Issues in Bioequivalence: Complicated cases

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Need for Less expensive Medications

The Case of a Today's Couple

- She has a family history of stroke in old age, and had hypertension for years.
- Moderate elevation of serum cholesterol
- Known allergy to penicillin
- Some depressive problems last year when he was ill.

Drug	She	He	$/Day
Losaec (opeprazole)	20 mg	20 mg	$4.40
Fosamax (alendronate)	10 mg	10 mg	$3.52
Aricept (donepexil)	5 mg	5 mg	$8.82
Apo-Atenol (atenolol)	50 MG		$0.38
Coreg (carvedilol)		6.25 mg	$1.37
Vasotec (enalapril)	10 mg	5 mg	$1.76
Pravachol (pravastin)	20 mg	40 mg	$3.94
Proscar (finasteride)		5 mg	$1.63
Estraderm (estradiol 17β)	25 μg		$0.57
Effexor (venalafaxine)	75 mg		$1.56
Becloforte (beclomethasone)		250 mg	$0.72
Serevent (sameterol)		25 μg	$0.83
Aterovent (ipratropium)		20 μg	$0.47
Apo-Temazepam	15 mg	15 mg	$0.24
Total			$30.21

$11,026/Year

Generic Drugs

Bioequivalence Guidance; Different approaches:

- Canadian TPD: Categories
- US FDA: Individual drugs or products

Drug categories for bioequivalence studies:

1. Conventional (immediate) release formulation with uncomplicated or non-variable pharmacokinetics
2. Modified release formulation with uncomplicated or non-variable pharmacokinetics
3. Conventional release formulation with complicated or variable pharmacokinetics
4. Modified release formulation with complicated or variable pharmacokinetics

Special cases

1. Narrow Therapeutic Range
2. Non-linear kinetics
3. Highly toxic
4. Multiple active ingredients
5. PD instead of PK
6. Critical time of onset or rate of absorption
7. Long $t_{1/2}$
8. Oral Non-systemic Preparations

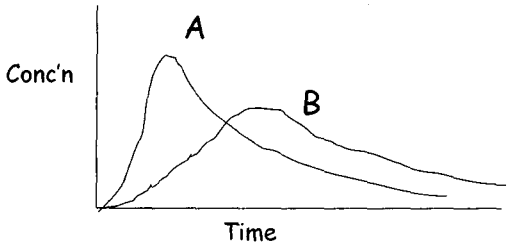
Examples:

1. Category:
   - Modified release formulation with uncomplicated or non-variable pharmacokinetics
     - Critical time of onset or rate of absorption

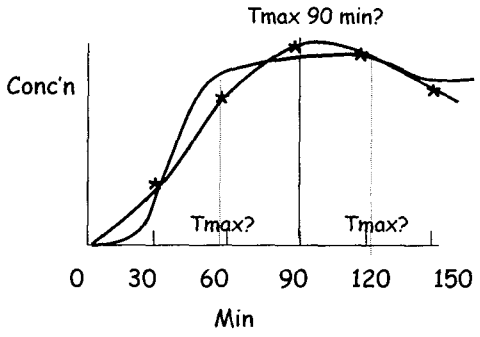
2. Individual Drug
   - Oral non-systemic preparations

Modified Release Formulations:

- Similar FDA, TPD Guidelines
- Single Dose and Steady-State Bioequivalence Studies
- Single dose (Fasting and with meal)
- AUC and Cmax
  80-125%, 90% CI
- ~~Tmax~~

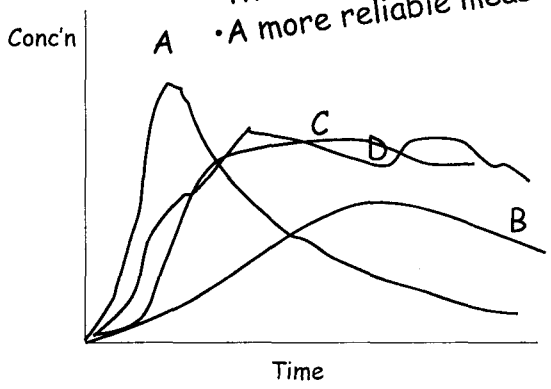


1. Tmax hard to pinpoint:

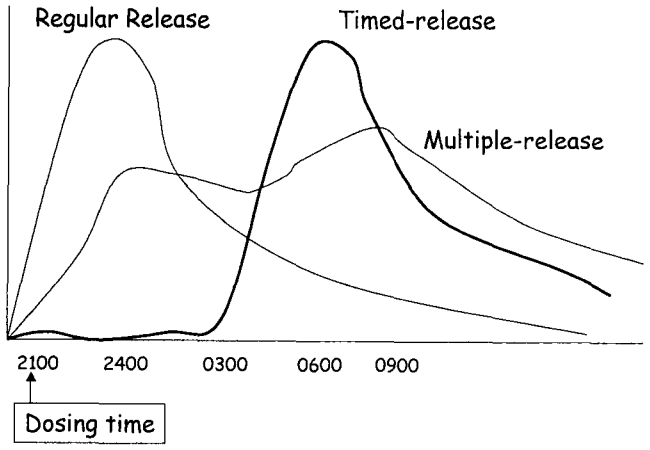


Monitoring Cmax = time course

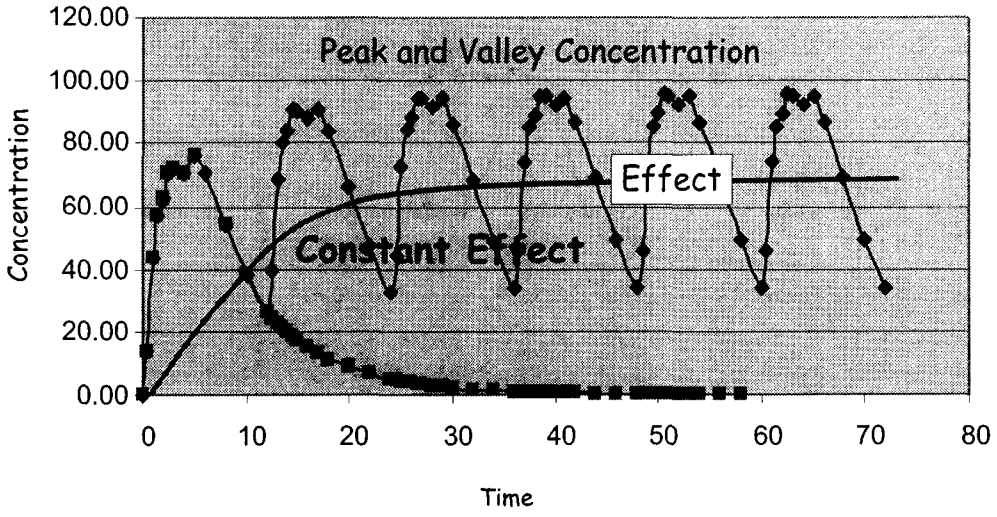
- The faster the absorption, the higher the peak
- A more reliable measure!



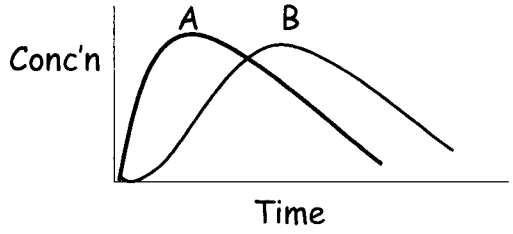
Exceptions:

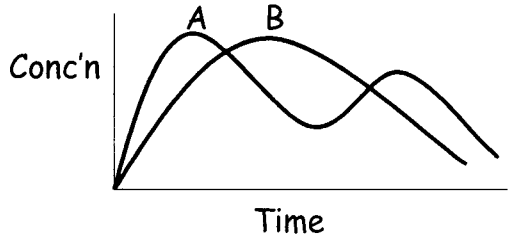


2. Since Modified-release formulations are intended for chronic use, the PK time-course of the drug is unimportant.



Therefore:





$AUC_A = AUC_B$

$Cmax_A = Cmax_B$

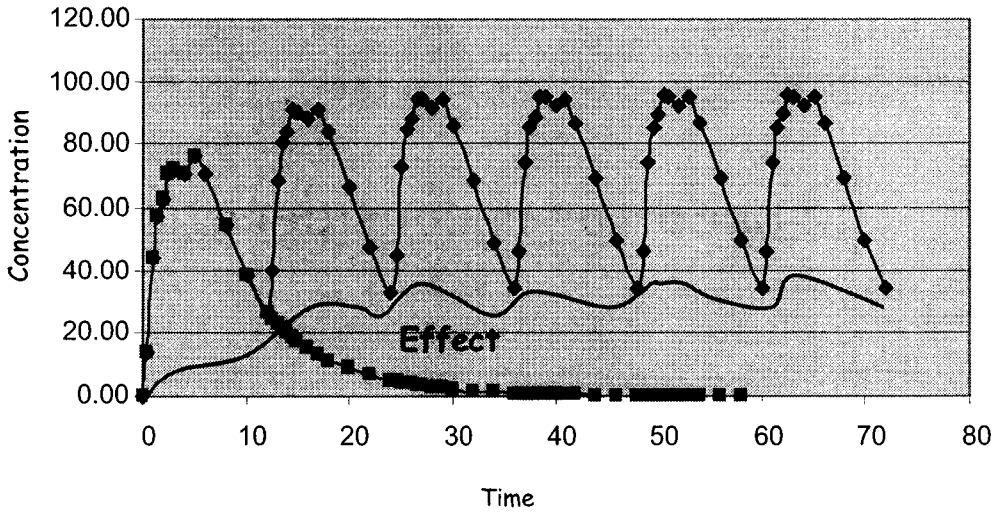
Bioequivalence, A = B

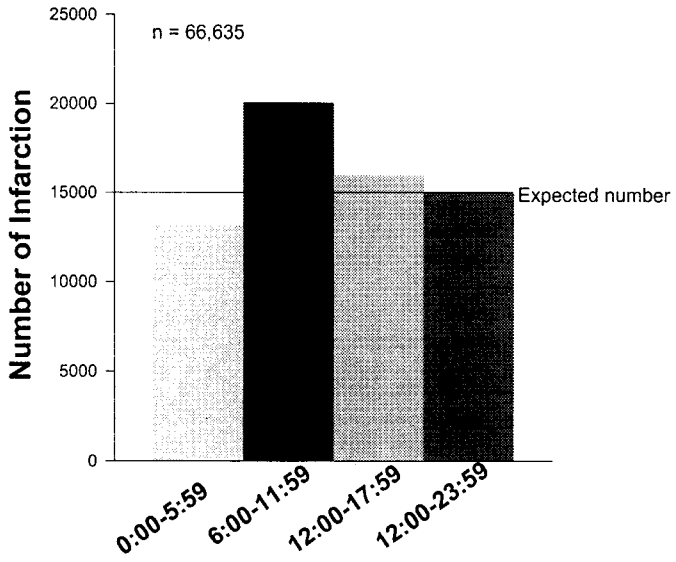
The need for reconsideration!

Chronobiology

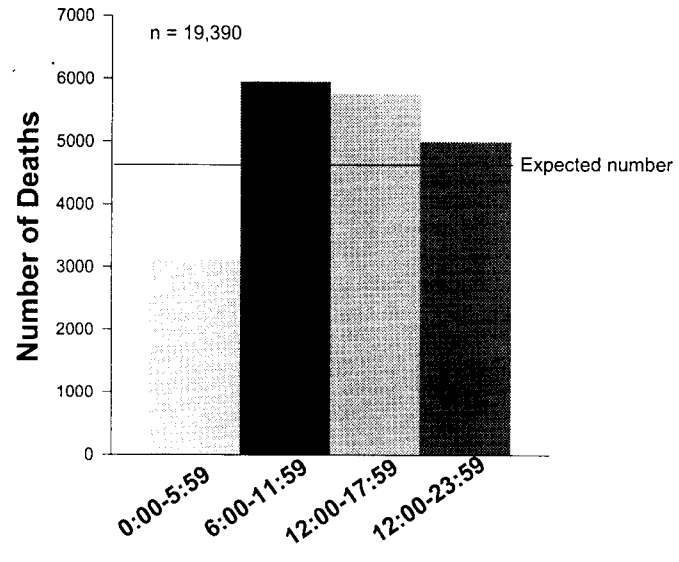
Examples:

- Cardiovascular events
- Asthma attacks
- Allergic reactions
- Morning stiffness
- .....

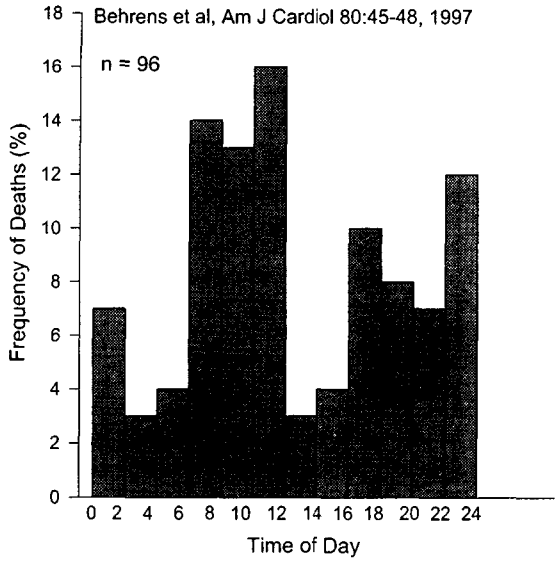


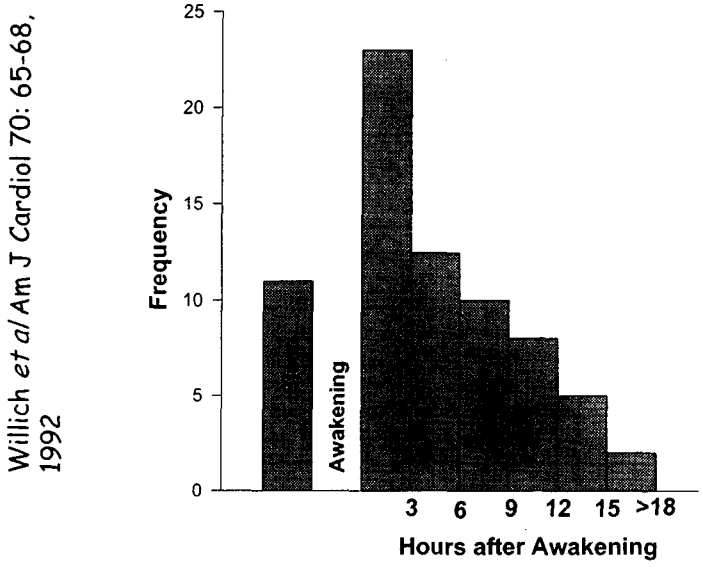


Cohen *et al* Am J Cardiol 79:1512-1516, 1977

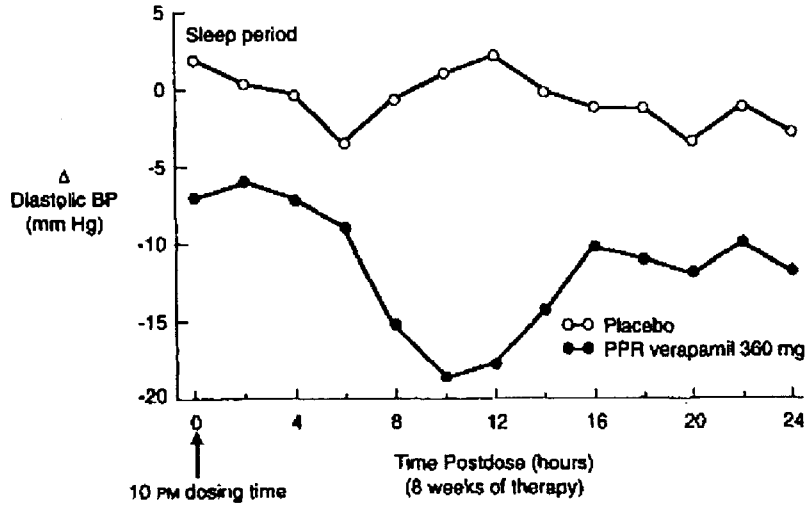


Cohen *et al* Am J Cardiol 79:1512-1516, 1977


Behrens et al, Am J Cardiol 80:45-48, 1997
n = 96
Frequency of Deaths (%)
0
2
4
6
8
10
12
14
16
18
0 2 4 6 8 10 12 14 16 18 20 22 24
Time of Day

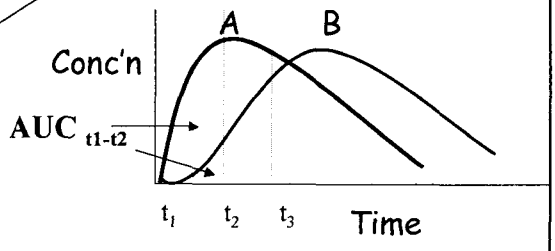

Willich et al Am J Cardiol 70: 65-68, 1992
Frequency
0
5
10
15
20
25
Awakening
3 6 9 12 15 >18
Hours after Awakening

W.B. White Am J Hypertens 9:29S-33S, 1996.



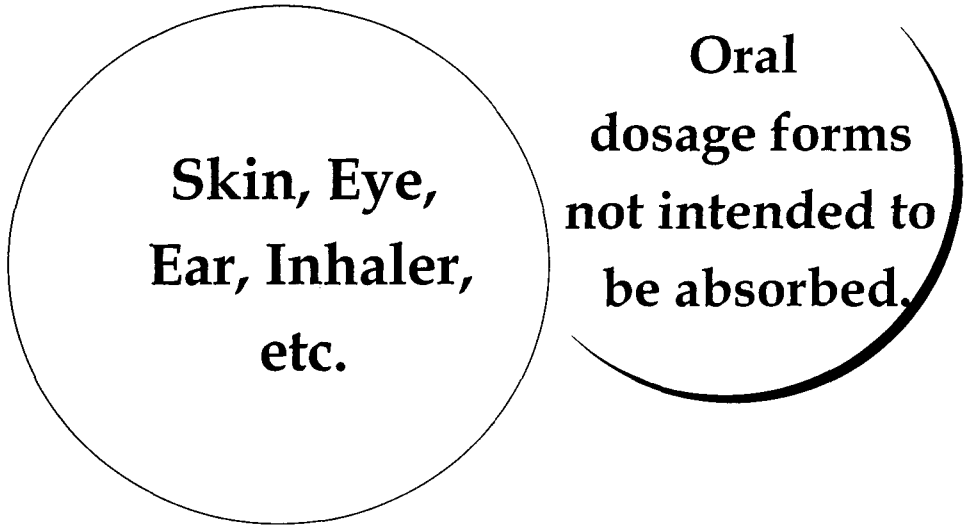
In assessing bioequivalence of modified release formulations, in addition to AUC and Cmax, the **time-course of absorption** should be considered.

Partial AUC!



Bioequivalence based on Individual Drugs

Locally Acting Medications:



Examples Oral Nonsystemic Preparations

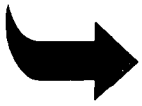
- **Treatment of Gastrointestinal tract**
  - Antacids
  - Antidiarrhea agents
    - Loperamide
  - Misoprostol
  - Sucralfate
  - Sulfasalazine
  - 5-ASA
  - Misoprostol
- **Anthelmantics**
  - Mebendazole
- **Diagnostics**
  - Radiopaque media
- **Cholestrol-Lowering agents**
  - Cholestyramine

Bioequivalence

Parity in the rate and extent to which the active ingredient becomes available at the site of action.

Systemic drugs:

Circulating Concentration

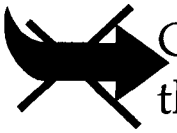


Concentration at the site of action

Oral **Nonsystemic** Preparations:

Site of action: Gut

Circulating Concentration



Concentration at the site of action

Mebendazole (Vermox®)

Form:	Chewable 100 mg tablets
Indication:	Eradication of intestinal helminths
Activity:	Local, directly on the parasites
Absorption:	Very low after first pass metabolism in the liver
Elimination:	Fecal as intact and inactive metabolites

Citizen Petition by Janssen Research Foundation on October 21, 1988 requested:

Interchangeability of **mebendazole** products based on:

Efficacy:	Full clinical studies (hookworm, roundworm, whipworm and pinworm)
Safety:	Bioequivalence and excretion (urine and feces)
In vitro:	Dissolution, polymorphism

Mebendazole

Petition:

Efficacy: Full clinical studies (hookworm, roundworm, whipworm and pinworm)

Safety: Bioequivalence and excretion (urine and feces)

In vitro: Dissolution, polymorphism

FDA's Decision:

Efficacy: Clinical studies (pinworm)

Safety: Bioequivalence (with a standard fatty meal)

In vitro: Dissolution, polymorphism

Food and Drug Administration, HHS

[57 FR 17999, Apr. 28, 1992]

"320.24 Type of evidence to establish bioavailability or bioequivalence.

(a) Bioavailability or ....."

"... [**Clinical trials**] may be considered sufficiently accurate for determining the bioavailability or bioequivalence of dosage forms intended to deliver the active moiety locally, e.g., topical preparations for the skin, eye, and mucous membrane; **oral dosage forms not intended to be absorbed** .... "

Food and Drug Administration, HHS
57 FR 17999, Apr. 28, 19

Sucralfate

Chugai ●
Marion Merrell Dow (Carafate®)
Merck

- Antiulcer
- A sulfated disaccharide-aluminum complex
- Forms a gel (at acidic pH); adheres to epithelium cells and the base of ulcer craters.
- The coating has a low permeability to H_3O^+

Sucralfate

- Tablets, Chewable Tablets, Suspension, Granules
- Low bioavailability
- Toxicity concern (some Al^{3+} absorption formulation and particle size dependent?)

Sucralfate

Local Effcet, Potential for Systemic Side Effects

Interchangeability:

- Based on Clinical Trials
  - USA, Germany ...
- Austria?