Partial Area Under Curve (pAUC): Product-Specific Guidance Development and Practice for Product Evaluation

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Partial Area Under Curve (pAUC)

- For two products to be considered bioequivalent, there should be no significant difference in the rate and extent of absorption of the active moiety, which are usually measured by Cmax (the maximum drug concentration) and AUC (the area under the concentration-time curve), respectively.

- For some products with complex pharmacokinetic (PK) profiles, the traditional metrics of AUC and Cmax may not be sufficient to ensure therapeutic equivalence.

- An additional PK metric, such as a pAUC to assess exposure during particular time interval(s), may be necessary to assess potential differences in bioavailability (BA) or bioequivalence (BE).

Regulatory History of pAUC (FDA)

- Year 2010: Pharmaceutical Science and Clinical Pharmacology Advisory Committee meeting
  - Modified Release (MR) products: multiphasic drug release

- Year 2021 FDA draft guidance "Bioequivalence Studies with PK Endpoints for Drugs Submitted Under an ANDA" and Year 2022 draft guidance "Bioavailability Studies Submitted in NDAs or INDs: General Considerations"
  - The use of partial AUC as an early exposure measure under certain circumstances
  - The time to truncate the partial area should be related to a **clinically relevant pharmacodynamic (PD) measure or response**.

- Product-Specific Guidances (PSGs) for generic drug development recommending pAUC

- Year 2018: Initiation of CDER-wide efforts regarding pAUC

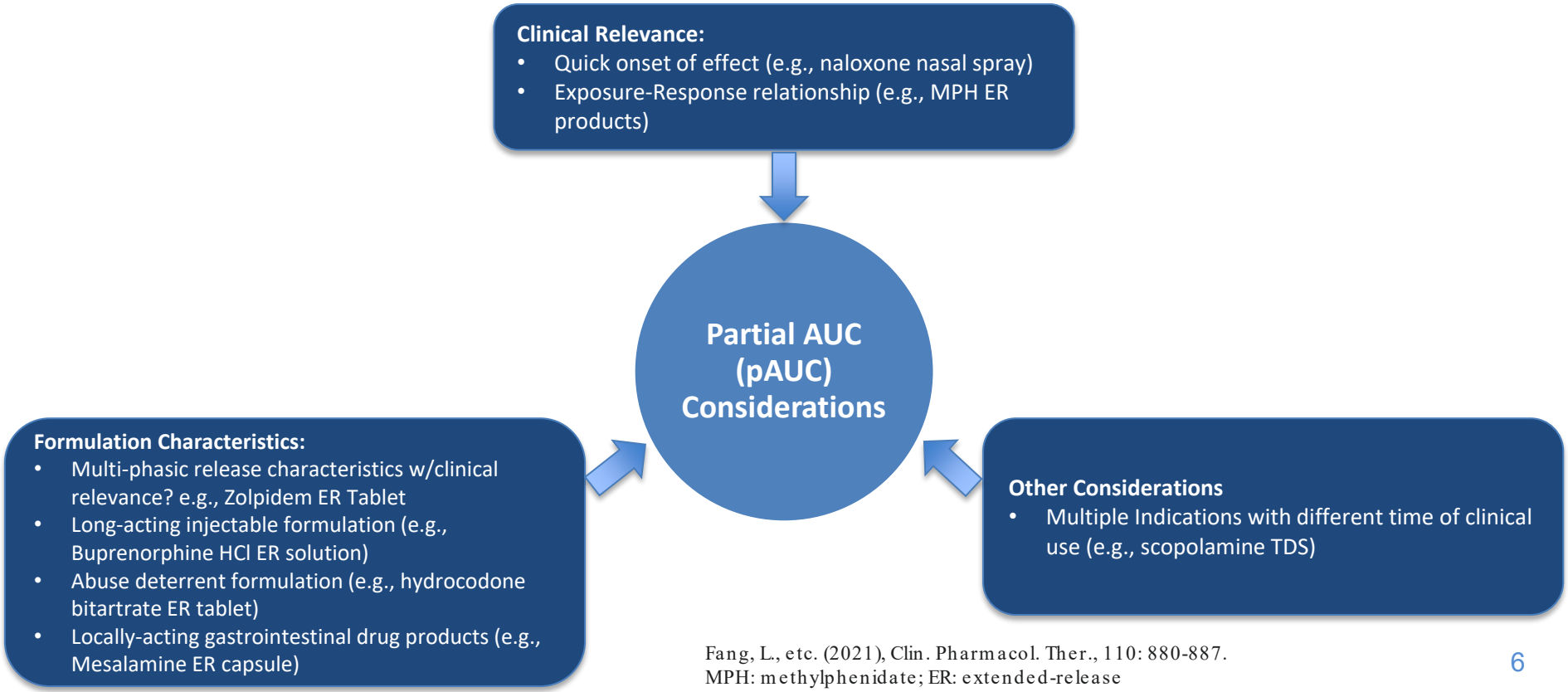
CDER Efforts Regarding pAUC

- Discuss and address questions related to use and determination of appropriate pAUC metric for BE assessment to ensure efficacy and safety of new and generic products

- Develop a consistent regulatory approach to determining pAUCs

- Provide harmonized and consistent pAUC recommendations applicable to both new and generic drugs

General Framework for pAUC(s) Considerations



Fang, L., etc. (2021), Clin. Pharmacol. Ther., 110: 880-887.
MPH: methylphenidate; ER: extended-release

Representative PSGs w/ pAUC

Rationale for recommendation	Active Ingredient	Dosage Form	Partial AUC recommended
pAUC recommended based on clinical relevance			
Quick onset of drug effect	Naloxone HCl	Nasal spray	$AUC_{0\text{-}4\ min}$, $AUC_{0\text{-}10\ min}$, $AUC_{10\text{-}30\ min}$
	Loxapine	**Inhalation Powder**	**$AUC_{0\text{-}30\ min}$ (pivotal BE metric)**
Well-characterized PK/PD relationship & PK profile similarity is important!	Methylphenidate HCl	Transdermal system	$AUC_{2\text{-}9\ h}$
		Extended-release tablets, capsules, and suspension	Fasting: $AUC_{0\text{-}3\ h}$, $AUC_{3\text{-}7\ h}$, $AUC_{7\text{-}12\ h}$ Fed: $AUC_{0\text{-}4\ h}$, $AUC_{4\text{-}8\ h}$, $AUC_{8\text{-}12\ h}$
	Dexmethylphenidate hydrochloride	Extended-release capsules	Fasting: $AUC_{0\text{-}3\ h}$, $AUC_{3\text{-}7\ h}$, $AUC_{7\text{-}12\ h}$ Fed: $AUC_{0\text{-}4\ h}$, $AUC_{4\text{-}8\ h}$, $AUC_{8\text{-}12\ h}$
	Dextroamphetamine sulfate	Extended-release capsules	$AUC_{0\text{-}4\ h}$, $AUC_{4h\text{-}t}$
	Amphetamine	Extended-release suspension	$AUC_{0\text{-}4\ h}$, $AUC_{4h\text{-}t}$
		Extended-release orally disintegrating tablets	$AUC_{0\text{-}5\ h}$, $AUC_{5h\text{-}t}$
	Amphetamine aspartate, Amphetamine sulfate, Dextroamphetamine saccharate, Dextroamphetamine sulfate	Extended-release capsules	$AUC_{0\text{-}5\ h}$, $AUC_{5h\text{-}t}$
	Zolpidem	Extended-release tablets	$AUC_{0\text{-}1.5\ h}$, $AUC_{1.5h\text{-}t}$

Representative PSGs w/ pAUC

pAUC recommended for formulation characteristics/complexities			
Abuse-deterrent	Hydrocodone bitartrate	Extended-release tablets	$AUC_{0\text{-}3\ h}$, $AUC_{0\text{-}4\ h}$
	Morphine sulfate	Extended-release tablets	$AUC_{0\text{-}3\ h}$, $AUC_{0\text{-}4\ h}$
	Morphine Sulfate; Naltrexone hydrochloride	Extended-release capsules	$AUC_{0\text{-}2\ h}$
	Oxycodone	Extended-release capsules	$AUC_{0\text{-}3\ h}$, $AUC_{0\text{-}4\ h}$
	Oxycodone HCl	Tablets and extended-release tablets	$AUC_{0\text{-}3\ h}$, $AUC_{0\text{-}4\ h}$
Long-acting injectable	Naltrexone	Extended-release suspension	$AUC_{1\text{-}10\ d}$, $AUC_{10\text{-}28\ d}$
	Leuprolide acetate	Injectable and injectable depot	$AUC_{7d\text{-}t}$
	Leuprolide acetate, Norethindrone acetate	Injectable depot / tablet	$AUC_{7d\text{-}t}$
	Triptorelin pamoate	Injectable	$AUC_{7d\text{-}t}$
	Buprenorphine	Injectable	$AUC_{3week\text{-}4week}$
	Octreotide acetate	Injectable	$AUC_{0\text{-}28\ d}$, $AUC_{28\text{-}56\ d}$
GI locally-acting	Budesonide	Extended-release tablets	$AUC_{8\text{-}48\ h}$
		Extended-release capsules	$AUC_{0\text{-}4\ h}$, $AUC_{4h\text{-}t}$
	Mesalamine	Extended-release capsules	$AUC_{3h\text{-}t}$
		Delayed-release capsules and tablets	$AUC_{8\text{-}48\ h}$
Other considerations			
Multiple indications with different dosing frequencies	Scopolamine	Transdermal, Film extended-release	$AUC_{0\text{-}36\ h}$

Case #1

pAUC Recommendation for Loxapine Inhalation Powder: Quick Onset is Important

Partial AUC is Clinically Important

ADASUVE (Loxapine, NDA 022549)

Quick onset of drug effect is important: loxapine inhalation power is indicated for **acute treatment** of agitation associated with schizophrenia or bipolar I disorder

$pAUC_{0\text{-}30min}$ is a reasonable BE matrix because:

- it is close to the onset of drug effect (i.e., 10 min)
- a substantial drug effect (>80%) can also be seen at 30 min
- it allows the estimation of PK parameters with a reasonable precision (lower variability compared to $pAUC_{0\text{-}10min}$)
- approximately 85% of drug is cleared from the circulation within 30 min

Figure 9. Mean Change from Baseline in PEC Score through 2 Hours after Dose 1 (ITT Population with LOCF)-Schizophrenia

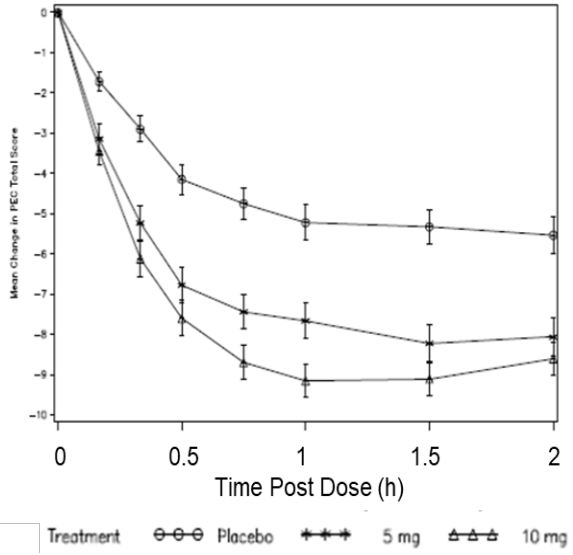
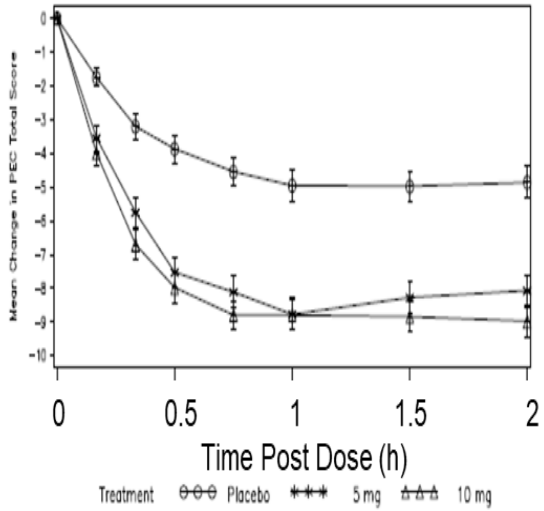
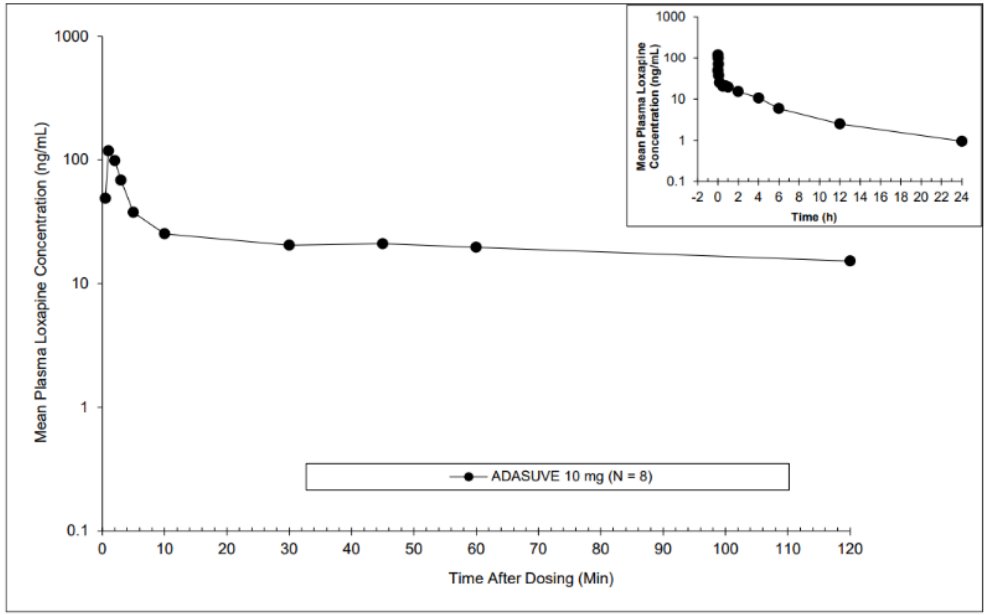


Figure 10. Mean Change from Baseline in PEC Score through 2 Hours after Dose 1 (ITT Population with LOCF) for patients with bipolar I disorder



Clinpharm review of ADASUVE (Loxapine) inhalation powder, 10mg (NDA 022549)

Cmax as Supportive Data



Mean plasma concentrations of loxapine following single-dose administration of ADASUVE (10 mg) in healthy subjects

- Tmax: ~2 minutes
- Collecting PK at early time points and obtaining Cmax at 2 minutes is practically challenging
- Cmax is expected to have a much larger intrasubject variability than pAUC

Drugs@FDA, Labeling-Package Insert of ADASUVE

PSG for Loxapine Inhalation Powder

$AUC_{0\text{-}30min}$ is pivotal while C_{max} is supportive BE data

One in vivo bioequivalence study with pharmacokinetic endpoints:

1. Type of study: Fasting
   Design: Single-dose, two-way crossover
   Strength: 10 mg
   Dose: 10 mg of loxapine (single inhalation)
   Subjects: Healthy males and non-pregnant females
   Additional comments: Loxapine inhalation powder is approved with a Risk Evaluation and Mitigation Strategy (REMS) with an Elements to Assure Safe Use (ETASU), which restricts its use. All pertinent elements of the REMS must be incorporated into the protocol and informed consent. Exclude subjects with current and history of bronchospasm, asthma, COPD, or any other acute or chronic pulmonary disease, and/or a history of hypotension or orthostatic hypotension.

Analyte to measure: Loxapine in plasma

Equivalence based on: $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}\infty}$. The 90% confidence intervals for the geometric mean T/R ratios of $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}\infty}$ should fall within the limits of 80.00% - 125.00%.

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022549.pdf

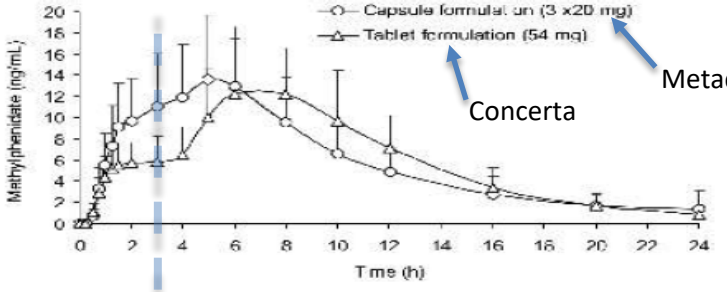
Case #2

pAUC Recommendation for Methylphenidate (MPH) ER Products: Shape of PK Profile Matters

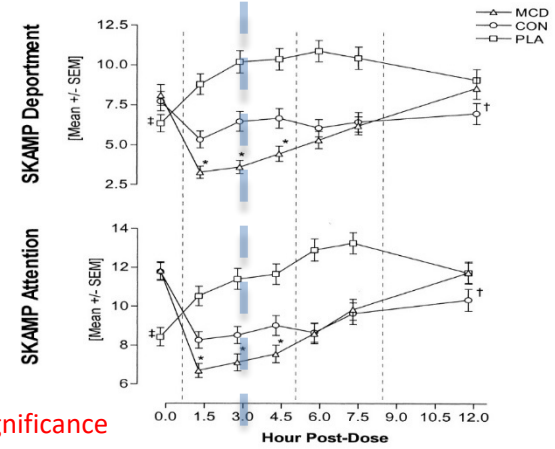
Shape of PK Profile Matters: MPH ER Products

Indicated for attention deficit hyperactivity disorder (ADHD)

Strong PK/PD link: differences in PK is reflected in the SKAMP (**S**wanson, **K**otkin, **A**gler, **M**-Flynn, and **P**elham Rating Scale) ratings over clinically relevant time windows



Gonzalez, M. A., et al. "Methylphenidate bioavailability from two extended-release formulations." *International journal of clinical pharmacology and therapeutics* 40.4 (2002): 175-184.



MCD = Metadate CD
CON = Concerta
PLA = placebo

Swanson, James M., et al. "A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study)." *Pediatrics* 113.3 (2004): e206-e216.

* and †: statistically significance between active treatments

PSG for MPH ER Tablets

- The shape of PK profile is clinically important
- pAUC Recommendation: $pAUC_{0\text{-}3/4hr}$, $pAUC_{3/4\text{-}7/8hr}$ and $pAUC_{7/8\text{-}12hr}$
- Comparable drug exposures over clinically relevant time windows to ensure therapeutic equivalence

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Methylphenidate_draft_Orally%20disintegrating%20tab%20ER_RLD%20205489_RC07-18.pdf

Case #3

No pAUC Recommendation for Torsemide Oral Tablets: PK/PD Analysis

SOAANZ® (torsemide oral tablets)

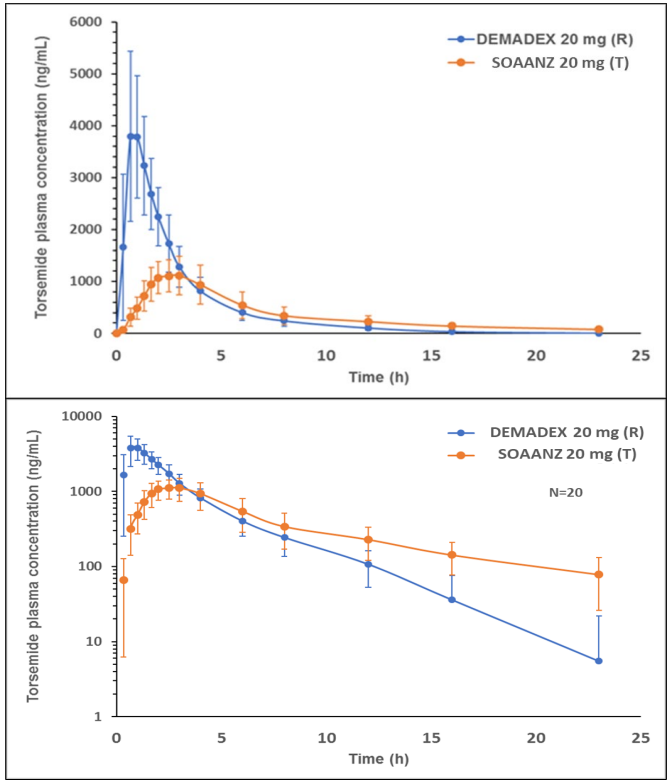
- **Drug class:** Loop diuretic
- **Indication and usage:** Treatment of edema associated with heart failure and renal disease
- Filed through 505(b)(2) [NDA 213218] with DEMADEX® (torsemide IR tablets) as the listed drug
- The applicant formulated product with the intent to slow down torsemide absorption to provide gradual diuresis compared to IR listed drug.

Clinical Studies	Design
Relative bioavailability study	Randomized, four-period, two-treatment, two-sequence, full-replicate crossover study comparative bioavailability study in healthy adults following single oral dose in fasted state Test: Torsemide 20 mg tablet Reference: DEMADEX® 20 mg (IR tablet) PK: Torsemide plasma levels PD: Urine volume excretion, Na+ and K+ excretion
Food effect study	Open-label, balanced, randomized, two-period (fasting versus fed), cross-over, single-dose food effect study in healthy adults

- Fully-replicated study was completed to characterize the within-subject variability of the Test product and how it compares with the listed drug.

IR: Immediate Release; Source: NDA213218 Clinical Pharmacology Review, SOAANZ ® Package Insert (Drugs@FDA: FDA-Approved Drugs)

Slower Absorption and Lower Exposures



PK Parameter	Geometric Least Square Mean		T/R Ratio (%) 90% C.I
	Torsemide 20 mg Test (n=20)	Torsemide IR 20 mg Ref (n=20)	
C_{max} (ng/mL)	1249.0	4354.7	28.7 (25.8, 31.8)
AUC_{0-t} (ng*h/mL)	7820.5	10839.8	72.2 (68.0, 76.7)
AUC_{0-inf} (ng*h/mL)	9011.7	11132.8	81.9 (78.3, 85.5)

Torsemide Test product shows:

- Reduction in Cmax (70% lower) and delay in Tmax (delayed by ~100 minutes)
- Slower decline in torsemide plasma concentration
- Overall lower systemic exposures (20-30% reduction)

Source: NDA213218 Clinical Pharmacology Review (Drugs@FDA: FDA-Approved Drugs)

Similar Urine Volume Excreted over Inter-Dosing Interval

	Mean urine volume excreted (mL)								
Time after dose (h)	0-2	2-4	4-6	6-8	8-13	13-23	8-23	0-8	0-23
Torsemide 20 mg (Test)	1176	1208	392	312	370	911	1281	3088	4369
Torsemide IR 20 mg (Ref)	1740	1052	296	250	258	956	1214	3338	4552

- Reduced Cmax and delayed Tmax associated with 32.4% lower urine volume over the first 2 hours for Test product
- Mean urine volume over 0-23 hours post dose are similar for Test and torsemide IR listed drug

pAUC recommendation is not needed:

- Despite the differences in the PK profiles, there is no clinically meaningful difference in therapeutic effect (i.e., urinary output over the dosing interval) between the two products.

Source: NDA213218 Clinical Pharmacology Review (Drugs@FDA: FDA-Approved Drugs)

Considerations for Recommending pAUC for Modified Release (MR) Products

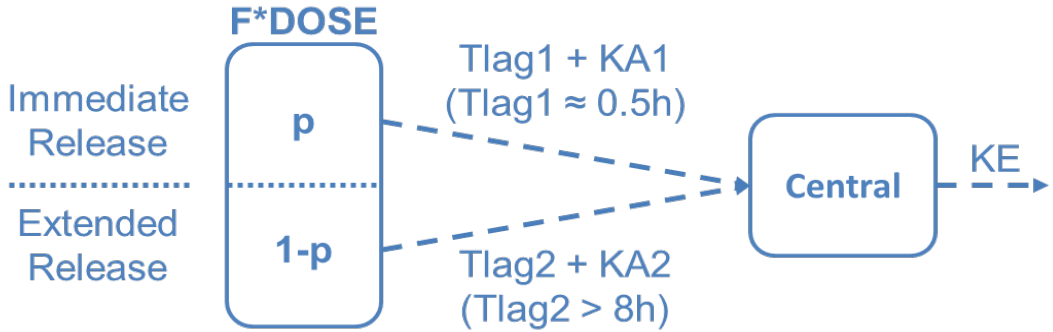
Recommended BE studies for MR Products: FDA vs. EMA

	FDA	EMA
Single dose study	Yes	Yes
Multiple dose study	Generally not recommended.	**Yes**, unless a single dose study has been performed which demonstrates the drug has a low extent of accumulation ($AUC_{0-\tau}$ > 90% AUC_{0-inf}) for both T and R.
pAUC*	pAUC is recommended as additional metrics in some PSGs of products considering clinical relevance and/or formulation characteristics.	pAUC is recommended regardless of the clinical relevance. pAUC is separated by half of the dosing interval, unless otherwise scientifically justified.

*pAUC cut-off time and purpose of pAUC from FDA and EMA are different.

Simulation Method

- 1-compartment model with one immediate-release first-order absorption and one extended-release first-order absorption.



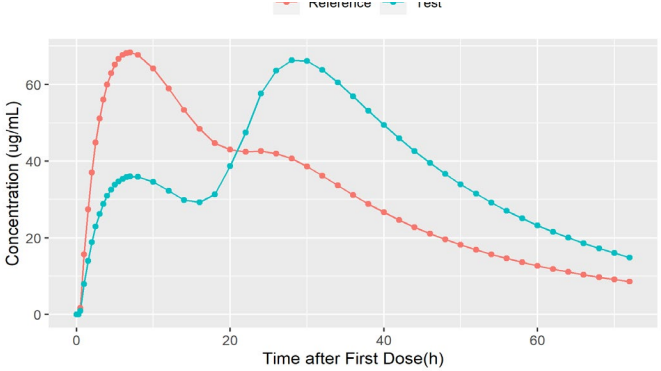
- Formulation difference simulated in both bioavailability and absorption rate (adjusting both F and KA to create different absorption profiles).

- Incorporated different levels of variabilities (between-subject and within-subject variabilities).

- 1000 simulated clinical trials (n=24) were constructed for each simulation scenario.

One MR Product w/ High Extent of Accumulation

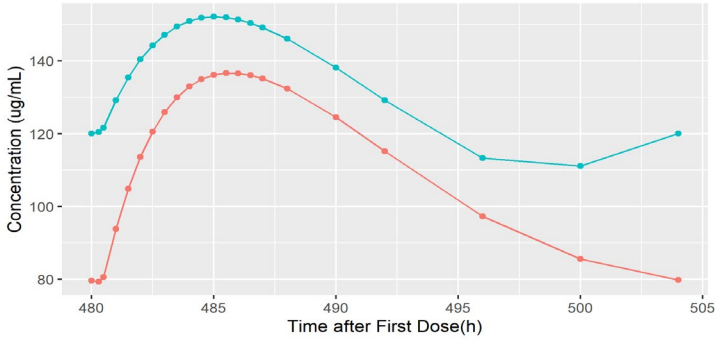
Single dose PK profile (0-72 h)



PK parameters	GMR*	BE passing rate	CV%
Cmax	96.8745	99%	16.29
AUCt	117.4704	92%	7.12
Cmax & AUCt		91%	

*Mean value estimated from 1000 simulations

Steady state PK profile during a dosing interval (24 h)

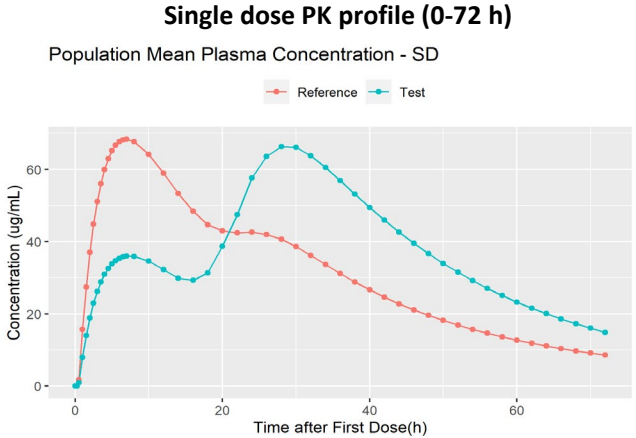


PK parameters	GMR*	BE passing rate	CV%
Cmax	111.0343	100%	10.35
AUCt	120.1599	52%	7.80
Cmax & AUCt		52%	

Similar GMR for Cmin compared to AUCt, but with much greater CV%

- Different PK profiles were observed between single-dose and steady state conditions, which resulted in different BE results when there was a high extent of accumulation.
- GMR estimation for Cmax was flipped in multiple dose study compared to single dose study.

Including pAUC in Single Dose PK



PK parameters		GMR*	BE passing rate	CV%
Conventional single dose PK parameters	Cmax	96.8745	99%	16.29
	AUCt	117.4704	92%	7.12
	Cmax & AUCt		91%	
Single dose pAUC	AUC0-7 (0-tmax)	51.5306	0	7.94
	AUC7-t (tmax-t)	129.1373	0	7.51
Steady state PK parameters	Cmax	111.0343	100%	10.35
	AUCt	120.1599	52%	7.80
	Cmax & AUCt		52%	

*Mean value estimated from 1000 simulations

- The listed drug Tmax observed in the study was used as the cut-off for pAUCs in the simulated case example.

- **pAUC maybe more efficient than multi-dose study at ensuring similar PK profile and Cmin at steady state. Inclusion of pAUC should be based on clinical-relevancy.**

Potential Challenges in pAUC Evaluation

- High variabilities
  - Pivotal versus supportive BE evidence
- Maybe challenging to characterize early or late pAUCs due to undetectable concentrations
  - Unequal data exclusion between Test and listed drug

Summary

- CDER has created a center-wide framework to increase coordination between offices for the standards applied to new drug and generic drug approval
  - FDA focuses on clinical relevancy
  - FDA strives to provide harmonized and consistent pAUC recommendations applicable to both new and generic drugs

- It is challenging to prospectively identify the need for pAUC
  - Exposure-Response information may be unavailable to assess the clinical relevance of pAUC recommendations
  - The use of pAUC may be product-specific (i.e., variability or PK sampling)

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pAUC WG

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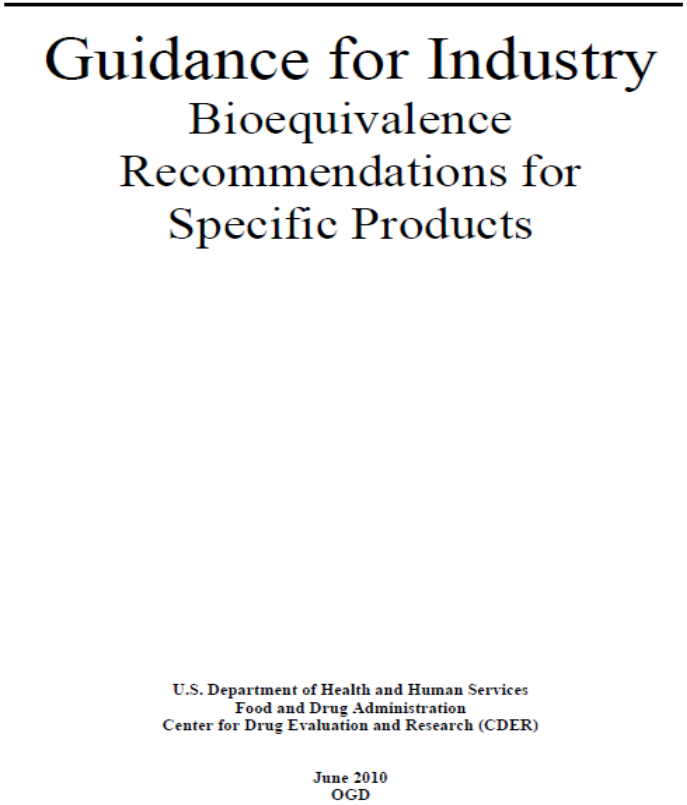
Product-Specific Guidances (PSGs)


Guidance for Industry

Bioequivalence Recommendations for Specific Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2010
OGD

- Provide drug-specific recommendations for demonstrating BE between test and reference drug products: study design, strengths, study population, analytes to measure, dissolution method, and other special considerations
- Enhance transparency between the FDA and generic drug industry
- Reduce industry inquiries on BE recommendations
- Improve quality of submitted ANDAs (i.e., faster approval times)
- Promote FDA's generic drug approval process