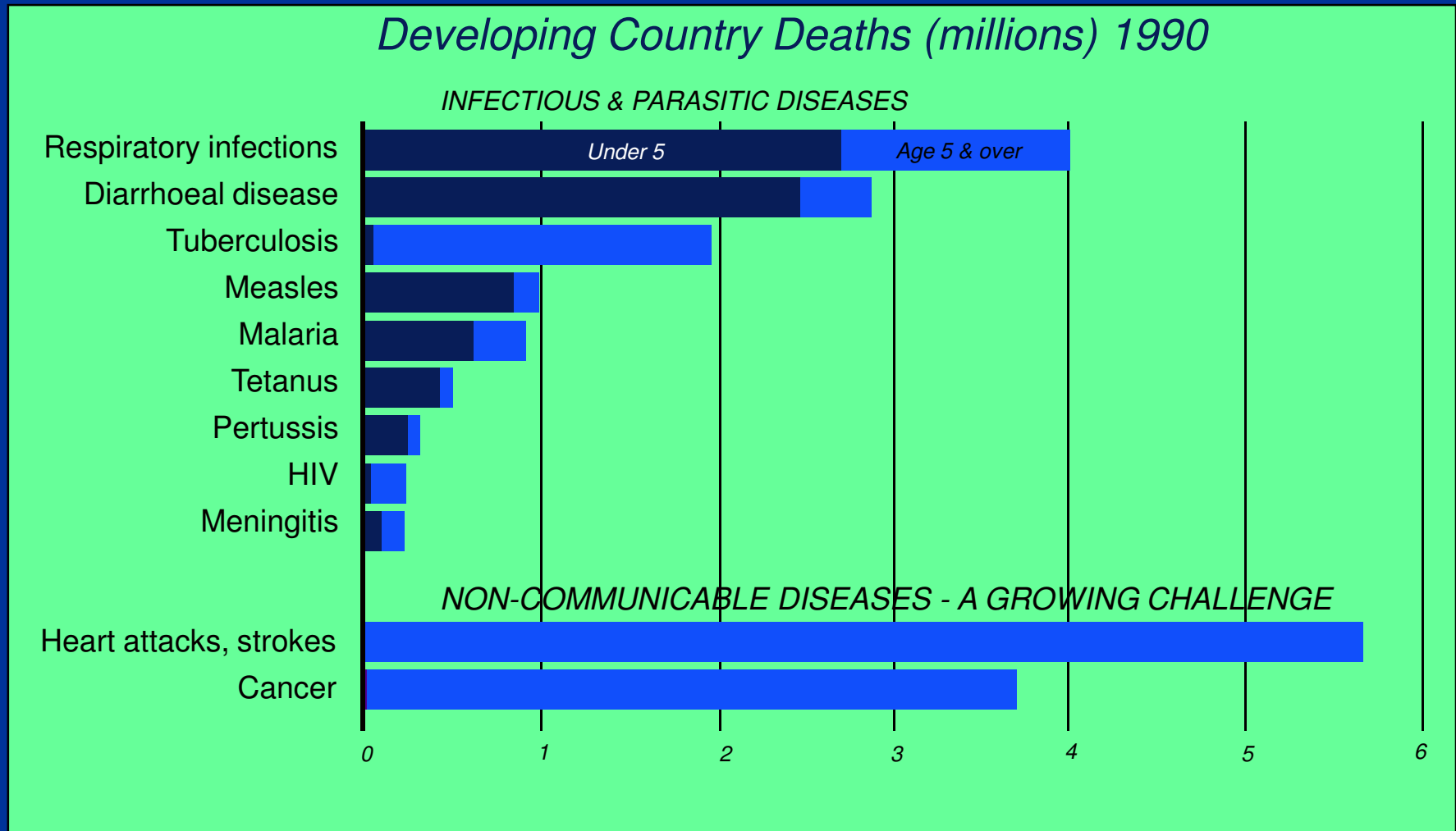| Country	Tuberculosis	Shigellosis	Gonorrhoea
Tanzania	500	460	120
Zimbabwe	100	100	20
Thailand	20	20	6
Switzerland	1.4	1.4	0.4

Y-axis: 0, 100, 200, 300, 400, 500, 600

Based on average worldwide price and national per capita income. *Source: WHO/DAP*

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Millions of children and adults still die from diseases readily treated with generic essential drugs

Developing Country Deaths (millions) 1990

INFECTIOUS & PARASITIC DISEASES

Respiratory infections	*Under 5* / *Age 5 & over*
Diarrhoeal disease	
Tuberculosis	
Measles	
Malaria	
Tetanus	
Pertussis	
HIV	
Meningitis	

NON-COMMUNICABLE DISEASES - A GROWING CHALLENGE

Heart attacks, strokes	
Cancer	

0   1   2   3   4   5   6

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National strategies

As of the mid-1990's, few countries had achieved large generic coverage

DEVELOPED COUNTRIES

% prescriptions generic
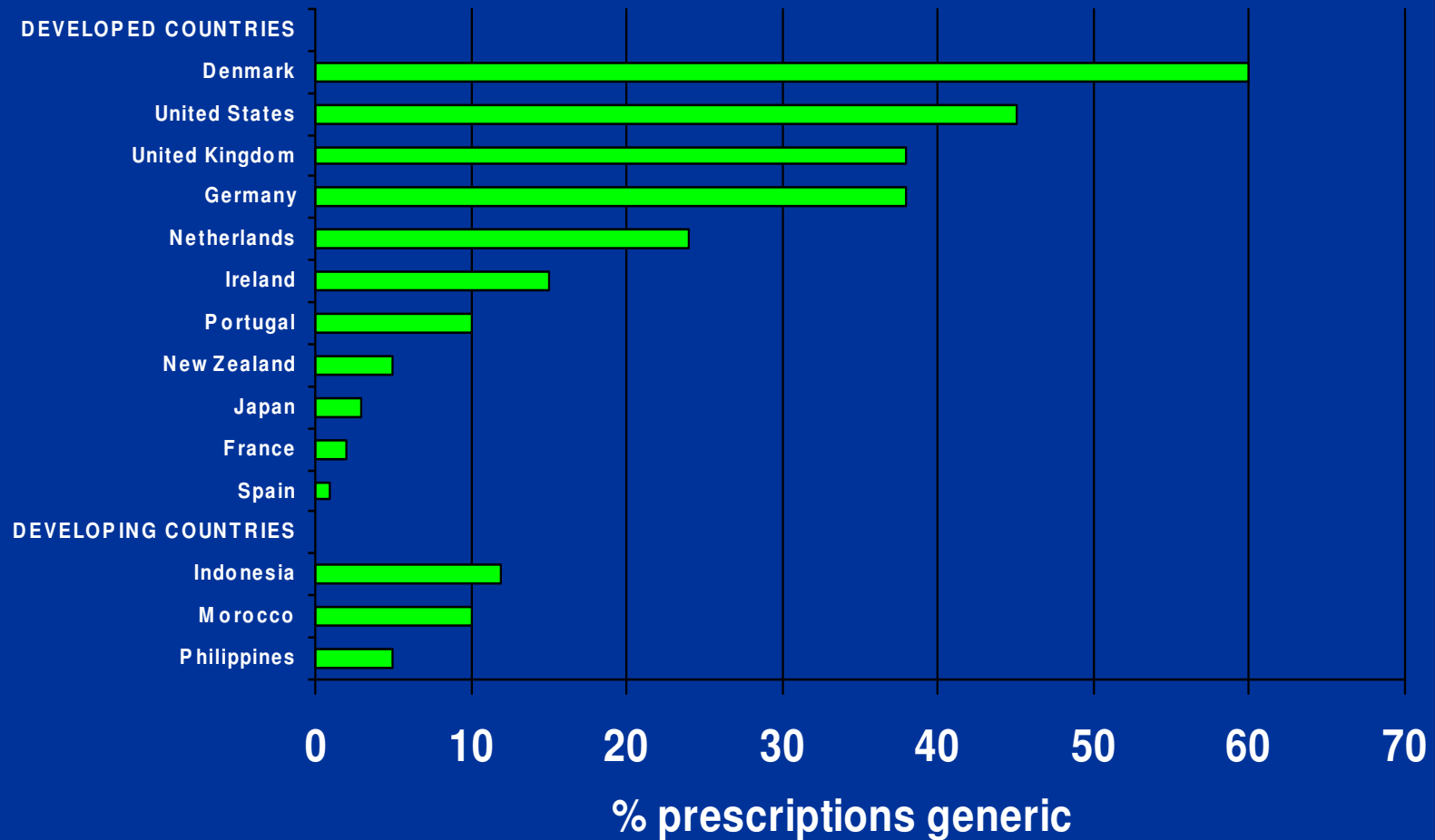
Source: DAP *Global comparative pharmaceutical expenditures* and IGPA
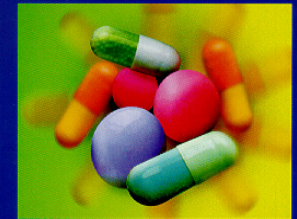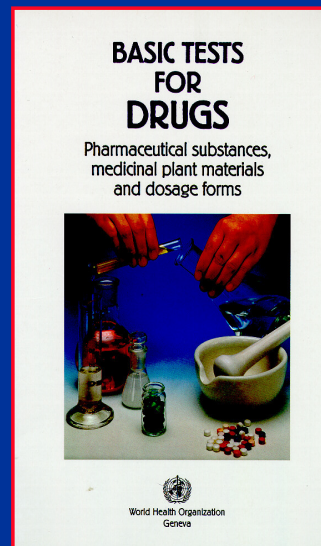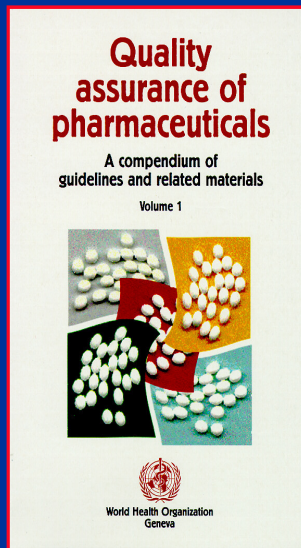
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National strategies

Reliable quality

- **substitution / non-substitution lists**
- **national regulatory capacity**
- **enforcement of good manufacturing practices (GMP)**
- **distribution system inspection and enforcement**

GMP

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General Concepts

- Bioavailability

  – Indicates measurement of both the rate of drug absorption and total amount (extent) of drug that reaches the general circulation from an administered dosage form. It is specific to the active drug substance as contrasted to metabolites.

General Concepts

- <u>Equivalence</u>
  - General, relative terms that indicates a comparison of one drug product with another or a set of established standards:
    - 1. Chemical
      - Indicates that two or more dosage forms contain the same labeled quantities (plus or minus specified range limits) of the drug

General Concepts

- Equivalence
  - General, relative terms that indicates a comparison of one drug product with another or a set of established standards:
    - 2. Clinical
      - Occurs when the same drug from two or more dosage forms gives identical *in vivo* effects as measured by a pharmacological response or by control of a symptom or disease.

General Concepts

- Equivalence

  – General, relative terms that indicates a comparison of one drug product with another or a set of established standards:

    - 3. Therapeutic

      – Implies that two brands of a drug product are expected to yield the same clinical result. The FDA specifically uses the term therapeutic equivalence in the evaluation of multisource prescription drug products.

General Concepts

- <u>Bioequivalence</u>
    - Indicates that a drug in two or more similar dosage forms reaches the general circulation at the same relative rate and the same relative extent (i.e., the plasma level profiles of the drug obtained using the two dosage forms are the same)

Therapeutic Equivalence Evaluations

- <u>General criteria of the FDA</u>
    - 1. They are approved as safe and effective
    - 2. They are pharmaceutical equivalents
    - 3. They are bioequivalent
    - 4. They are adequately labeled
    - 5. They are manufactured in compliance with current GMP regulations.

Therapeutic Equivalence Evaluations

- **General criteria of the FDA**
  - 2. They are pharmaceutical equivalents
    - A. The contain identical amounts of the same active drug ingredient in the same dosage form and route of administration
    - B. Meet compendial or other applicable standards of strength, quality, purity and identity

Therapeutic Equivalence Evaluations

- General criteria of the FDA
  - 1. They are approved as safe and effective
  - 2. They are pharmaceutical equivalents
  - 3. They are bioequivalent
  - 4. They are adequately labeled
  - 5. They are manufactured in compliance with current GMP regulations.

Therapeutic Equivalence Evaluations

- ## General criteria of the FDA
  - 3. They are bioequivalent
    - A. they do not present a known or potential bioequivalence problems, and they meet an acceptable in vitro standards, OR
    - B. if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard

Methods for Determining Bioequivalence

- The FDA has categorized (21CFR320.24) various *in vivo* and *in vitro* approaches that may be utilized to establish bioequivalence. In descending order of accuracy, sensitivity, and reproducibility, they are:

- 1. An *in vivo* test in humans in which the active drug substances, as well as active metabolites when appropriate, is measured in plasma.

- 2. An *in vitro* test that has been correlated with human in vivo bioavailability data. This approach is most likely for oral extended release products.

- 3. An *in vivo* test in animals that has been correlated with human bioavailability data.

- 4. An *in vitro* test in human, where urinary excretion of the active drug substance, as well as active metabolites when appropriate is measured.

- 5. An *in vivo* test in humans in which an appropriate acute pharmacological effect is measured.

- 6. Well-controlled clinical trials in humans that establish the safety and efficacy of the drug product, for establishing bioavailability. For bioequivalence, comparative clinical trials may be considered. This approach is <u>the least accurate, sensitive, and reproducible approach and should be considered only if other approaches are not feasible.</u>

- 7. A currently available *in vitro* test, acceptable to FDA, that ensures bioavailability. This approach is intended only when *in vitro* testing is deemed adequate, but no *in vitro in vivo* correlation has been established. It also can related to considerations involving the Biopharmaceutics Classification Systems (BCS).

Minimizing the need for BE studies

- 1. Situation where no changes are made for an approved, marketed product

- 2. Situation where changes are made for an approved, marketed drug product

- 3. Situation where human bioequivalence testing may not be needed for initial approval or for major post-approval changes

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What is BCS?

- Classification system that provides a scientific framework for classifying drugs based on solubility and intestinal permeability.

- Criteria for rapid dissolution
  - Not less than 85% dissolved in 30 minutes, using mild agitation and physiological media

What is BCS?

- Permits waivers of in vivo bioequivalence testing for high solubility, high permeability drugs (Class I), which are formulated into immediate release dosage forms having rapid dissolution.

What is BCS?

- Basic concept behind BCS is that solutions of drugs are thought to have few bioavailability or bioequivalence issues.
  - Dosage forms that contain high solubility drugs that exhibit rapid dissolution behave similar to solutions when either a solution or the highly soluble drug is in the stomach.
  - Highly permeable (well absorbed) drugs, the likelihood of bioavailability issues is quite small and consequently, *in vivo* bioavailability testing and bioequivalence for such drugs is unnecessary.

Additional information

- 1. Dosage forms

- 2. Dissolution

Dosage forms

- There are several major absorption factors that can affect the general shape of a blood-level curve and thus drug response:
  - 1. The dose of the drug administered
  - 2. The amount of drug absorbed from a given dosage form
  - 3. The rate of absorption of the drug
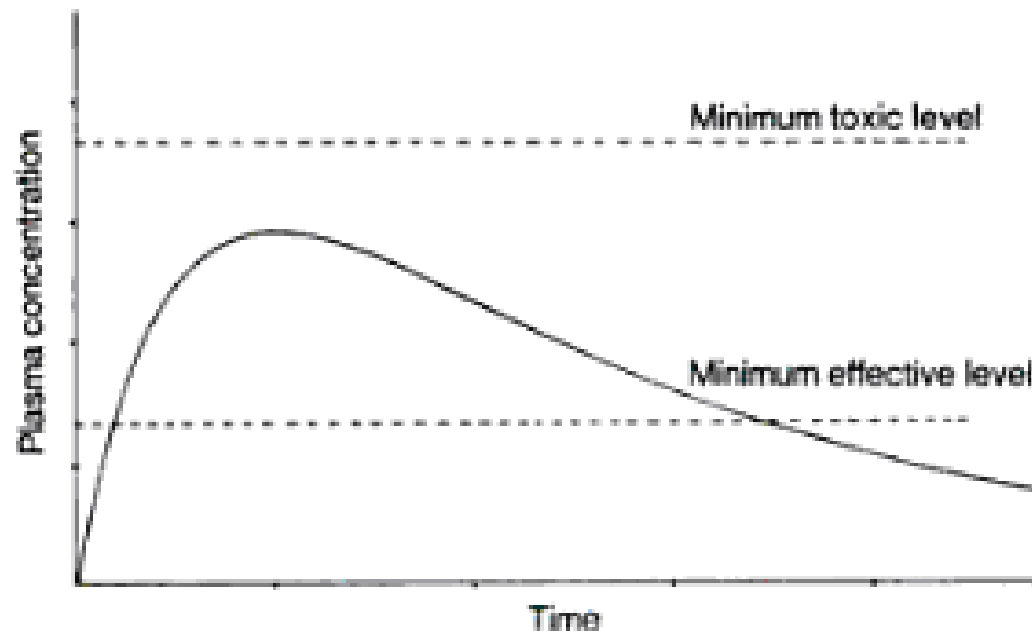 - 4. A combination of these last 2 factors

Figure 53-1. Typical plasma-level curve of a drug with effective and toxic (side-effect) profile levels defined.

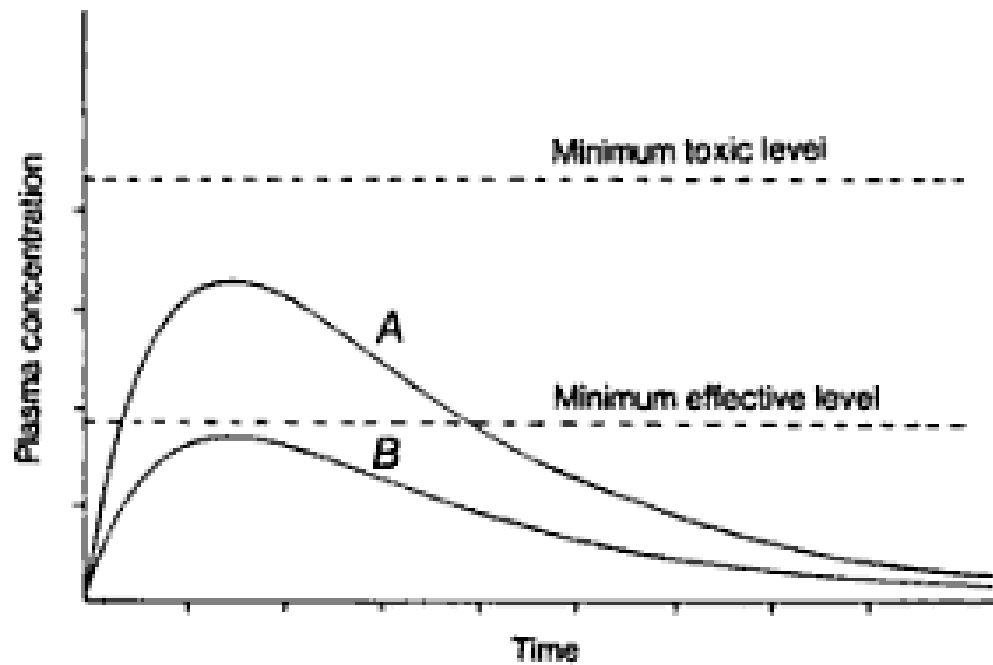Plasma-level curve for effective and toxic levels

Figure 53-2. Effect of the extent of drug absorption from a dosage form on drug-plasma levels and efficacy. The extent of absorption from dosage form B is 50% of that from dosage form A.

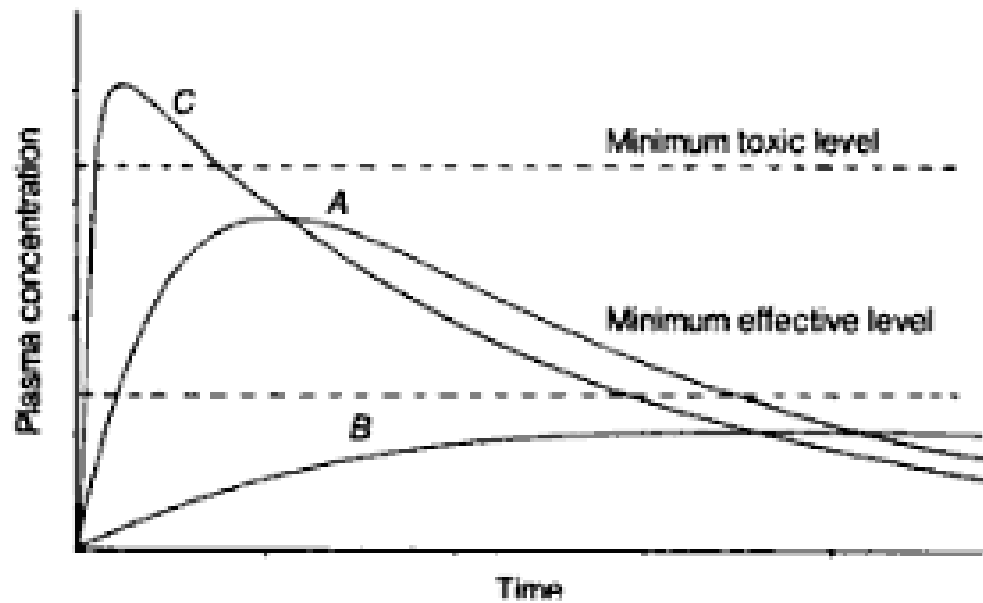Amount of drug absorbed from a given dosage form

Figure 53-3. Effect of the rate of drug absorption from a dosage form on the plasma-level profile and efficacy. The rates of absorption from dosage forms B and C and 1/10 and 10 times those from dosage form A.
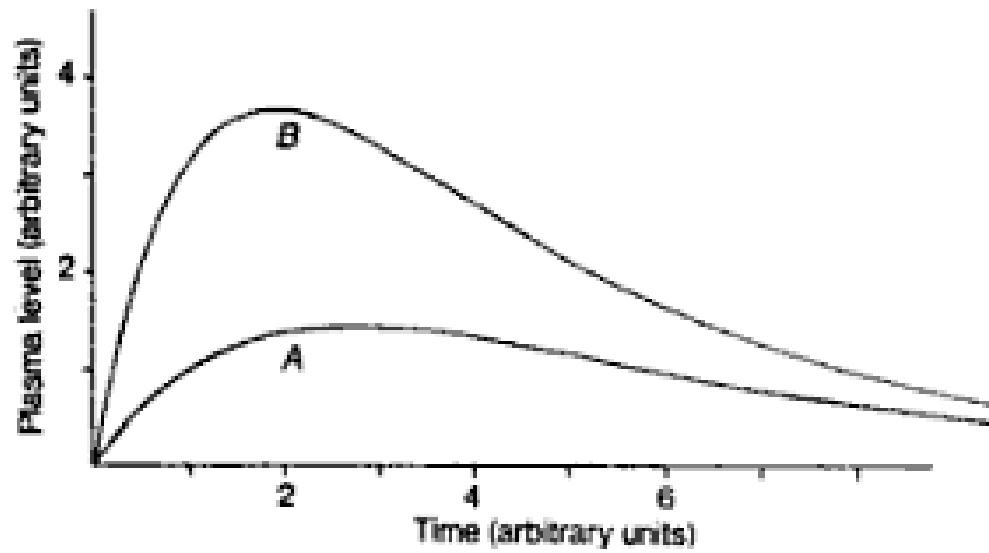
Rate of absorption of the drug

Figure 53-4. Computer simulation of the plasma-level curves for two dosage forms of the same drug assuming that the rate and extent of drug absorption for dosage form A were 50% and 50%, respectively, of those for dosage form B.

Combination of rate and extent of absorption
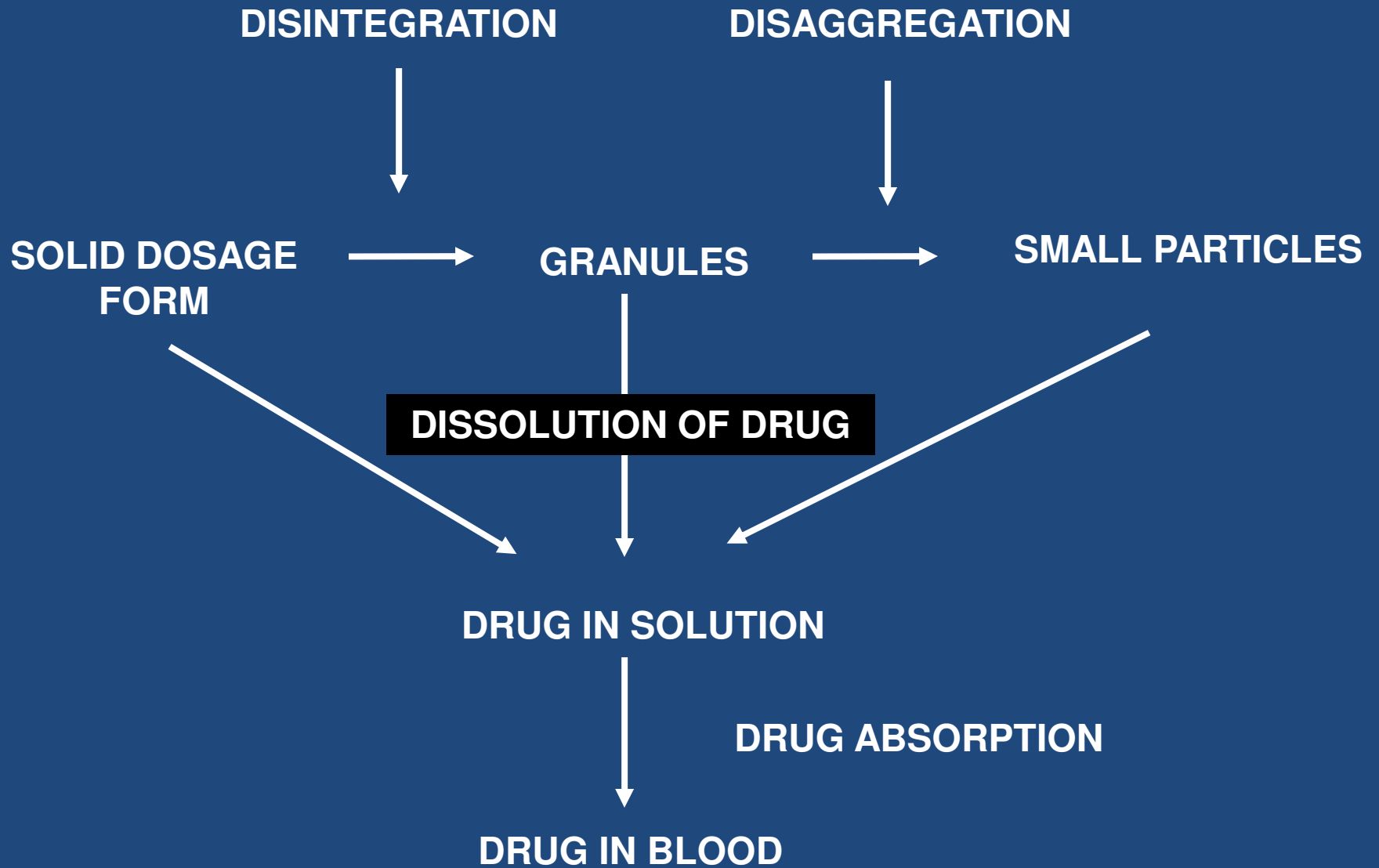
Properties of the dosage form

- In addition to the active ingredient, a tablet product usually will contain the following types of inactive ingredients:
  - 1. Glidants
  - 2. Binders
  - 3. Fillers
  - 4. Disintegrants
  - 5. Lubricants

Properties of the dosage form

– 1. Glidants

- Used to provide free-flowing powder from the mix of tablet ingredients so that the material will flow when used on a tablet machine

– 2. Binders

- Provide cohesiveness to the tablet. Too little will provide tablets that do not maintain their integrity. Too much may affect the release (dissolution rate) of the drug from the tablet

Properties of the dosage form

- 3. Fillers
  - Gives the powder bulk to an acceptable tablet size. Most commercial tablets weigh 100-500 mg so it is obvious for many potent drugs the filler constitutes a large portion of the tablet. Binding of the drug to the fillers may occur and affect bioavailability
- 4. Disintegrants
  - Used to cause tablets to disintegrate when exposed to an aqueous environment. Too much and tablets may disintegrate in the bottle because of atmospheric moisture. Too little may be insufficient for disintegration and alter rate and extent of release of the drug from dosage form.

Properties of the dosage form

– 5. Lubricants

- Enhances flow of the powder through the tablet machine and prevents sticking of the tablet in the die of the machine of the tablet after the tablet is compressed. Usually these are hydrophobic materials (stearic acid, magnesium or calcium stearate). Too little will not permit satisfactory tablets while too much may produce a tablet with water-impervious hydrophic coat, which an inhibit the disintegration of the tablet and dissolution of the drug.

Bioequivalence studies

Are they gold standards?

Clinical Relevance of Bioequivalence Issues
FDA Recommendations

- To help avoid complications arising from product substitution, the FDA established a list of generic drugs that can be safely and appropriately substituted for brand products
- The FDA does not recommend substituting drugs that have not been determined to be bioequivalent

Approved Drug Products With Therapeutic Equivalence Evaluations. 23rd ed. 2003. FDA/CDER Web site. Available at: http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm. Accessed September 29, 2003.

FDA Policy on Drug Substitution

- The FDA has prepared a list of drugs that are bioequivalent; they can be substituted for each other

- These drugs are listed in a federal publication called *Approved Drug Products With Therapeutic Equivalence Evaluations*, known as the *Orange Book*

- Drugs that are not listed as bioequivalent should not be substituted for each other

Approved Drug Products With Therapeutic Equivalence Evaluations. 23rd ed. 2003.
FDA/CDER Web site. Available at: http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm.
Accessed September 29, 2003.

Why do BE testing?
The concept of INTERCHANGEABILITY is the rule for generic products

FIRST DO NO HARM is a dictum which not only doctors should observe but the pharmaceutical companies as well.

Is and should BE testing be a gold standard?

Factors that determine establishing BE requirements by FDA

- **Therapeutic factors** evidence from
  - Clinical trials
  - Controlled observations on patients
  - Well-controlled BE studies that
    - The drug exhibits a low therapeutic ratio
    - The drug requires careful dosage titration
    - Bioinequivalence would produce adverse prophylactic or therapeutic effects

Factors that determine establishing BE requirements by FDA

- **Pharmacokinetic factors** evidence that the drug entity
  - Is absorbed from localized sites in the GIT
  - Is subject to poor absorption
  - Is subject to first-pass metabolism
  - Requires rapid dissolution and absorption for effectiveness
  - Is unstable in specific portion of the GIT
  - Is subject to dose-dependent kinetics in or near the therapeutic range

Factors that determine establishing BE requirements by FDA

- **Physicochemical factors** evidence that the drug
  - Possesses low solubility in water or gastric fluids
  - Is dissolved slowly from one or more of its dosage forms
  - Particle size and/or surface area affects BA
  - Exhibits certain physical-structural characteristics which modify its BA
  - High ratio of excipients to active ingredients as formulated
  - BA which may be affected by the presence or absence of hydrophilic or hydrophobic excipients and lubricants

REMEMBER THAT THE CONCEPT OF BIOEQUIVALENCE TESTING…

Interchangeability of generic drugs!

Study designs

- 1. Average or population bioequivalence

- 2. Individual bioequivalence

Study designs

- 1. Average or population bioequivalence
  - Conventional, non-replicated cross over design (two-formulation, two period, two sequence cross over design) or parallel designs or replicated-cross over designs

- 2. Individual bioequivalence (replicated-cross over design)
  - Three important parameters:
    - 1. within-subject variability for test
    - 2. within-subject variability for reference
    - 3. subject-by-formulation interaction variability components

Bioequivalence (1)

Compare two formulations to determine whether they provide substantially the same amount of active substance at a comparable rate.

It is applied for authorizing :
- 'scaling up'
- post-approval changes
- generics

Almost no product is marketed in the same formulation used in phase I, II, and III clinical trials.
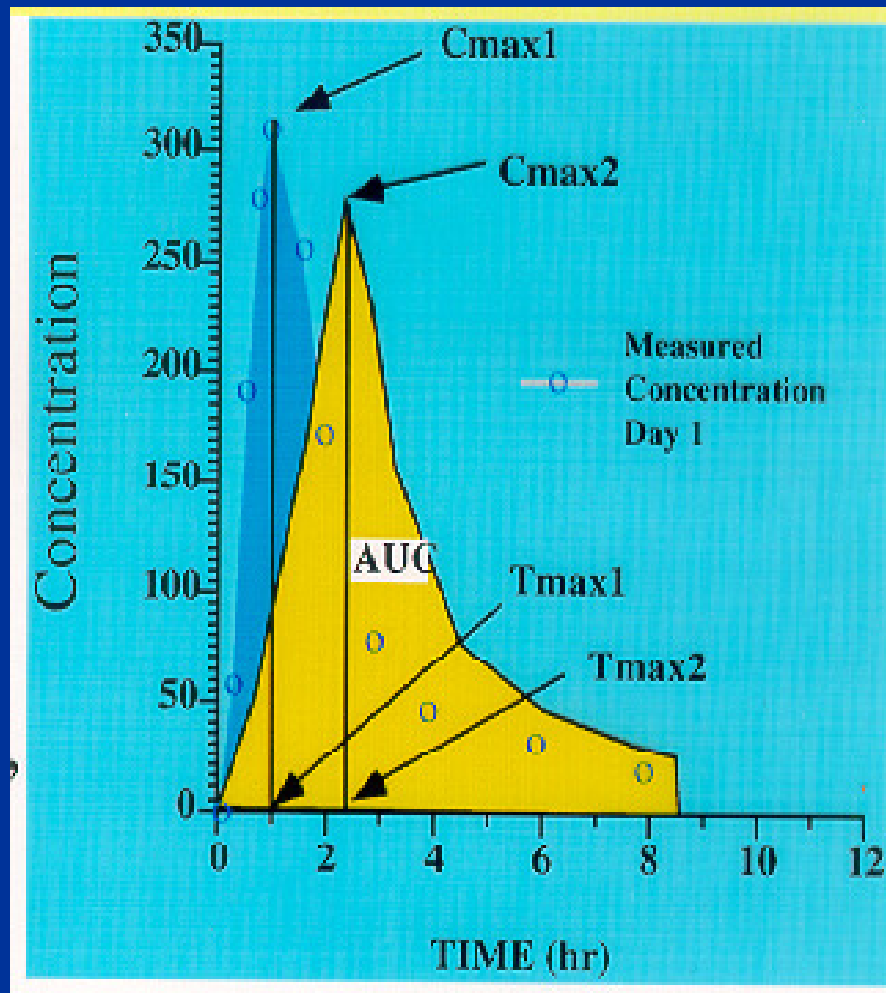
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Bioequivalence (2)

Design:

‣ 12-36 healthy volunteers (males, age 18-36)

‣ possible effects of disease/age/sex assumed identical for the 2 formulations

‣ each volunteer receives at least one dose of each formulation after suitable washout period

Specific designs (~100 FDA, USP)

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Bioequivalence (3)

3 bioavailability parameters (including active metabolites if applicable):
Cmax
AUC
Tmax*

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Bioequivalence (4)

Evaluation:
- AUC:
    - 90% CI of ratio of average AUC of the 2 products (both directions),
    - 90% confidence interval should generally be within 80 to 125% (EEUU, UE, Canadá, Australia)
- Cmax:
    wider acceptance criteria
- Tmax:
    considered only when clinically relevant

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Bioequivalence (5)

<u>1962:</u> FDA establishes BE requirement, implementation 'from now on', AUC and Cmax of TD/RD must be between +/-20% in majority of subjects

<u>1977:</u> 75/75-125: 75% of subjects must fall within 75-125%

<u>1979:</u> First Orange Book

<u>1991:</u> 90%CI must fall within 0.80-1.25

<u>1999:</u> Biopharmaceutics Classification System - BE waiver in selected cases.

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Characteristics of a BE study

- A product's BE study is a "Science based regulatory affairs' project" to be submitted to health authorities

- A combination of studies based on specializations/expertise

- All these factors should be based on a very good documentation system

- This is possible with "BE studies project management"

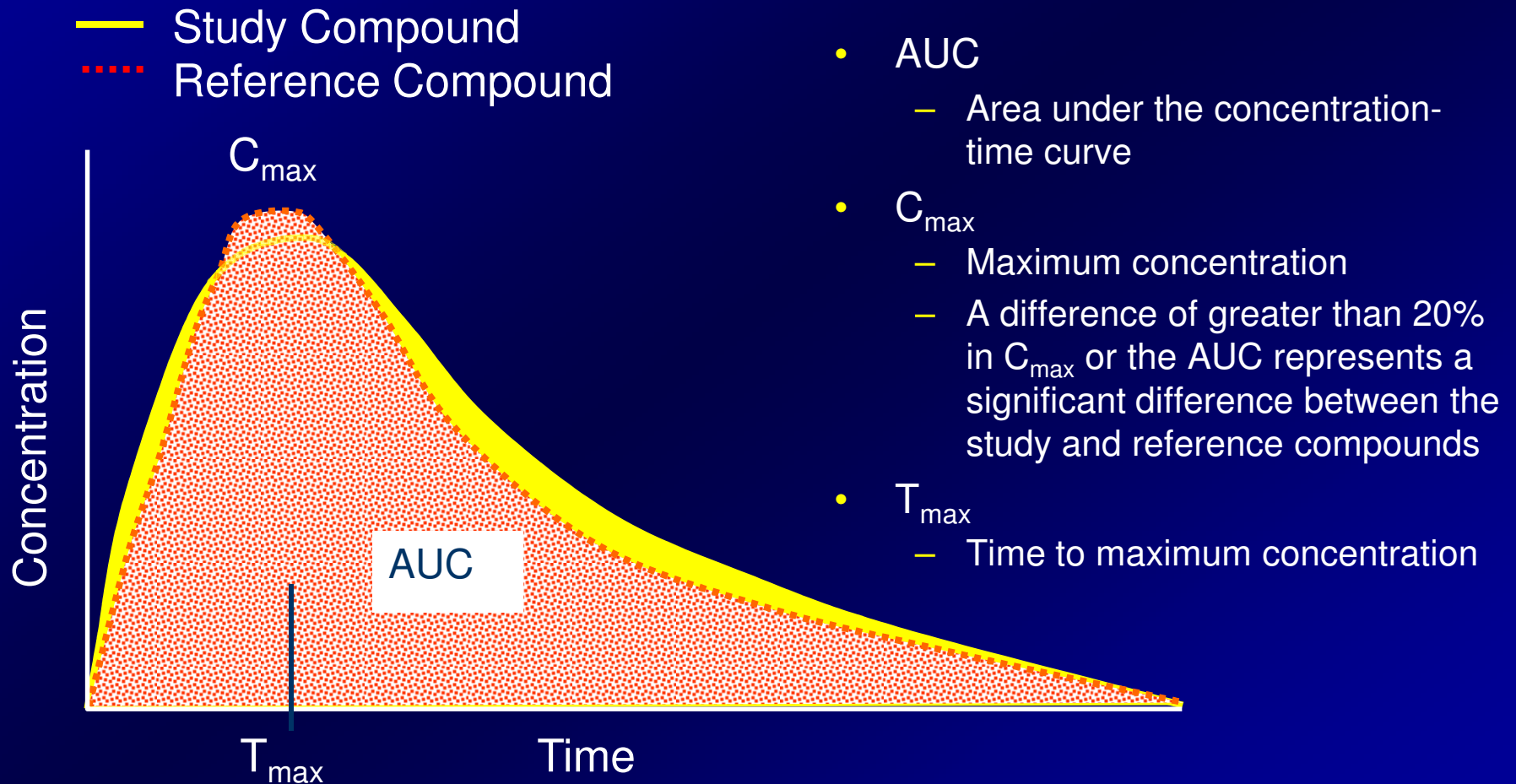# Required stages of a product before it reaches the patient

- Research

- Development

- Clinical research

- Production

- Control, Analysis

- Distribution

- Purchasing

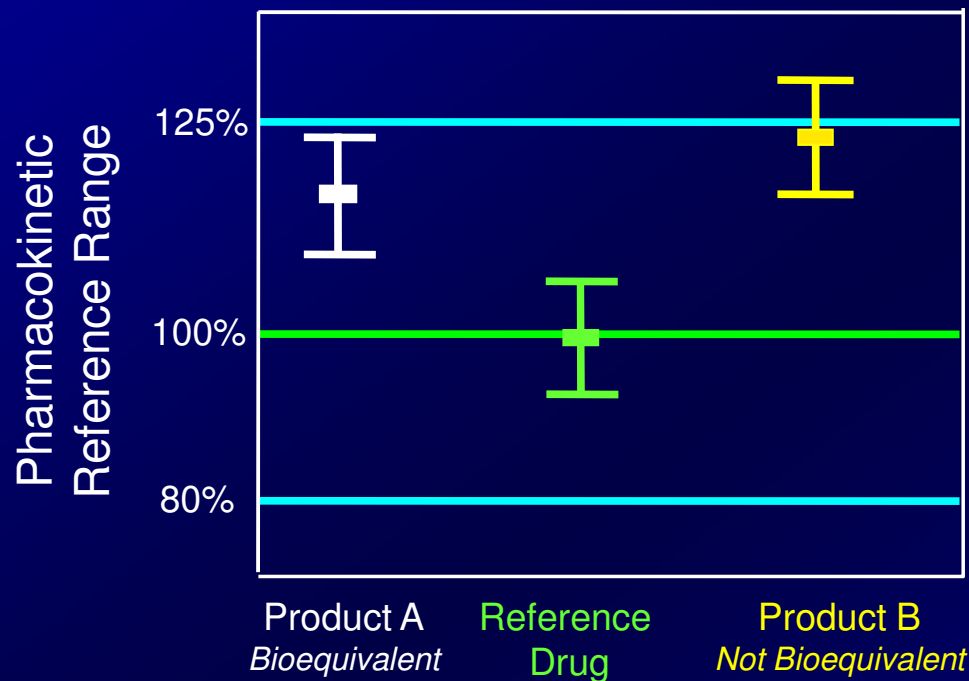# What is required to carry out these studies?

- Cost/expenses
- Sources: Location challenges
- Know-how, problem shooting
- Specialty
- Quality
- Industrial risk
- Obtaining rapid results
- Complete service
- Finance risks

Pharmacokinetic Studies Key Measurements

— Study Compound
···· Reference Compound

C_{max}

Concentration

AUC

T_{max}

Time

- AUC
  - Area under the concentration-time curve
- C_{max}
  - Maximum concentration
  - A difference of greater than 20% in C_{max} or the AUC represents a significant difference between the study and reference compounds
- T_{max}
  - Time to maximum concentration

Approved Drug Products With Therapeutic Equivalence Evaluations. 23rd ed. 2003. FDA/CDER Web site. Available at: http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm#Therapeutic Equivalence-Related Terms. Accessed September 29, 2003.

FDA Requirements for Bioequivalence

- Product A is bioequivalent to the reference drug; its 90% confidence interval of the AUC falls within 80% to 125% of the reference drug
- Product B is not bioequivalent to the reference drug; its 90% confidence interval of the AUC falls outside of 80% to 125% of the reference drug

Approved Drug Products With Therapeutic Equivalence Evaluations. 23rd ed. 2003. FDA/CDER Web site. Available at: http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm#Therapeutic Equivalence-Related Terms. Accessed September 29, 2003.

FDA Requirements for Bioequivalence

Pharmacokinetic Reference Range (y-axis): 125%, 100%, 80%

Product A *Bioequivalent* — Reference Drug — Product B *Bioequivalent*
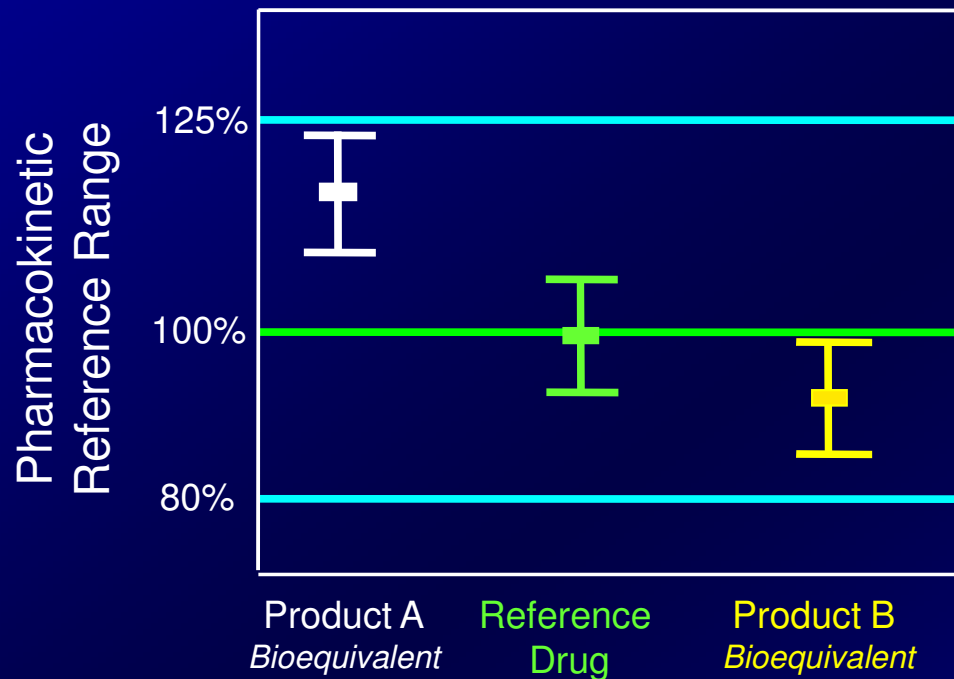
- Compare now Product A to another Product B, both of which are bioequivalent to the innovator
- Is A interchangeable with B?
- Is the comparator the same?
- BE concept is test vs. reference and not TEST vs TEST

Approved Drug Products With Therapeutic Equivalence Evaluations. 23rd ed. 2003. FDA/CDER Web site. Available at: http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm#Therapeutic Equivalence-Related Terms. Accessed September 29, 2003.

Pharmacokinetic Studies
Healthy Volunteers Versus Patients

- **If 2 drug products perform the same in healthy volunteers, the assumption is made that they will perform the same in patients with the disease, except in the case of some drugs that are potentially toxic**

Welage LS, et al. *J Am Pharm Assoc.* 2001;41:856-867.

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Pitfalls with cross-over comparisons

- 1. Different subject populations

- 2. Different study conditions

- 3. Different assay methodology

Different study populations

Research lot compared with reference standard

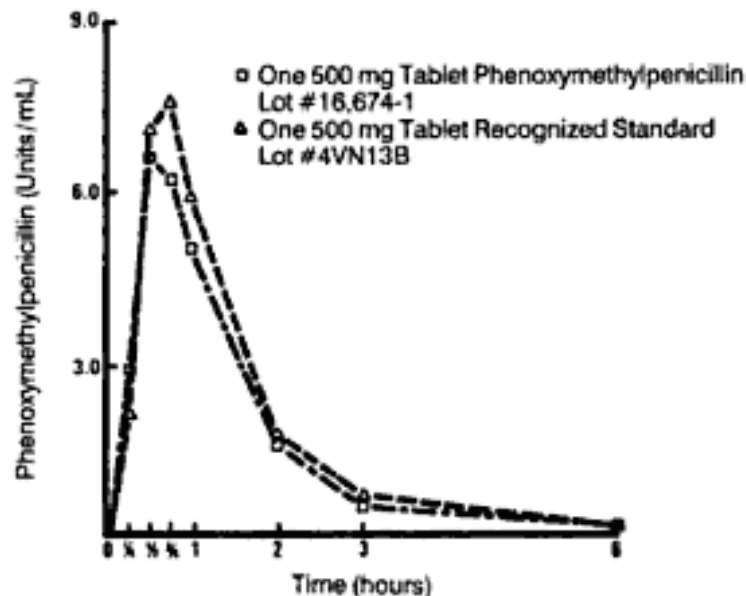**Full manufacture lot of test product and same lot of reference standard**

Figure 53-10. Average serum concentration of phenoxymethyl penicillin following oral administration of 500 mg given as one tablet of recognized standard (Δ) or of test product, research lot (□).
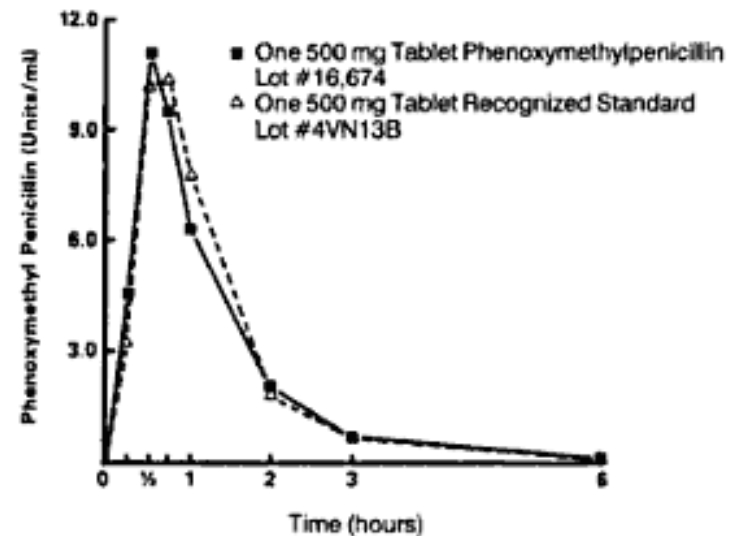

Figure 53-11. Average serum concentration of phenoxymethyl-pencillin following oral administration of 500 mg given as one tablet of recognized standard (Δ) or of test product full mfg lot (■).
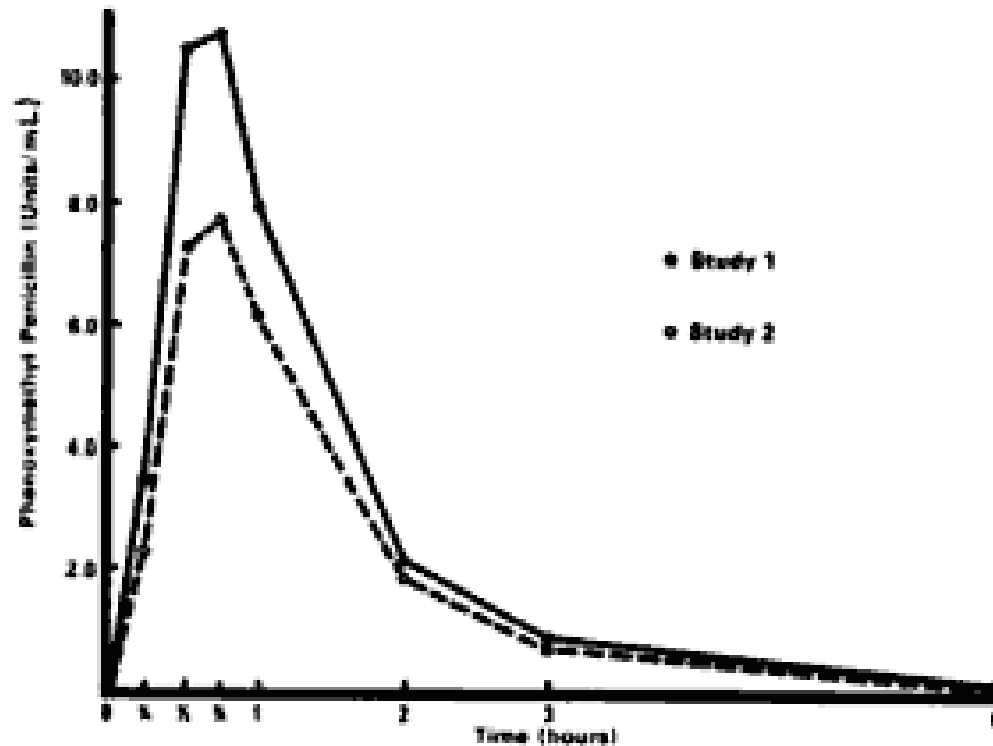
Comparing the two different populations

Figure 53-12. Average serum concentration of phenoxymethyl-penicillin following a single oral 500-mg dose of recognized standard, in two different subject populations.

Different study conditions

3-way crossover with patients 12 hr overnight and 2 hrs after drug given

Same tablets with study conditions changed to only 2 hr preadministration fast with 2 hr postadministration fast

Figure 53-13. Average serum erythromycin concentration administered in 500-mg doses as three different tablet dosage forms. The results were obtained from 21 healthy adult subjects following an overnight fast of 12 hr before, and 2 hr after, drug administration.
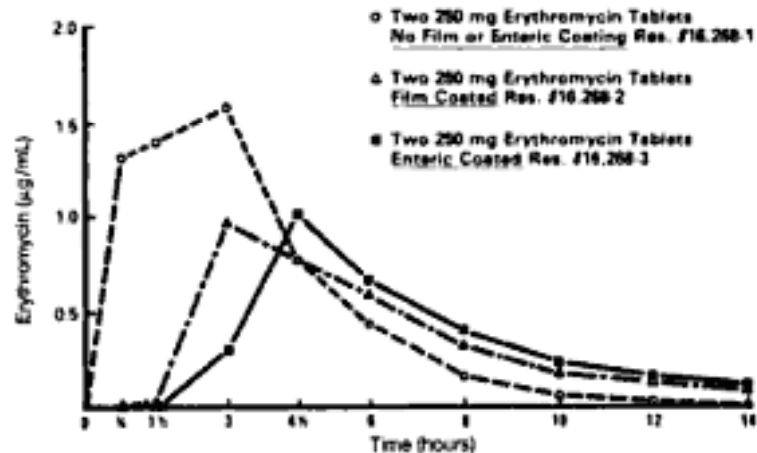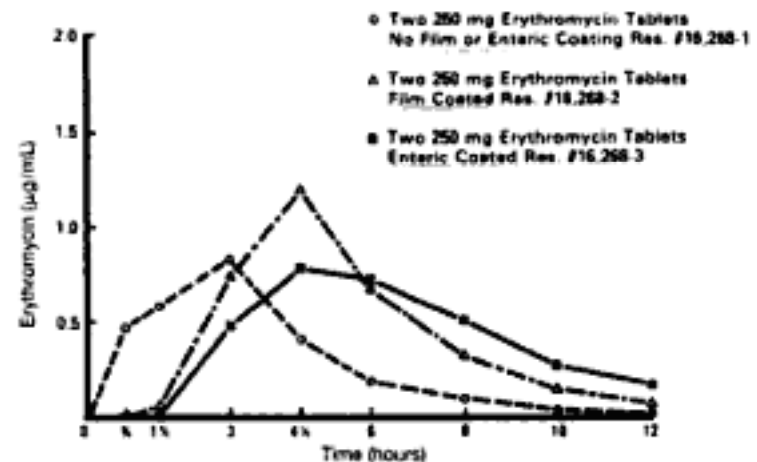

Figure 53-14. Average serum erythromycin concentration administered in 500-mg doses as three different tablet dosage forms. The results were obtained from 12 healthy adult subjects with only a 2-hr fast before drug administration.

Multiple dose study with enteric coated tablets and film-coated tablets given 4x a day after meals
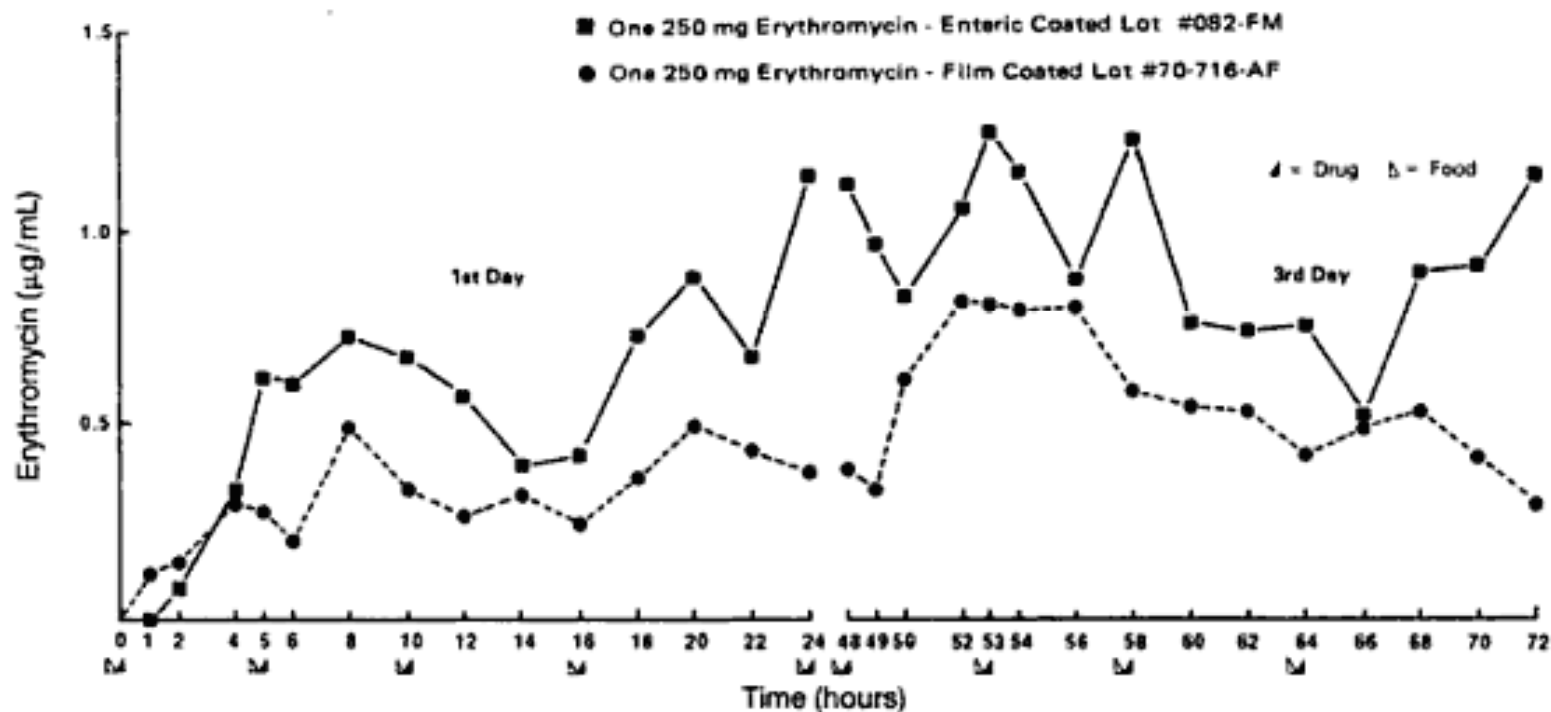

Figure 53-15. Average serum erythromycin concentration-time profiles from drug administered in two different tablet dosage forms. The results were obtained from 24 healthy adult subjects, following administration of 250 mg, four times a day, with meals and at bedtime.

Examples of drug with high first-pass metabolism

- Alprenolol
- Amitriptyline
- Chlormethiazole
- Desipramine
- Dextropropoxyphene
- Dihydroergotamine
- Diltiazem
- 5-Fluorouracil
- Hydralazine
- Isoproterenol
- Labetolol
- Testosterone

- Lidocaine
- Methylphenidate
- Morphine
- Neostigmine
- Nifedipine
- Nitroglycerin
- Papaverine
- Pentazocine
- Phenacetin
- Propranolol
- Salicylamide
- Verapamil

FA= 0.5 or less. From: Pond, S.M. and Tozer, T.N. : First-pass elimination. B concepts and clinical consequences. Clin Pharmacokinetics 1984; 9:1-25

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Examples of drugs with "possible" BA/BE problems (104 substances)

Acebutolol	Acetohexamide	Ajmaline	Alprenolol	Aminophylline
Amiodarone	Amitryptyline	Atenolol	Betamethasone	Bevantolol
Bromocryptine	Busulfan	Butriptyline	Captopril	Carbamazepine
Cefalexin	Cefazolin	Chlorambucil	Chloramphenicol	Chlorpromazine
Chlorpropamide	Clomifene	Clonazepam	Clonidene	Conjugated Estrogens
Cyclophosphamide	Cyproterone	Deslanoside	Dexamethasone	Diethylstilbestrol
Digitoxin	Digoxin	Diltiazem	Disopyramide	Dosulepin
Droperidol	Dydrogesterone	Enalapril	Epinephrine	Erythromycin
Ethinylestradiol	Ethosuximide	Ethylestrenol	Felodipine	Flecainide
Fluocortolone	Fluoxymesterone	Flupentixol	Fluphenazine	Flurazepam
Flutamide	Glibenclamide	Gliclazide	Glipizide	Guanfacine
Haloperidol	Hydrocortisone	Imipramine	Isosorb.-5-mononitrate	Isosorbide dinitrate
Labetalol	Levothyroxine	Liothyronine	Lithium Carb.	Magnesium sulfate
Medroxyprogesterone	Mesterolone	Metformin	Methotrexate	Methylergometrine
Methylprednisolone	Metoprolol	Midazolam	Nadolol	Nicardipine
Nifedipine	Nitrendipine	Nitroglycerin	Norethisterone	Oxandrolone
Oxprenolol	Perphenazine	Phenytoin	Pindolol	Prazosin
Procainamide	Propranolol	Pyrazinamide	Quinidine	Rifampicin
Temazepam	Terazosin	Testosterone	Theophylline	Thioridazine
Thyroglobulin	Tocainide	Tolbutamide	Triamcinolone	Triazolam
Trifluoperazine	Valproate	Verapamil	Warfarin	

Sources: too many to list

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FDA BE requirement for initial registration (April 27, 2006) in the Philippines

Active ingredient	Dosage form	Reference Drug	Company
Atenolol	tablet	Tenormin	AstraZeneca
Diltiazem	Tablet,capsule	Dilzem	Pfizer
Gliclazide	tablet	Diamicron	Servier
Metformin	tablet	Glucophage	Merck
Metoprolol	tablet	Betaloc	AstraZeneca
Nicardipine	Tablet, capsule	Cardipine	LR Imperial
Nifedipine	Tablet, capsule	Adalat softgel	Bayer
Phenytoin	Tablet, capsule	Dilantin	Pfizer
Propranolol	Tablet, capsule	Inderal	AstraZeneca
Pyrazinamide	Tablet, susp	PZA-Ciba	Novartis
Rifampicin	Tablet, cap, susp	Rimactane/Rifadin	Novartis/GSK
Theophylline	Tablet, capsule	Theodur	AstraZeneca

Products With a Narrow Therapeutic Range

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Narrow Therapeutic Range Definition

- The FDA defines a drug as having a narrow therapeutic range if
  - There is less than a 2-fold difference between median lethal dose and median effective dose values
  - There is less than a 2-fold difference between minimum toxic concentrations and minimum effective concentrations in the blood
  - Safe and effective use of the drug products require careful titration and patient monitoring

Food and Drug Administration. Code of Federal Regulations. Title 21, Part 320: Bioavailability and Bioequivalence Requirements. Section 320.33. 2003. Available at: http://www.accessdata.fda.gov. Accessed September 29, 2003.

Narrow Therapeutic Range Regulatory View

- For drugs containing certain substances subject to therapeutic drug concentration monitoring and/or where product labeling indicates a narrow therapeutic range designation, standard BE criteria will be used with the recommended limits of 80% to 125%

Guidance for Industry. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. FDA/CDER Web Site. Available at: http://www.fda.gov/cder/guidance/4964dft.pdf. Accessed September 29, 2003.

Narrow Therapeutic Range Clinical View

- A 20%-25% potential difference in bioavailability would alter therapeutic effects
- Current FDA bioequivalence and therapeutic equivalent evaluation guidelines may not be appropriate for assessment of narrow therapeutic range drugs

Average, Population, and Individual Approaches to Establishing Bioequivalence. 1999. FDA/CDER Web site. Available at: http://www.fda.gov/cder/guidance/1716dft.pdf. Accessed September 29, 2003.

Levothyroxine Bioequivalence Briefing Document. Available at: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3926B1_02_A-Abbott.pdf. Accessed October 7, 2003.

Take home message

Quality assurance of every drug product is a necessary requirement from every manufacturer. The physician should be able to discern which of the products in the market are interchangeable and which require BA/BE testing.

Post-marketing surveillance and pharmacovigilance are the key to making sure that generic drugs in the market are effective and safe for our patients!

Thank you for your kind attention