Changes Regarding Partial AUC
- GPhA Concerns of Implementation

Russell J. Rackley, Mylan Pharmaceuticals

GPhA-Sponsored Presentation to
FDA Advisory Committee Meeting
April 13, 2010

Partial AUC – Complexity

- We generally appreciate the conceptual examples and why other considerations might be applied … however, there is uncertainty to systematic application with respect to time (T) specification.
- Limited experience suggests Partial AUC may represent a significant barrier to generic innovation, owing to large variability related to assessment of a small portion of initial overall AUC.

Transparency

- In order to effect appropriate transparency with regard to meeting FDA expectations, there is a need to come to agreement to appropriate application of standardized methodology.

Generic Drug Dilemma – We don't know what we need to know

- Concern exists regarding timely guidance well in advance of initiating generic development efforts.
- Generic Industry will be inclined to anticipate appropriate scientific interpretation, which may not necessarily be aligned with Agency, potentially leading to false starts.

Need for greater forum to review

- The Agency has presented potential concerns; however, more time is needed to appropriately contemplate solutions to these problems . . .
- Thus, it is recommended that the Agency now consider these topics in larger forums with broad input from Industry and Academia, with the goal of agreeing to a systematic methodology.

Harmonization

- Without further review and consensus from not only Industry, Academia and Health Authority, we do not see this goal being met.
- We should endeavor to rationalize considerations from a global perspective.

Conclusion

- With regards to the challenge of developing appropriate metrics to properly evaluate bioequivalence, as applicable to Partial AUC, GPhA believes the Agency should utilize the same standards for the Generic Industry compared to that of the Brand Industry when evaluating its own product.

PARTIAL AUC AND OTHER METRICS

Laszlo Endrenyi, Ph.D., D.Sc.
University of Toronto

FDA Advisory Committee
April 13, 2010
Silver Spring, MD

QUESTIONS TO THE COMMITTEE

1. Revising the Bioequivalence (BE) Approaches for Critical Dose (CD) Drugs

1/3. Does the Committee have recommendations for future research?

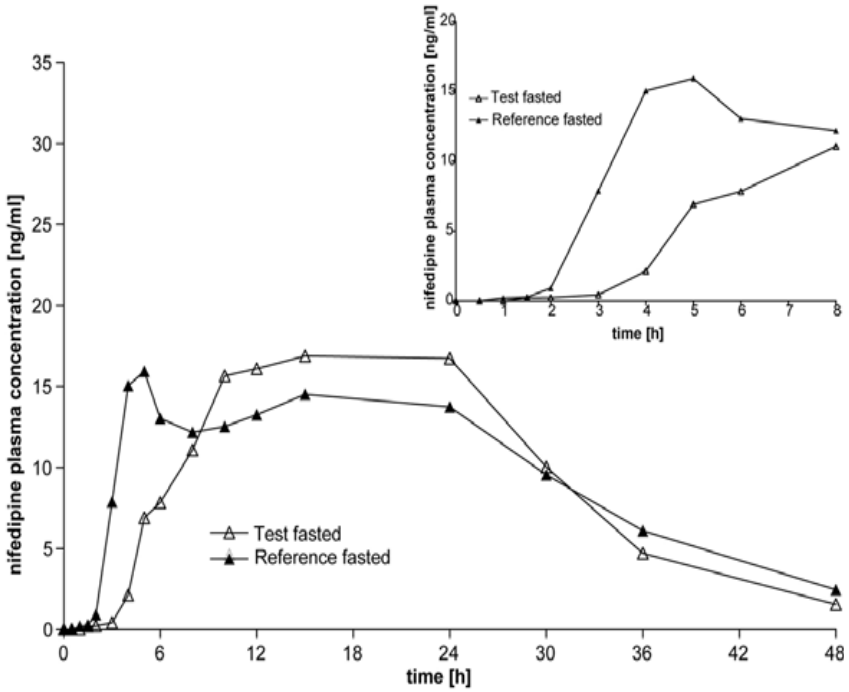
2. Use of Partial Area Under the Curve (AUC) for Products with a Complex Pharmacokinetic (PK) Profile

2/2. Are there other profile comparison metrics that FDA should consider?

MODIFIED-RELEASE FORMULATIONS: 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

MODIFIED-RELEASE FORMULATIONS: DURATION OF EFFECT IS IMPORTANT

Suggest:

Consider development and use of a metric such as Half-value duration

PARTIAL AUC CAN BE USEFUL ALSO FOR SOME CRITICAL DOSE DRUGS

CARBAMAZEPINE

Clinical study: 4-way crossover

1 brand, 3 generics

Usual metrics: bioequivalence demonstrated

Adverse effects: fatigue, drowsiness, diplopia…

H. Olling et al., Biopharm. Drug Dispos. **20:** 19-28 (1999)

PARTIAL AUC CAN BE USEFUL ALSO FOR SOME CRITICAL DOSE DRUGS

CARBAMAZEPINE

More detailed analysis of PK/PD relationship (pharmacokinetic/pharmacodynamic)

Adverse effects are due to acute tolerance (clockwise hysteresis)

Partial AUC reflects much more sensitively differing risks of adverse effects by the various formulations than Cmax (and AUC)

L. Tothfalusi et al., Br. J. Clin. Pharmacol. **65:** 110-122 (2008)

SUGGEST:

Consider (in some cases) applying partial AUC

rather than narrower limits for Cmax

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Application of Partial AUC (AUCp) Analysis for Evaluation of Bioequivalence of Generic Products

Keith Gallicano, Ph.D.
Director, Biopharmaceutics | Watson Pharmaceuticals
April 13, 2010

Outline

- Generic versus brand formulation differences for ER products
- What are the clinical and scientific issues for applying AUCp?
- Concerns with implementation of AUCp
- Rationale for applying AUCp

Generic Substitution - Primary BE Issue

Is it possible that two pharmaceutically equivalent and bioequivalent products (according to current standards) show clinically significant differences in either safety or efficacy?

Mode of Substitution

Switchability

- From brand to generic
- From one generic to another generic

Interchangeability

- Prescribe generic instead of brand

Generic ER vs. Brand ER Products

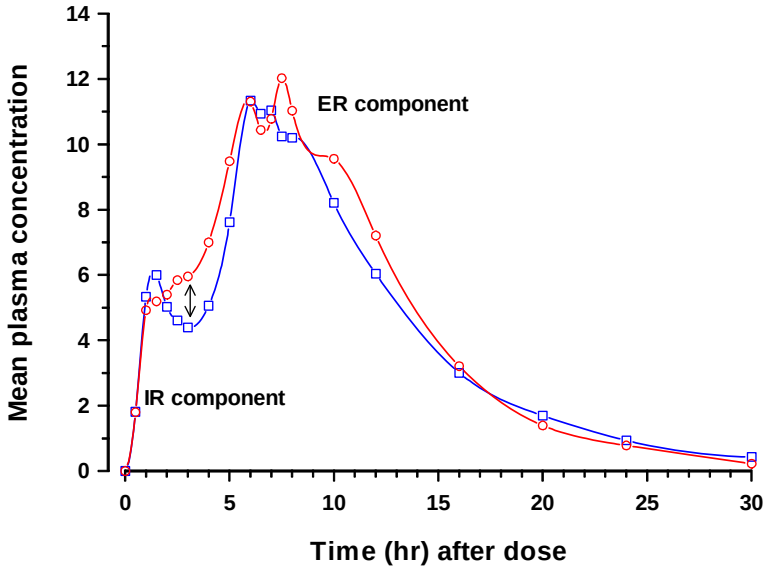
- Examples of formulation differences
  - Generic: ER components
    RLD: ER and IR components
  - Generic: Enteric coating and ER polymers
    RLD: ER polymers
- Such formulation differences can cause a difference in the shape of the corresponding plasma drug concentration-time profiles, despite bioequivalence on the basis of C_{max} and AUC
- Determine if these shape differences in early absorption profiles of two bioequivalent products have clinical relevance

Appropriateness of AUCp to Evaluate Shape Differences in Profiles

- A well-defined documented relationship between drug concentration and clinical effect (safety and efficacy) must be established
  - Early and late stage drug exposure
- Need to define early systemic exposure by AUCp
- Profile comparison
  - Different T_{max} values
  - Multiple early peaks (discrete) vs. shoulders (non-discrete)
  - Similarity in drug exposure or shape of profile
  - Equivalence of AUCp does not always ensure equivalent shape

Example of Profile Shape Differences

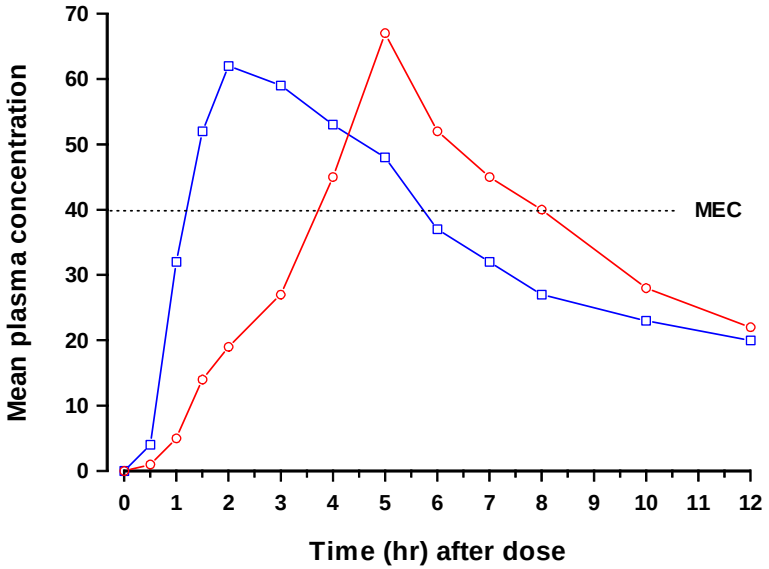
Peaks vs. Shoulders



Application of AUCp may not always result in equivalence of shape, for a product that would provide the same therapeutic effect.

T_{max} difference

Acute undesirable effects



With differences in T_{max}, rapidly raising concentrations can lead to acute adverse events and delay in T_{max} can lead to lack of efficacy.

Factors to Consider for Selection of AUCp

- Application of standards for AUCp should be science-based
  - The design of the formulation, mechanism of drug release, and therapeutic indication with respect to the demonstrated clinical effect (e.g., sleep, ADHD, pain, allergy, CNS) must be considered
  - The specific drug product and associated PK variability are critical (variability increases with earlier exposure and narrower AUCp)
- Potential of increased PK variability would require more subjects and blood samples to meet BE requirements on basis of AUCp

Concerns with Implementation of AUCp

- Implementation of AUCp should not negatively impact approval of drug products
  - Consider flexibility in AUCp criteria
  - What if AUC(0-1.5 hr) fails but AUC(0-2 hr) passes?
- Uncertainties exist regarding early/partial exposure as a mandatory additional criteria to show bioequivalence between two products
- More work is necessary to evaluate the characteristics of AUCp to establish its acceptability for regulatory approval of generic products

Rationale for Applying AUCp

Any requirement for AUCp should be:

- Scientifically sound
- Therapeutically value-added
- Patient focused

Watson is committed to working with the Agency to develop guidance that appropriately addresses therapeutic equivalence while establishing a science-based criteria that ensures timely review and approval

Conventional Bioequivalence Criteria May Not Ensure Clinical Equivalence and, Therefore, Interchangeability for Products with Complex Pharmacokinetic Profiles

Example – Extended-Release Methylphenidate

OROS® Tablets (CONCERTA®) vs Beaded Capsules (Metadate CD*)

Don Heald, PhD

Department of Clinical Pharmacology

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Raritan, NJ

Background

- Methylphenidate is a drug with a short duration of effect used in the treatment of ADHD in children, adolescents, and adults.
- Extended-release products eliminate the need for dosing during the school or work day.
- The clinical effects of methylphenidate are related to the pharmacokinetic profile of the drug.
- The metrics used to evaluate bioequivalence of extended release products take on great significance.

CONCERTA®[1] and Metadate CD*[2] Complex Methylphenidate Formulations

- CONCERTA® (OROS® technology)
  - 22% of dose in overcoat (IR)
  - Remainder released over a prolonged period from a tri-layer core by controlled osmotic process
  - 18, 27, 36, 54 mg tablets
- Metadate CD* (Diffucaps* technology)
  - MPH-coated beads, 30% IR, 70% ER
  - 10, 20, 30, 40, 50 mg capsules

[1]CONCERTA® is a registered trademark of McNeil Pediatrics, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
[2]Metadate CD* is a registered trademark of UCB Manufacturing, Inc. Diffucaps* is a registered trademank of Eurand.

Methylphenidate Bioavailability from Two Extended-Release Formulations

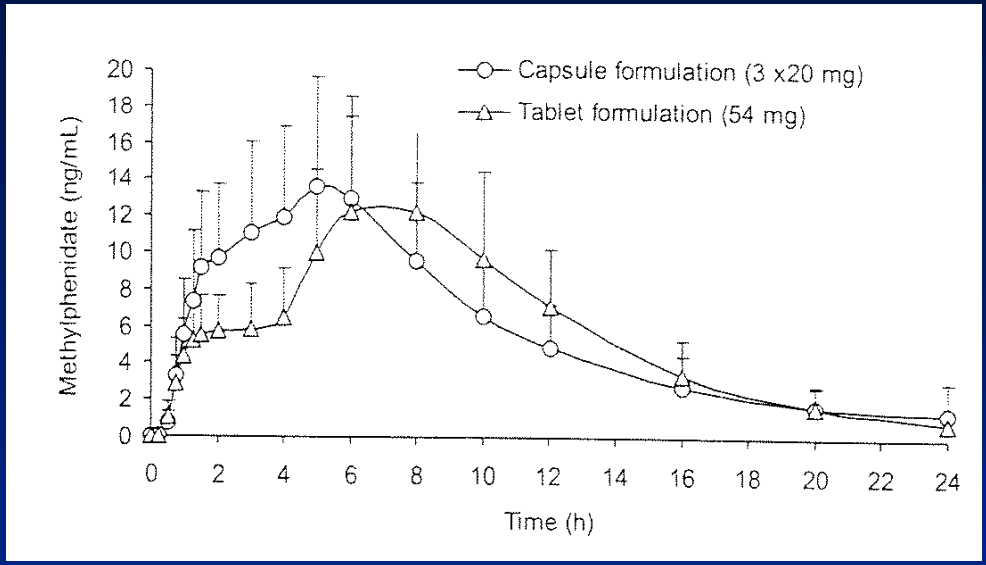
- **Objective:** Compare rate and extent of absorption of methylphenidate from capsule containing coated beads (Metadate CD*) and OROS® tablet (CONCERTA®)
- Methods: Two single-dose studies in healthy subjects
  - two-way crossover of 20 mg and 18 mg doses; n=36
  - four-way crossover of 2x20 mg, 36 mg, 3x20 mg, and 54 mg doses; n=24

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

Formulations Bioequivalent Using Conventional BE Criteria

Parameter	Ratio (LSM)	90% CI
C_{max}	101.05	93.64, 109.04
AUC_{last}	110.08	105.70, 114.63
AUC_{∞}	105.32	101.05, 109.77

Based on dose-normalized data, n=21
Similar results seen with unnormalized data



Capsule Formulation - Metadate CD*
Tablet Formulation - CONCERTA®

Based on conventional BE metrics (C_{max} and AUC), these formulations would be found "bioequivalent"

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

Comparison of PD Effects of Extended-Release Methylphenidate in Children with ADHD

- Multisite, double-blind, 3-way crossover study
- Three dose levels of Metadate CD* and CONCERTA® (based on total mg dose) and placebo, n=184
- One week of once-daily dosing, laboratory school on Day 7
- PD Assessments:
  - SKAMP Attention
  - SKAMP Deportment (behavior)
  - PERMP (performance - math problems)

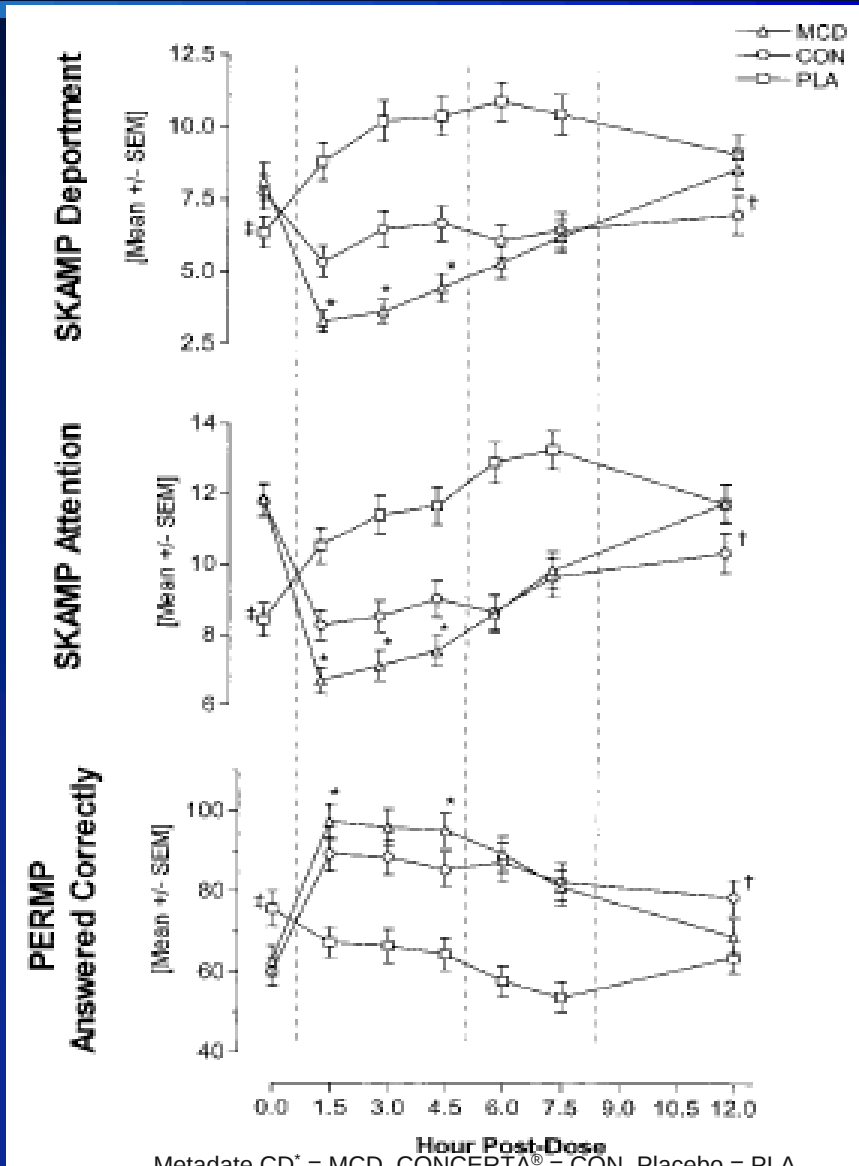
Swanson et al, Pediatrics 113:e206-e216 (2004)

Differences Observed in Pharmacodynamic Effects

Results:

- Both products are significantly different compared to placebo at 1.5 to 7.5 hr post-dose

- Early: MCD > CON
- Late: CON > MCD and PLA



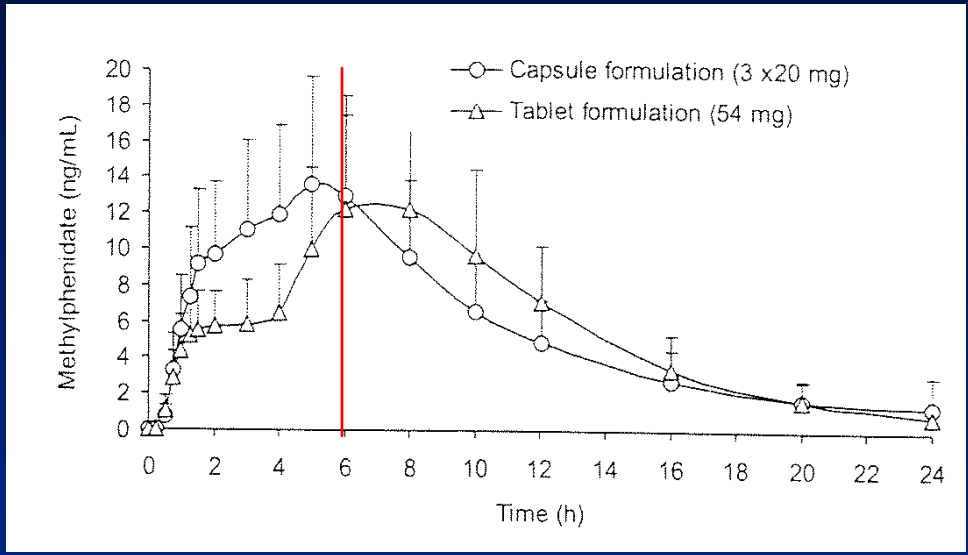
Metadate CD® = MCD CONCERTA® = CON Placebo = PLA

Swanson et al, Pediatrics 113:e206-e216 (2004)

Formulations Not Bioequivalent Using Additional BE Criteria (pAUC)

Parameter	Ratio (LSM)	90% CI
C_{max}	101.05	93.64, 109.04
AUC_{last}	110.08	105.70, 114.63
AUC_{∞}	105.32	101.05, 109.77
AUC_{0-4}	**65.50**	**61.75, 69.48**
AUC_{0-6}	**73.24**	**69.03, 77.69**

Based on dose-normalized data, n=21
Similar results seen with unnormalized data
Similar results seen at other doses studied



Capsule Formulation - Metadate CD*
Tablet Formulation – CONCERTA®

Adapted from Gonzalez 2002

Based on an additional metric (pAUC), these formulations would not be found "bioequivalent"

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

Conclusions

- Standard metrics of AUC and C_{max} may not ensure bioequivalence because they do not detect important PK and PD differences in certain products.
  - This may be demonstrated with methylphenidate extended release formulations approved by FDA.
- Without ensuring bioequivalence, two products may not be assumed to be therapeutically equivalent and, therefore, clinically interchangeable.
  - Extended release formulations of methylphenidate evidence a strong relationship between plasma drug concentration and pharmacological effect.
- Additional metrics should be used for certain products to ensure bioequivalence and, therefore, therapeutic equivalence.
  - The metric, pAUC, helps elucidate differences in the PK and PD profiles of extended release formulations of methylphenidate.