BIOEQUIVALENCE AND INTERCHANGEABILITY FOR MODIFIED-RELEASE FORMULATIONS WITH MULTIPHASIC CONCENTRATION PROFILES

Laszlo Endrenyi
University of Toronto

CSPS Workshop
Therapeutic Equivalence of Complex Molecules and Formulations
Ottawa, ON
September 10-11, 2018

SYNOPSIS

Introduction

Illustrative examples of multiphasic modified-release drug products

- **Nifedipine ER: Adalat XL**
- **Zolpidem tartrate ER: Ambien CR**
- **Methylphenidate HCl: Concerta**

Diverse multiphasic methylphenidate concentration profiles

- **Is a single regulation reasonable?**
- **Are products interchangeable?**

GOAL OF REGULATIONS: THERAPEUTIC EQUIVALENCE

Regulatory approvals aim to assure the safety and efficacy of drug products

Therefore, regulatory approvals aim to assure the therapeutic equivalence of second-entry ("Test") and reference drug products

Bioequivalence (BE) is surrogate for therapeutic equivalence

Are regulatory BE criteria always adequate to assure therapeutic equivalence?

NIFEDIPINE ER: ADALAT XL/ADALAT OROS

Treatment of high blood pressure
Prevention of chronic stable angina

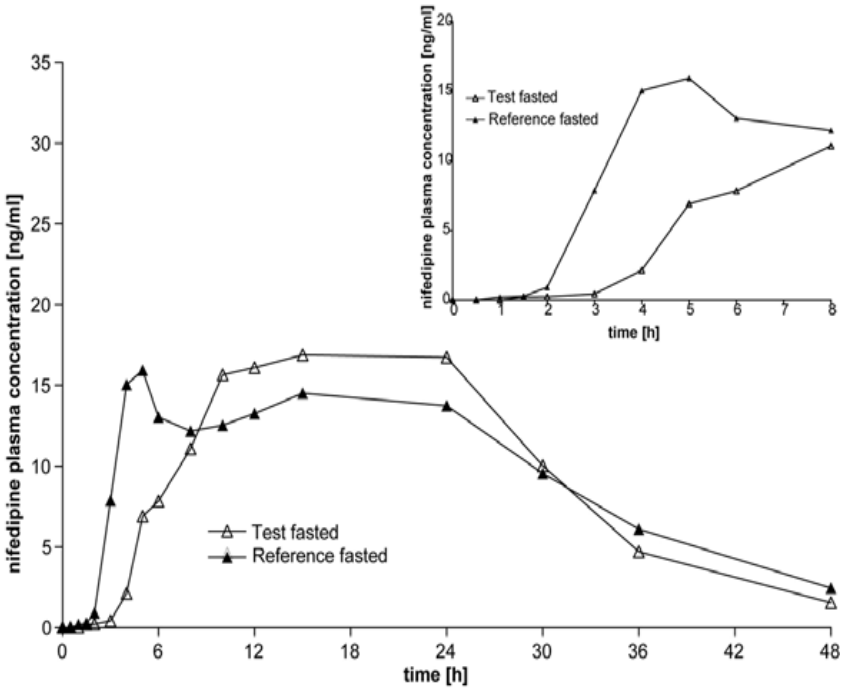
Bilayer core (water + nifedipine)
and osmotic polymer
Semipermeable outer membrane
with a laser-drilled hole

Zero-order delivery

NIFEDIPINE ER: DURATION OF EFFECT IS IMPORTANT

Osmotically active 60 mg nifedipine tablets

Anschutz et al., Int. J. Clin. Pharmacol . Ther. **48:** 158-170 (2010)



Longer plateau for reference than for test formulation

Half-value duration:

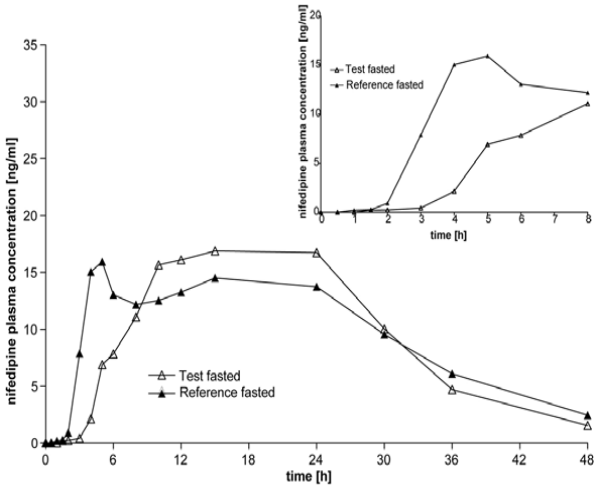
32.7 hr Reference product

25.2 hr Test product

NIFEDIPINE ER:
DELAY/LAG TIME IS IMPORTANT

Osmotically active 60 mg nifedipine tablets

Anschutz et al., Int. J. Clin. Pharmacol . Ther. **48:** 158-170 (2010)

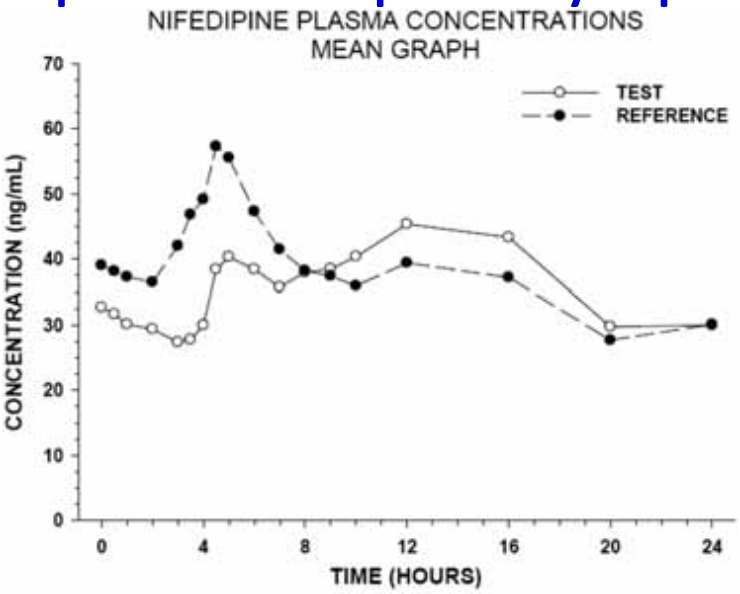


Lag-time:

Reference: 2 hours

Test: 4 hours

Consequence: Steady-state C_{min} is lower in the test product: therapeutically important!



NIFEDIPINE ER: PARTIAL AUC IS IMPORTANT

Pharmacokinetic parameters comparing Mylan-Nifedipine ER and Adalat XL (from Anschutz et al., et al., Int. J. Clin. Pharmacol . Ther. **48:** 158-170 (2010)

	GMR(%)	90% Confid. Limits	
AUC_T	91.8	79.9	105.5
C_{max}	99.8	88.6	112.4
AUC(0-9 hr)	54.8	45.8	65.5

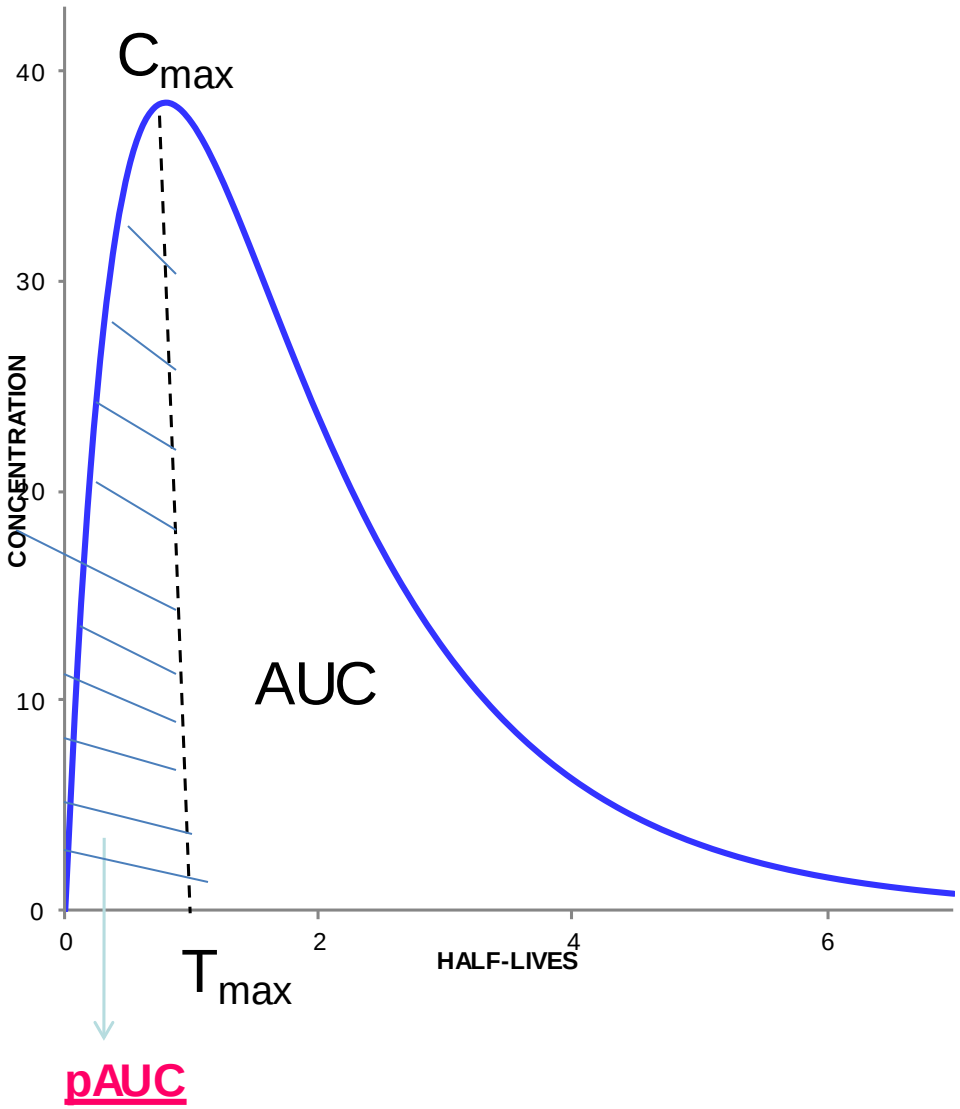
GMR: Ratio of geometric means (Test/Reference)

AUC_T and C_{max}: Bioequivalence stated

Partial AUC(0-9 hr): Discriminates between release profiles

PARTIAL AUC

Partial AUC **AUC between two time points**
Often between 0 and Tmax
Originally, when early onset is important



ZOLPIDEM TARTRATE ER (AMBIEN CR)

Non-benzodiazepine sedative hypnotic

Short-term treatment of insomnia:
difficulties with sleep onset and/or
sleep maintenance

Given once daily, at bedtime

Bilayer tablet
- **60% IR, delivered within 30 minutes**
  - **Comparable rate to that of the IR product alone**
- **40% extended release**

MULTIPHASIC MR PRODUCTS: RATIONAL APPROACH OF FDA

- **Zolpidem tartrate ER (Ambien CR)**

- **Partial AUCs to 1.5 hr and from 1.5 hr**

- **Drug must be present at sufficient levels to induce sleep**
- **Most subjects on active treatments are asleep 1.5 hours after dosing**
- **Minimum concentration to provide the clinical effect has not been established**
- **Therefore, to ensure therapeutic equivalence, drug concentrations over the 1.5-hr time period should be similar**
- **Ensures equivalent sleep maintenance and (absence of) residual effects**
- **No accumulation to steady state with the dosage form and recommended regimen**

- FDA Draft Guidance, November, 2011
- Lionberger RA, et al. Pharm. Res. 2012; 29: 1110-1120

METHYLPHENIDATE (MPH)

Treatment of attention deficit disorder (ADD)/ attention deficit hyperactivity disorder (ADHD)

MR products with multiphasic concentration profiles

Concerta tablet

- **22% IR outer coat**
- **78% ER tri-layer OROS core**

Metadate CD capsule

- **30% IR**
- **70% ER**

Ritalin LA capsule

- **50% IR beads**
- **50% enteric-coated, delayed-release beads**

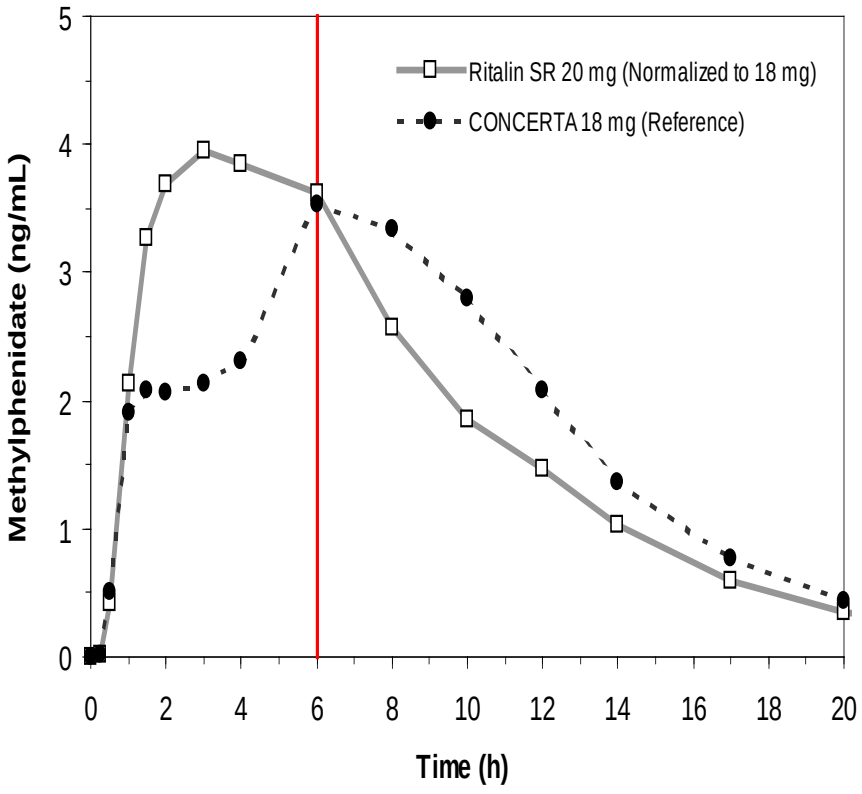
CONCERTA IS INTENTIONALLY MULTIPHASIC

Clinical rationale:

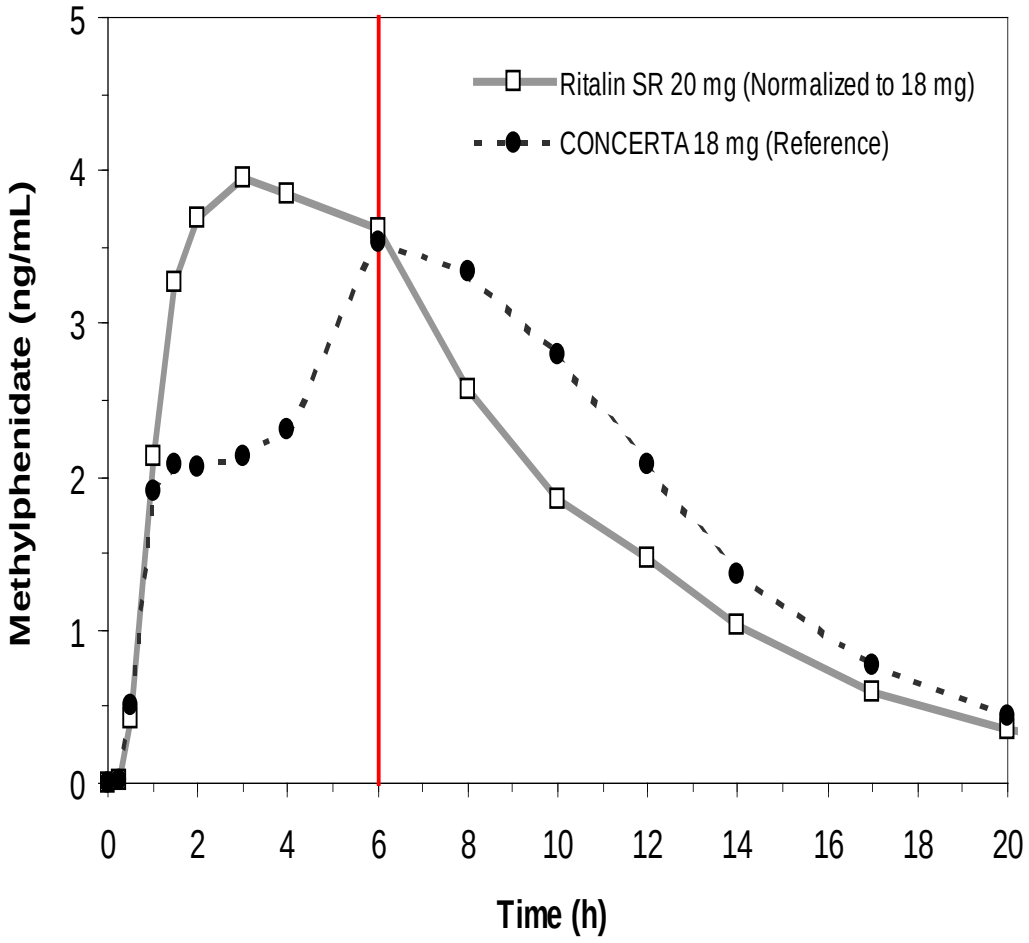
- To minimize acute tolerance (rapid early absorption)
- To extend the duration of therapeutic effect

Concentration profile:

- Initial rapid rise
- Approximate plateau to about 4 hr
- Ascent at more moderate rate to about 6-8 hr
- Decline at slower rate



PK Profiles of MPH after Dosing with Concerta (18 mg) and Ritalin SR (20 mg)



Cmax and AUCT of the two products are similar. Therefore, officially, bioequivalence can be stated.

However, concentration profiles strongly differ, again, especially in the early phase, until 6 hr.

MULTIPHASIC METHYLPHENIDATE CONCENTRATIONS

Concerta tablets (36 or 54 mg)
Metadate CD capsules (2x20 mg or 3x20 mg)

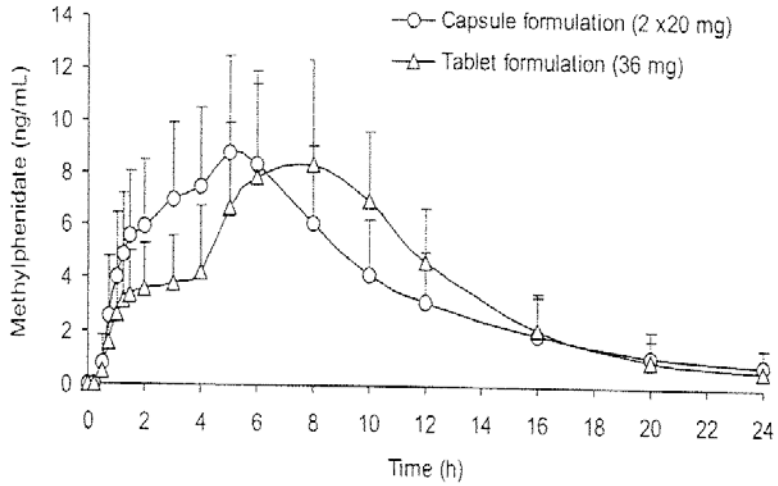


Figure 2a.

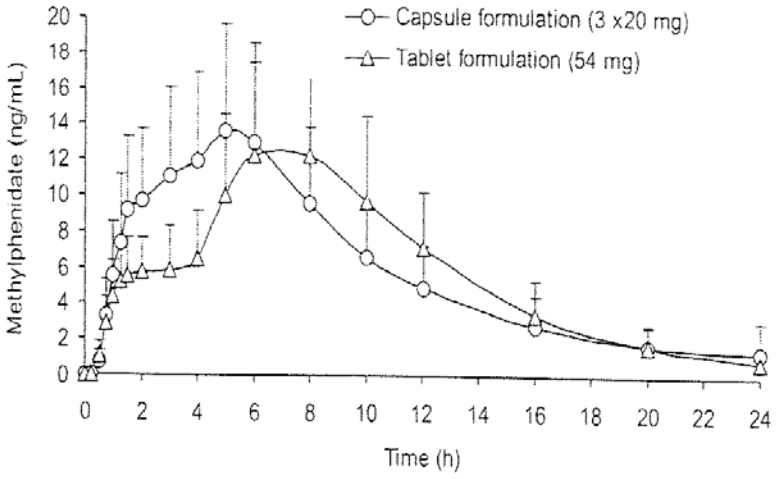


Figure 2b.

Figure 2a, b. Methylphenidate plasma concentration-time profiles following the administration of (2a) 2 × 20 mg capsules and one 36 mg tablet and (2b) 3 × 20 mg capsules and one 54 mg tablet. Data represent the mean ± SD, n = 21.

M.A. Gonzalez et al., Int. J. Clin. Pharmacol. Ther. 40: 175-184 (2002)

BIOEQUIVALENCE OF CONCERTA & METADATE?

	GMR (%)	90% Confid. Limits	
20 mg Metadate capsule			
18 mg Concerta tablet			
AUCT	107.78	103.74	111.97
Cmax	99.39	93.82	105.29
2x20 mg Metadate capsules			
36 mg Concerta tablet			
AUCT	113.44	108.93	118.14
Cmax	111.28	103.36	119.80
3x20 mg Metadate capsules			
54 mg Concerta tablet			
AUCT	110.08	105.70	114.83
Cmax	101.05	93.64	109.04

Note: Dose-adjusted parameter ratios

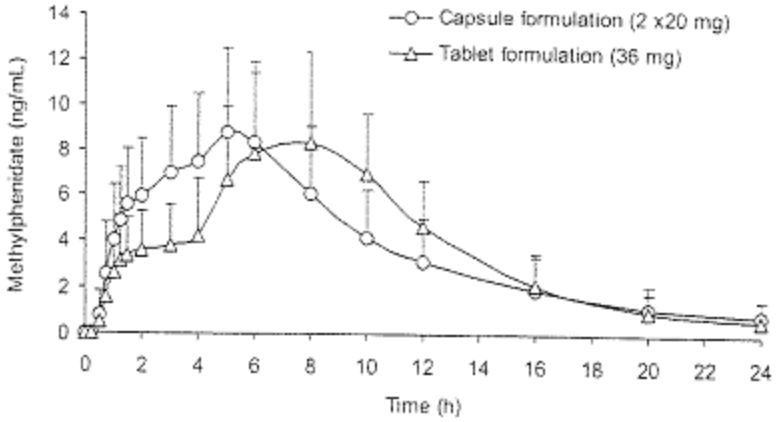
GMR: Ratio of geometric means (Test/Reference)

Based on the usual parameters (AUC & Cmax), the two drug products are bioequivalent

But are they therapeutically equivalent?

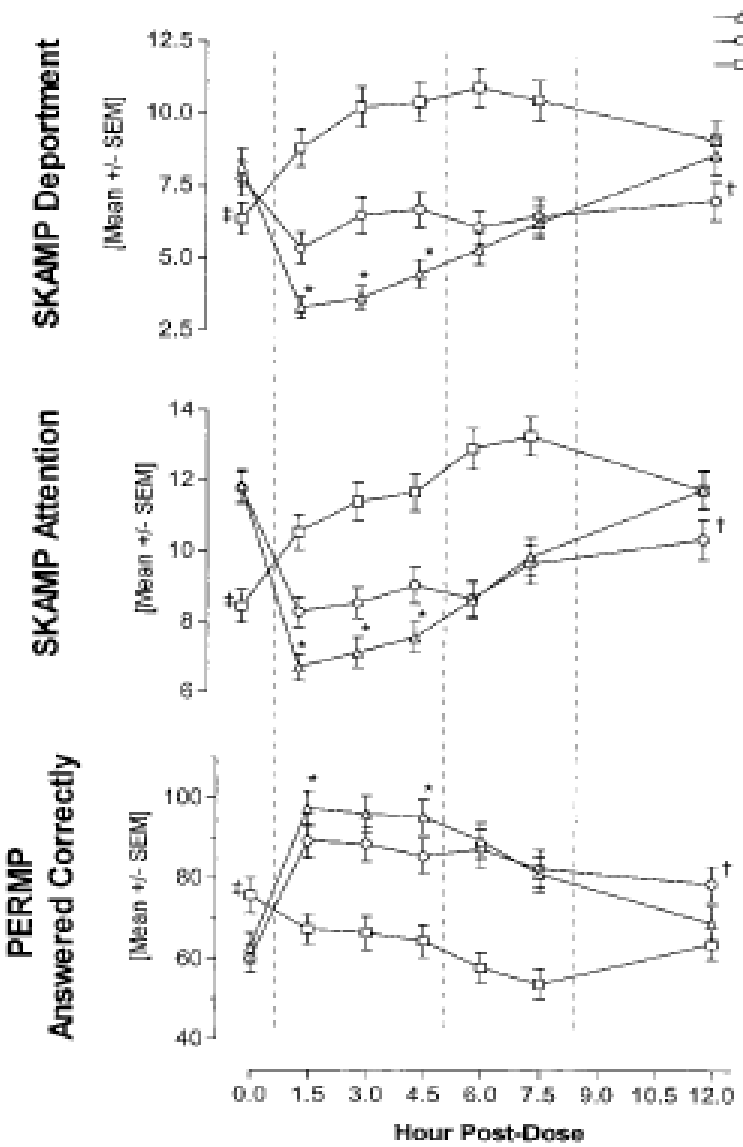
M.A. Gonzalez et al., Int. J. Clin. Pharmacol. Ther. 40: 175-184 (2002)

MPH CONCENTRATIONS vs. CLINICAL RESPONSES



M.A.Gonzalez, et al.
Int.J.Clin.Pharmcol.
Ther, 2002;40:175

Concerta tablets
Metadate CD capsules



J.M. Swanson, et al.
Pediatrics, 2004; 113:
e206

MCD: Metadate CD
CON: Concerta
PLA: Placebo

1.5-4.5 hr: MCD > CON
12 hr: CON > MCD

AUC(0-4hr) & AUC(0-6hr) DISCRIMINATE BETWEEN METADATE & CONCERTA

	GMR (%)	90% Confid. Limits	
20 mg Metadate capsule			
18 mg Concerta tablet			
AUCT	107.78	103.74	111.97
Cmax	99.39	93.82	105.29
AUC(0-4hr)	69.92	66.24	73.82
AUC(0-6hr)	77.94	74.21	81.85
2x20 mg Metadate capsules			
36 mg Concerta tablet			
AUCT	113.44	108.93	118.14
Cmax	111.28	103.36	119.80
AUC(0-4hr)	63.80	60.15	67.68
AUC(0-6hr)	72.15	68.01	76.54
3x20 mg Metadate capsules			
54 mg Concerta tablet			
AUCT	110.08	105.70	114.83
Cmax	101.05	93.64	109.04
AUC(0-4hr)	65.50	61.75	69.48
AUC(0-6hr)	73.24	69.03	77.69

Note: Dose-adjusted parameter ratios

GMR: Ratio of geometric means (Test/Reference)

M.A. Gonzalez et al., Int. J. Clin. Pharmacol. Ther. 40: 175-184 (2002)

MULTIPHASIC MR PRODUCTS: RATIONAL APPROACH OF FDA

Methylphenidate MR (Concerta)

In fasting subjects: Partial AUCs to and from 3 hr

Tmax for IR MPH is 2 ± 0.5 hr (mean ± S.D.)

2 hr is also the time when maximal response is achieved (compared to placebo)

By 3 hr, expect that 95% of patients should achieve maximal early onset of response

Mean ± 2S.D. = 95% of population response

95% of subjects should achieve maximal early onset of response by 2 hr + (2x0.5 hr) = 3 hr

Cut-off for partial AUC in fed condition: 4 hr

FDA Draft Guidance, September, 2012
Stier EM, et al., AAPS J. 2012; 14: 925-926.
Fourie Zirkelbach J, et al., Pharm. Res. 2013; 30-191-202

MULTIPHASIC METHYLPHENIDATE - FDA DRAFT GUIDANCE

Concerta (Nov., 2014)

4-period crossover

Fasting & fed

The usual metrics: AUC_{0-t}, AUC_{0-Inf}, C_{max}

In addition, partial AUCs

Cut-off times:

Fasting: 3, 7, 10 -->12 hours

AUC_{0-3}, AUC_{3-7}, AUC_{7-12}, AUC_{12-t}

Fed: 4, 8, 10 -->12 hours

AUC_{0-4}, AUC_{4-8}, AUC_{8-12}, AUC_{13-t}

Essentially empirical

However, background:

FDA, MPH ER Summary Report, June 11, 2014

Also: Subject-by-formulation interaction

[Statistically inappropriate]

MULTIPHASIC METHYLPHENIDATE - FDA Q & A

Concerta (Nov., 2014)

Approved generics by Mallinckrodt and Kudco

Reports of insufficient effects

FDA changed rating of therapeutic equivalence from AB to BX (from switchability to prescribability)

FDA asked the companies to confirm BE following the new (draft) guidance within 6 months, or voluntarily withdraw the products

MULTIPHASIC MODIFIED-RELEASE DRUG PRODUCTS

FDA

Apply partial AUCs, in addition to AUC and C_{max}

- **Advisory Committee, 2010**
- **Specific product guidances**

EMA (MR BE guideline, 2014)

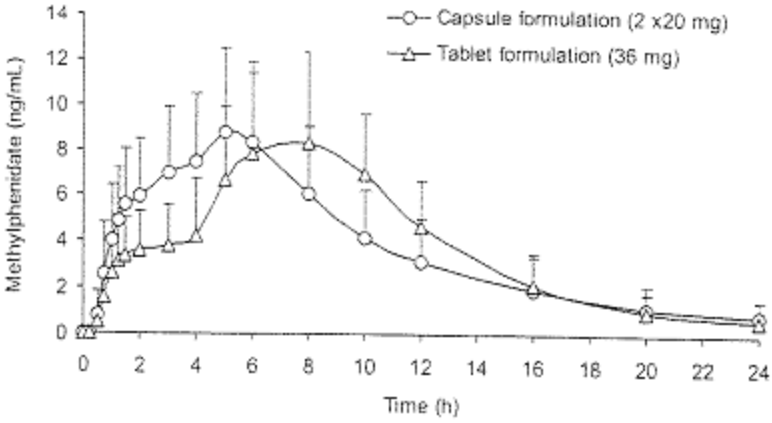
Apply partial AUCs, in addition to AUC and C_{max}

Health Canada (BE guidance, 2018)

Apply partial AUCs, in addition to AUC and C_{max}

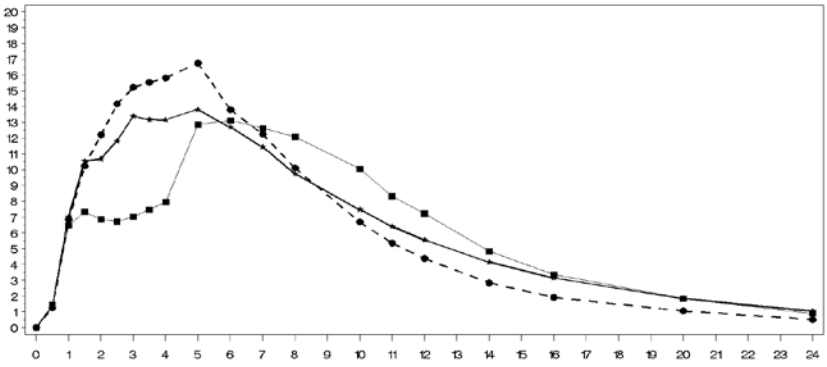
Timing, BE standard case-by-case

CONCENTRATION OF CONCERTA vs. EXTENDED RELEASE MPH



Metadate CD capsules
Concerta tablets

Largest separation:
4 hours



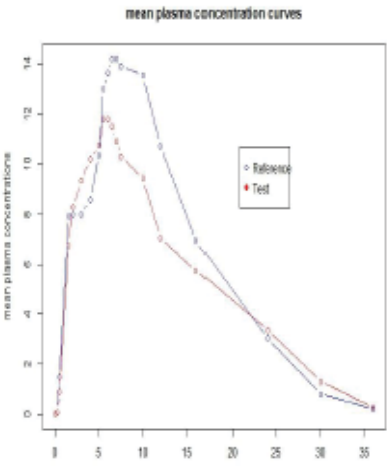
- Ritalin SR

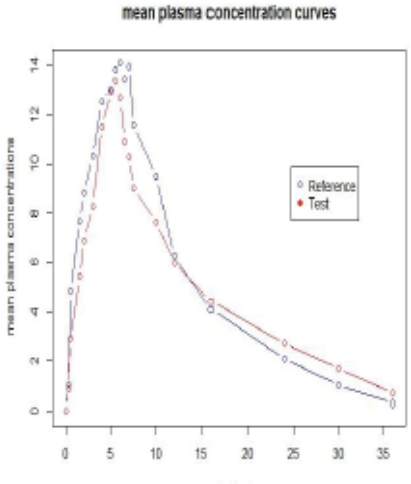
*MPH-ER-C Teva Canada

▪ Concerta

Largest separation:
3 hours

Mallinckrodt-Kudco mean concentration curves

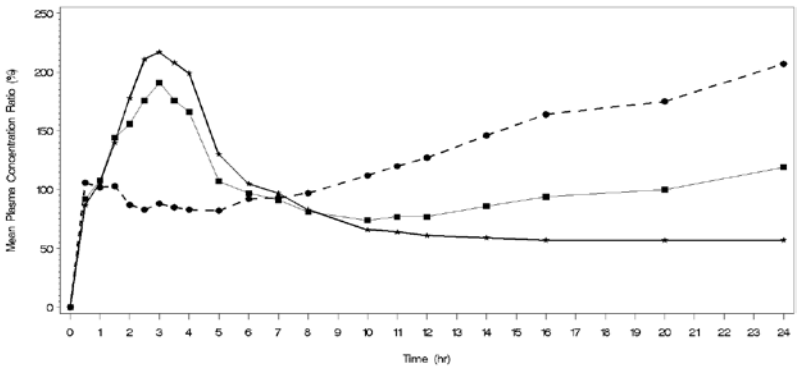




Reference: Concerta

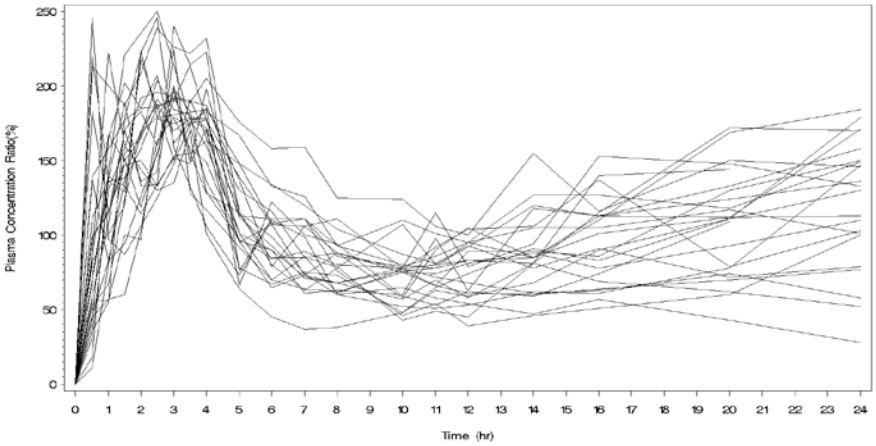
Largest separation:
10-12 hours

DEMONSTRATION OF SEPARATIONS CONCERTA vs. MPH-ER



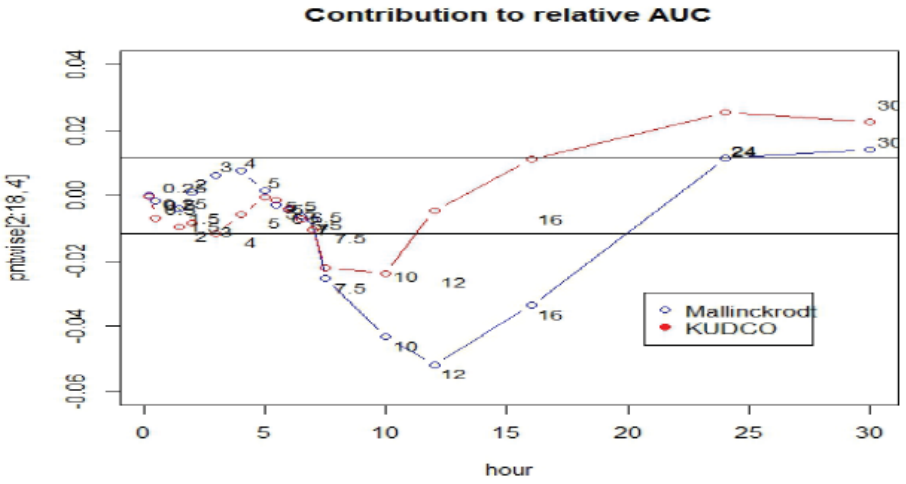
Ratios of average concentrations

- ▪ Teva ER/Concerta
- * Ritalin SR/Concerta
- • Teva ER/Ritalin SR



Ratios of individual concentrations

Teva ER/Concerta



Contribution to relative AUC

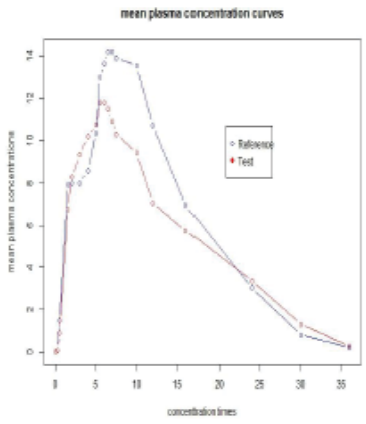
Mallincrodt
Kudco

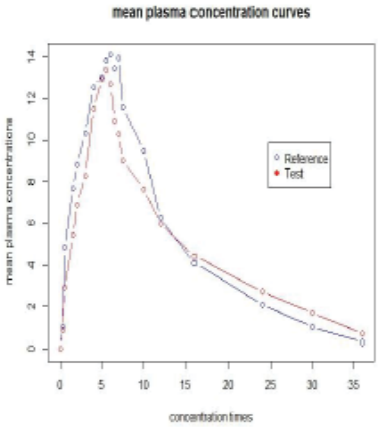
Demonstration of largest separation can be <u>easy, sensitive, Illustrative</u>

Can studies be designed for such demonstrations?

CONCENTRATION OF CONCERTA vs. EXTENDED RELEASE MPH

Mallinckrodt-Kudco mean concentration curves





Reference: Concerta

Largest separation:
10-12 hours

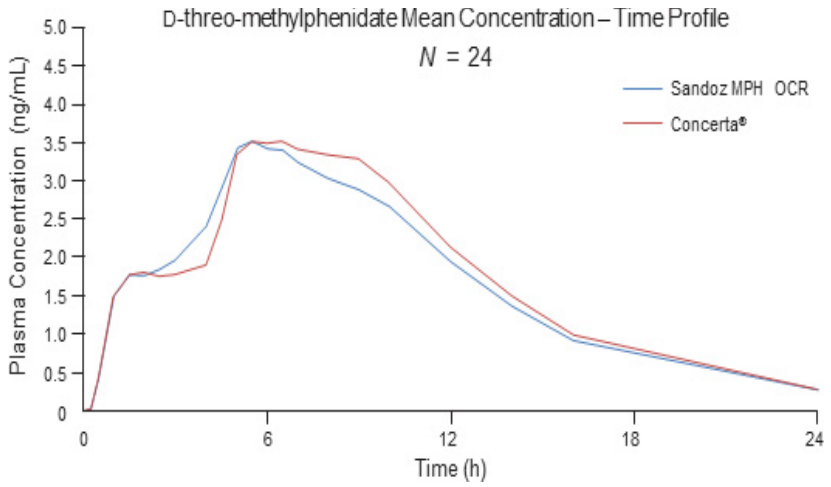


Figure 1. Methylphenidate ER Tablets

Sandoz OCR (Germany)
Concerta

"Bioequivalent"

Separation at 4 hr
and 10hr

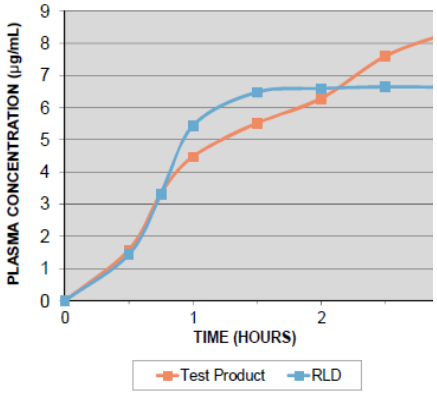
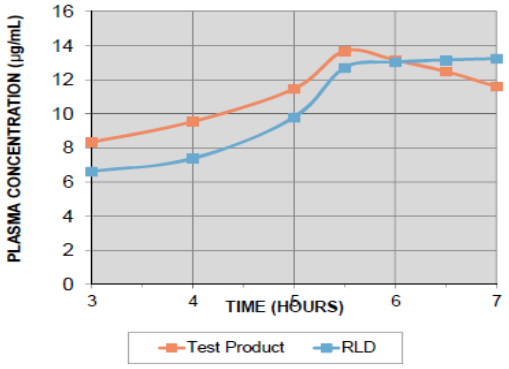


Figure 2. Methylphenidate ER Tablets



Generic
Concerta

Separation at
1.5 hr and 3-4 hr

SEPARATIONS OF ER MPH AND CONCERTA CONCENTRATIONS ARE DIVERSE

Time of largest separation between concentrations of Concerta and modified-release MPH formulations

MR Methylphenidate	Widest separation	Reference
Metadate CD	4 hr	Gonzalez
Mallinckrodt	10 hr	FDA report
Kudco	12 hr	FDA report
MPH ER-C	3 hr	Shram
MPH SR	3 hr	Shram
Sandoz MPH OCR	4, 10 hr	Schapperer
Generic	1.5, 3-4 hr	He

Concentration profiles of ER MPH products are very diverse.

So are the times of the largest separations.

SAME CUT-OFF TIMES FOR ALL MPH-ER PREPARATIONS?

In view of the diverse concentration profiles of MPH-ER preparations:

It may not be useful to set the same rule for all on the cut-off times of partial AUCs.

Note:
EMA: "The time point for truncating the partial AUC should be based on the PK profile for the e.g. IR and the MR parts respectively and should be justified and pre-specified in the study protocol."

Cut-off times to be established for each study
(Note: EMA still considers rational separation of IR and MR components.)

Essentially empirical

WITH DIVERSE CONCENTRATION PROFILES: INTERCHANGEABILITY?

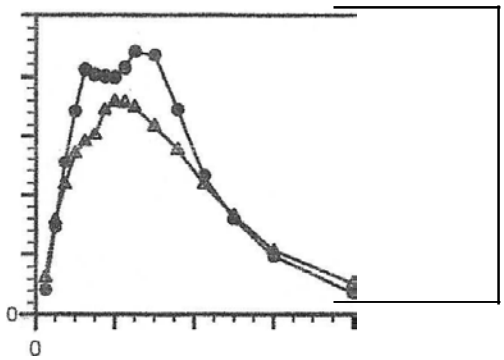
In view of the diverse concentration profiles of MPH-ER (and multiphasic MR) preparations:

Does regulatory approval ensure interchangeability?

Or: Does prescribability imply switchability?

E.g.: Comparison of 2 German ER MPH products (Equasym Retard and Medikinet Retard)

H. Schutz et al., Int. J. Clin. Pharmacol. Ther. 2009; 47: m761-769



CONCLUSIONS, QUESTIONS

Generic MPH ER formulations have diverse concentration profiles

It is difficult to set the same cut-off time(s) for partial AUCs

Determination of cut-off times could be established, easily, for each product

Question: Are approved MPH ER formulations interchangeable?

THANK YOU!!