Title: Using partial AUC to characterize the impact of shape of pharmacokinetic profiles on bioequivalence evaluation

PRESENTER:

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BACKGROUND:

AUC and C_{max} are routinely employed to assess bioequivalence (BE) between the two products. However, situations may merit additional or alternative metrics to characterize the impact of the shape of pharmacokinetic profiles on BE.

The objective of this study was to summarize the use and recommendations for partial area under the curve (pAUC) and other metrics (e.g., C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$) to compare pharmacokinetics (PK) profiles based on review of literature.

METHODS

1. An extensive literature search was conducted using OVID-Medline and PubMed up to August 2020.
2. Key mesh terms included PK terms: partial AUC, therapeutic equivalency and bioequivalence. Also included were names of several drugs with the desire of pAUC evaluation based on our prior knowledge: budesonide, mesalamine, methylphenidate, amphetamine, zolpidem, scopolamine, sumatriptan, hydrocodone, morphine, oxycodone, and naloxone. Also included were eight indications for which early onset, sustainable or targeting effect is needed: Crohn's, ulcerative colitis, Attention Deficit Hyperactivity Disorder (ADHD), insomnia, nausea, migraine, pain and opioid overdose.
3. Combinations of PK terms, drug names and disease indications were used to search for key articles.

* FDA Product Specific Guidance (PSG), available at :https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

pAUC generally involved the consideration of the onset of drug action and sustained effect. pAUC recommendations can depend on T_{max} or desired effective time considerations.

When to recommend	How to recommend (e.g., based on T_{max}, etc.)	Drug Product (given orally unless otherwise indicated)	Indications	pAUC recommendations	References	pAUC recommendations in PSG
Control of early onset	1) based on Tmax 2) release characteristics 3) abuse-deterrent formulation	Oxycodone DETERx ® 40 mg	Moderate to severe pain	AUC0-1.75 hour	Gudin et al. Pain Med. 2015. doi:10.1111/pme.12834.	AUC up to time to maximum concentration (Tmax) (e.g., AUC0-3 hour and AUC0-4 hour).
Rapid onset	1) based on Tmax 2) PK/PD relationship	Naloxone nasal spray	Reversal of opioid overdose	AUC0-1min, AUC0-2min, AUC0-4min, AUC0-10min, AUC0-20min and AUC0-30min	Mundin et al. Addiction. 2017. doi: 10.1111/add.13849.	• AUC of early time points as supportive data to assess the onset of naloxone effect. • Compare exposure to naloxone between T and the R product within the first 4 minutes, 10 minutes, and 10-30 minutes after administration.
	1) based on Tmax 2) release characteristics	6 mg subcutaneous sumatriptan, 25 mg sumatriptan oral tablet, 25 mg sumatriptan suppository and 20 mg sumatriptan intranasal spray.	Migraine	AUC0-tmax Median Tmax: S.c., 6mg = 0.17 hour Oral, 25mg = 1.50 hour Suppository, 25mg = 1.00 hour Intranasal, 20mg =1.50 hour	Duquesnoy et al. Eur J Pharm Sci. 1998. doi: 10.1016/s0928-0987(97)00073-0.	pAUC was not mentioned in PSG
Rapid onset + Sustained Effect	1) based on Tmax 2) release characteristics	Amphetamine XR tab (AMP XR-ODT (fasted or fed) or MAS ER (fasted))	ADHD	AU0-5 hour, AUC5-last	Stark et al. Postgrad Med. 2016. doi: 10.1080/00325481.2016.1216716.	All amphetamine products: AUC0-5 and AUC5-t to evaluate drug bioavailability for the rapid onset and sustained maintenance of the clinical response throughout the 24-hour dosing interval.
	1) based on Tmax 2) release characteristics	Amphetamine ER Oral Liquid Suspension (AMP XR-OS) (fasted/fed) Extended-release mixed amphetamine salts (MAS ER)† ONLY under fed conditions.	ADHD	AU0-5 hour, AUC5-last	Sikes et al. Clin Ther. 2017. doi: 10.1016/j.clinthera.2017.10.018.	
	1) based on Tmax 2) release characteristics 3) food-impact	Methylphenidate ER – ODT: two 30-mg tablets given under fed or fasted conditions.	ADHD	AUC0-3 hour, AUC3-7 hour and AUC7-12 hour	Weisler et al. Clin Pharmacol Drug Dev. 2018. doi: 10.1002/cpdd.361.	All Methylphenidate HCL Products: pAUCs recommended to compare test & reference systemic exposure at different time points during 24-hour dosing interval: • AUC0-T1 for early onset of response; • AUCT1-T2 for sustaining the response in the middle of the once-daily dosing interval; and • AUCT2-T3 for maintenance of the response in late stage of the once-daily dosing interval.
	1) based on Tmax 2) release characteristics	Methylphenidate modified release product with a bi-model release profile	ADHD	AUC0-4hour, AUC0-6hour	Fourie et al. Pharm Res. 2013. doi:10.1007/s11095-012-0862-x.	
	1) based on Tmax 2) release-characteristics 3) food-impact	MPH IR products MPH MMR (Multiphasic Modified Release) formulations (Ritalin LA®)	ADHD	AUC0-3 hour (fast), AUC0-4hour (fed), AUC3-T (fast), and AUC4-T (fed)	Stier et al. AAPS J. 2012. doi:10.1208/s12248-012-9397-7.	
	PK/PD relationship and desired effective time	Zolpidem IR and Zolpidem tartrate ER tablets	Insomnia	AUC0-1.5 hour, and AUC1.5-t	Lionberger et al. Pharm Res. 2012. doi:10.1007/s11095-011-0662-8.	AUC0-1.5 hour and AUC1.5-t to evaluate the sleep onset and sleep maintenance phases, respectively.

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RESULTS

1. There were 92 article hits, spanning from 1998 to 2019. The majority of article hits did not calculate a pAUC or provided pAUC calculation as recommended in FDA's product-specific guidances (PSGs) (e.g., $AUC_{0\text{-}4hr}$ for methylphenidate immediate release (IR) product). Some articles provided pAUC calculation but were deemed not feasible (e.g., $AUC_{0\text{-}1min}$ for naloxone nasal spray).
2. Out of these 92 articles, 9 representative articles provided recommendations about the use of pAUC to compare PK profiles for BE assessment
3. As shown in Table 1, situations to recommend pAUC include: rapid onset and rapid onset plus sustained effect, but not targeting effect due to lack of articles. pAUC was in general recommended based on T_{max} or desirable effective time period.

ACKNOWLEDGEMENTS

This project (M-CERSI Research Scientist Collaboration Program to Dr. Fang Wu and Dr. James Polli) was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award U01FD005946 with 100 percent funded by FDA/HHS.

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