Use of Partial Area Under the Curve in Bioavailability or Bioequivalence Assessments: A Regulatory Perspective

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Peak drug concentration (C_{max}) and total exposure, such as area under the concentration-time curve (AUC) from time zero to infinity may be insufficient for assessing relative bioavailability (BA) or bioequivalence (BE) among two products in cases where rapid onset of action or controlled duration of effect is needed to ensure similar drug efficacy. Regulatory agencies have recommended the use of partial AUC (pAUC) as an additional exposure measure for relative BA or BE assessments. The pAUC metric describes pharmacokinetic profiles with the focus on quantification of exposures over specific time intervals to support the determination of relative BA or BE for these drug products in relation to respective reference products. The principles and rationales for using pAUCs are included in the US Food and Drug Administration (FDA)'s general BA or BE guidances. Specific pAUC recommendations are also reflected in product-specific guidances for generic drug development published by the FDA. Rationales for the use of pAUCs in relative BA or BE assessments are based on drug-specific and product-specific considerations. This white paper introduces the general framework, including rationales for pAUC recommendations, and provides an overview of the current status, challenges, and the FDA considerations on the use of pAUC for relative BA or BE assessments in the United States.

Assessments of bioavailability (BA) and bioequivalence (BE) are routinely performed during new or generic drug development. The Code of Federal Regulations defines BA as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action" (21 Code of Federal Regulation (CFR) 314.3(b)). BE is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study" (21 CFR 314.3(b)). Demonstration of BE is essential for evaluating therapeutic equivalence or substitutability of generic drugs. The US Food and Drug Administration (FDA) has issued general guidances of (i) BA studies for drugs submitted under new drug applications or investigational new drug applications and (ii) BE studies with pharmacokinetic (PK) end points for abbreviated new drug applications (ANDA).[1,2]

Under the FDA regulations, an applicant must use the most accurate, sensitive, and reproducible approach available among those described in 21 CFR 320.24(b) to determine BA or demonstrate BE. For most products, BA or BE studies focus on the release of the drug substance from the product and absorption into systemic circulation. Traditionally, peak drug concentration (C_{max}), area under the concentration–time curve from time 0 to last sampling time point with a measurable concentration (AUC_t) and from time 0 to infinity (AUC_{inf}) are recommended for BA and BE assessments.[3] However, for certain drugs with rapid onset of effect or long-acting effect, or for which the shape of PK profiles affects the clinical performance because of well-characterized PK/pharmacodynamic (PK/PD) relationships, the traditionally applied PK parameters of C_{max} and AUC may be insufficient for PK profile characterization or comparison. Furthermore, advances in pharmaceutical science have given rise to new formulation technologies to achieve optimal treatment effect. These unique product features and complexities pose challenges in determining BA or BE using traditionally applied C_{max} and AUC parameters. Thus, additional PK metrics are needed to better characterize the rate and extent of absorption for these products in the clinically relevant time windows. For instance, an evaluation of the partial exposure during the first few minutes or hours may be needed to support the determination of the relative BA or BE of analgesic drug products that require a rapid onset for pain management.[4] Later partial exposure is suggested to characterize the PK of some long-acting injectable products, with the aim of sustained drug release and clinical effect.[2,5]

Consequently, the FDA has recommended partial AUC (pAUC) as an additional PK metric for BA or BE assessments. Partial AUC focuses on the extent of exposure over a specified

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time interval of interest. In the general guidances for relative BA and BE studies, the FDA recommends an evaluation of pAUC as a measure of partial exposure to support the determination of the relative BA/BE for drug products, such as analgesic drug products. Although analgesic drug products are mentioned as an example in the general BA or BE guidance for pAUC considerations, pAUC can be used for other types of products (e.g., modified-release products). In such products, the differences in the shape of the systemic concentration-time profiles between the test and reference products could imply that the test product may not produce the same clinical response as the reference product. The time to truncate the pAUC should be related to a clinically relevant PD measure. A sponsor or applicant should collect enough quantifiable samples to enable an adequate estimation of pAUC.[1,2] Other regulatory agencies, such as Health Canada and the European Medicines Agency (EMA), make similar guideline recommendations on the use of pAUC for BA or BE studies of products with modified-release formulations.[6–8]

In addition to the general guidances, as of August 2020, the FDA has issued 44 product-specific guidances (PSGs) recommending the use of pAUC to determine BE for drugs submitted under an ANDA. The PSGs were developed based on scientific recommendations describing the FDA's current thinking and expectations of how to prove that generic drug products are therapeutically equivalent to specific reference listed drugs. Rationales for the use of pAUCs in BE assessments and the selection of time intervals to truncate the AUC are based on drug-specific and product-specific considerations. This white paper aims to introduce the general framework, including rationales for pAUC recommendations and provide an overview of the current status, challenges, and agency considerations for the use of pAUC in the BA or BE assessment in the United States.

DEFINITION OF PAUC

Partial AUC is defined as the area under the plasma concentration (C_t) vs. the time profile over two specified time points (t_0 and t_p) as shown in the equation below[9,10]:

$$\text{pAUC}_{t0-tp} = \int_{t0}^{tp} c_t \times \mathrm{d}t$$

It can be applied to describe an early exposure and/or exposures of different time intervals of interest. Partial AUC generally is calculated by using the trapezoidal rule.[10] Because each pAUC represents the drug exposure for each time interval of interest, all pAUCs together contain the shape information of the PK profile. Thus, equivalence of pAUCs across all time intervals of interest between two PK profiles indicates that clinically significant PK features are the same or similar. The pAUCs are therefore useful in describing PK profiles of products for which the shape of PK profiles impacts clinical performance, based on a well-characterized PK/PD relationship.

REGULATORY HISTORY OF PAUC IN THE UNITED STATES

Figure 1 shows the regulatory history of pAUC in the United States. A pAUC approach was first proposed for the evaluation of equivalence in the rate of absorption of immediate-release formulations in 1992, and it was found to be more discriminating than C_{max} and/or time of maximum plasma concentration (T_{max}) in the evaluation of drug absorption rates.[11] An early exposure measure may be informative based on PK/PD relationships that call for a better control of drug absorption into systemic circulation (e.g., to ensure rapid onset of an analgesic effect or to counteract an opioid overdose). In this setting, the FDA's general BA/BE guidance (2002) recommended the use of pAUC as an early exposure measure.[12] However, its application in regulatory practice at that time was limited.

In the 2010 meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee, pAUC (pAUC_{t0-tp}) was defined as the area under the plasma concentration vs. time profile over two specified time points (t_0 and tp).[9] Subsequently in 2011, the FDA recommended the use of pAUC for demonstrating BE of zolpidem extended-release (ER) tablets and methylphenidate hydrochloride ER capsules based on their PK/PD relationships.[13,14] In 2013, the FDA's draft guidance for industry, "Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA," recommended the use of pAUC under certain circumstances. The time to truncate the partial area should be related to a clinically relevant PD measure, and enough quantifiable samples should be collected to enable adequate estimation of pAUC.[2]

As of August 2020, the FDA has issued 44 PSGs with recommendations for using pAUC to determine BE for products having well-characterized PK/PD relationships in which the PK profile shape affects clinical performance, or with complex modified-release formulations (**Table 1**). Modeling and simulation analysis aided the FDA in understanding the need for pAUC measures and the proper pAUC truncation times.[15–17] Sixteen of the 44 FDA PSGs are for stimulant products that treat attention-deficit/hyperactivity disorder (ADHD). For these products, PK profile shape affects clinical performance due to well-defined PK/PD relationships. The PSG for naloxone HCl nasal spray product, which needs a quick onset of effect, recommends early pAUCs. Twenty-six PSGs are for products with modified-release or complex formulations, including 7 PSGs for abuse-deterrent formulations, 10 PSGs for long-acting injectable products, and 9 PSGs for gastrointestinal (GI) locally acting drug products for which pAUC serves as a surrogate PK metric of GI local delivery. Partial AUC is recommended in the PSG of scopolamine transdermal delivery system, as it has multiple indications, each with different time intervals of clinical use.

Rationales for the use of pAUCs in BE assessments and determination of the pAUCs in PSGs are based on product-specific considerations. To develop a consistent, science-based and risk-based regulatory approach in the determination of when and how to use appropriate pAUC metrics for BE assessment, the FDA formed a Center for Drug Evaluation and Research (CDER)-wide pAUC working group in 2018.

REGULATORY CONSIDERATIONS FOR THE USE OF PAUC IN BA OR BE ASSESSMENTS

Regulatory considerations for the use of pAUC in BA or BE assessments focus on the clinical relevance of the proposed pAUC

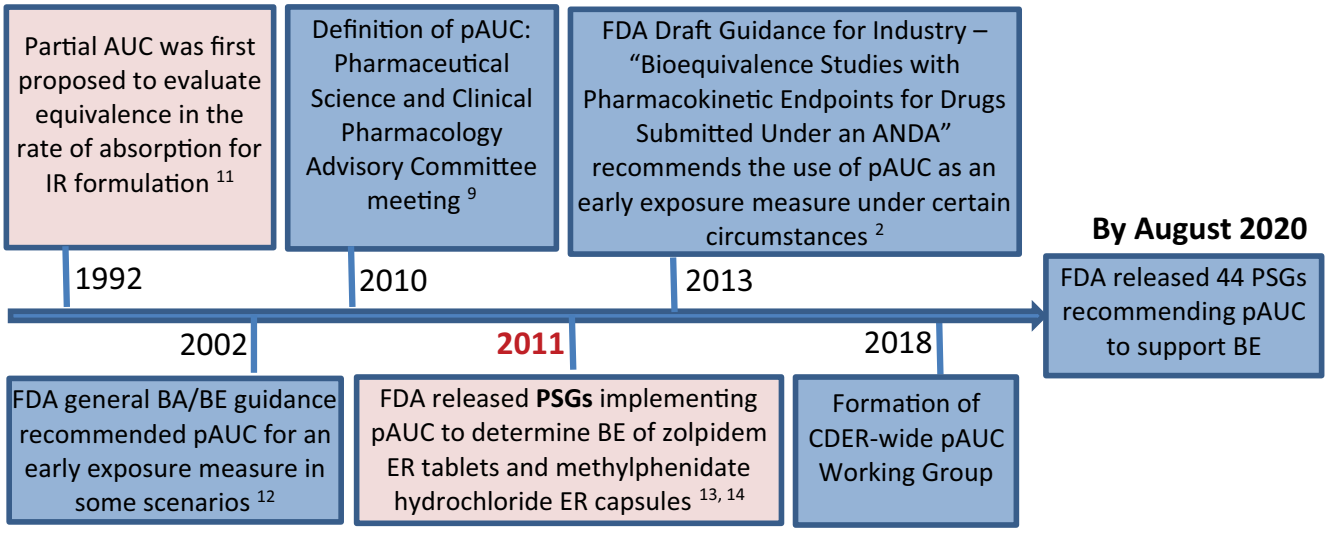

Figure 1 Regulatory history of pAUC considerations in the United States. The superscript numbers in the bulletins indicate the corresponding references. AUC, area under the concentration-time curve; IR, immediate-release; FDA, Food and Drug Administration; BA, Bioavailability; BE, Bioequivalence; PSG, Product-Specific Guidance; ANDA, Abbreviated New Drug Application; ER, extended-release; CDER, Center for Drug Evaluation and Research.

metric. In cases in which pAUC metrics are recommended, reasonable evidence exists demonstrating the shape of the PK profile or drug exposures during certain time windows affects clinical performance based on PK/PD and exposure-response relationships. Additionally, the pAUC metrics can mitigate the risk of potential underperformance and substitutability issues of generic drugs with complex formulation characteristics, such as abuse-deterrent formulations.

Partial AUC recommended based on clinical relevance

Clinical relevance of the proposed pAUC metric is critical. NARCAN (naloxone HCl nasal spray), an opioid antagonist, is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. It is intended for immediate administration as emergency therapy in settings where opioids overdoses may be present. Opioid overdose is immediately life-threatening and must be reversed as soon as possible. Therefore, systemic exposure to the generic product during the early absorption phase after dosing must be no less than (i.e., comparable to or exceed) that of the reference product. As such, the PSG recommends early drug exposures (i.e., $pAUC_{0-4min}$, $pAUC_{0-10min}$, and $pAUC_{10-30min}$) as supportive evidence of BE, in addition to C_{max} and total AUC, to ensure early exposure that would lead to quick reversal of opioid overdosing.[18] There is no clinical rationale for recommending that the upper limit of the 90% confidence interval (CI) for geometric mean ratios between generic and reference products for early pAUC should not exceed the upper boundary of the BE limit (i.e., 125.00%). Therefore, there is no specific recommendation that the 90% CIs of the geometric mean test/reference (T/R) ratios for the early pAUCs should fall within the limits of 80.00–125.00%, but a lower limit < 80.00% may be concerning.

CONCERTA (methylphenidate HCl (MPH) ER tablet) is indicated for the treatment of ADHD in children 6 years of age and older, adolescents, and adults up to age 65 years. CONCERTA's package insert states that the duration of effect is 12 hours. The preferred pattern of drug release for MPH was based on well-characterized PK/PD correlation of the products demonstrated in clinical studies.[19] A comparative bioavailability study in adults with MPH ER tablet and METADATE CD (MPH ER capsule) products showed comparable overall MPH exposure and maximum MPH concentration; however, there were noticeable differences between the representative PK profiles of each product.[20] Comparing the PK and PD time courses of MPH ER capsule and tablet products, Swanson *et al*. noted that, at nearly equal daily doses, the anticipated higher plasma MPH concentrations in the morning associated with MPH ER capsule were reflected in superior clinical outcome during the early postdosing period (1.5–4.5 hours postdose) as compared with MPH ER tablet.[19] In the afternoon (6.0–7.5 hours postdose), when MPH ER capsule and tablet were anticipated to produce approximately the same plasma concentrations of MPH, the two treatments did not differ greatly in clinical outcome. In the early evening (12 hours postdose), however, when MPH ER tablet was anticipated to deliver more MPH than that of MPH ER capsule, MPH ER tablet showed statistical superiority over MPH ER capsule in clinical performance.[19] This, along with clinical experience that patients on one ADHD stimulant cannot easily be switched to another, further illustrated the impact of the shape of the PK profile on the anticipated clinical response.[21]

To ensure comparable PK profiles for potential generic formulations, three pAUC time windows have generally been recommended to ensure comparable clinical and product performance based on the labeled efficacy duration for children and on formulation characteristics. For example, MPH ER tablet has a

Table 1 Representative FDA-released PSGs with recommendations on using partial AUC to determine BE

Rationale for recommendation	Active ingredient	Dosage form	pAUC recommended
pAUC recommended based on clinical relevance			
Quick onset of drug effect	Naloxone HCl	Nasal spray	AUC_{0-4min}, $AUC_{0-10min}$, $AUC_{10-30min}$
Well-characterized PK/PD relationship	Methylphenidate HCl	Transdermal system	$AUC_{2-9hours}$
		ER tablets, capsules, and suspension	Fasting: $AUC_{0-3hours}$, $AUC_{3-7hours}$, $AUC_{7-12hours}$ Fed: $AUC_{0-4hours}$, $AUC_{4-8hours}$, $AUC_{8-12hours}$
	Dexmethylphenidate hydrochloride	ER capsules	Fasting: $AUC_{0-3hours}$, $AUC_{3-7hours}$, $AUC_{7-12hours}$ Fed: $AUC_{0-4hours}$, $AUC_{4-8hours}$, $AUC_{8-12hours}$
	Dextroamphetamine sulfate	ER capsules	$AUC_{0-4hours}$, $AUC_{4hours-t}$
	Amphetamine	ER suspension	$AUC_{0-4hours}$, $AUC_{4hours-t}$
		ER orally disintegrating tablets	$AUC_{0-5hours}$, $AUC_{5hours-t}$
	Amphetamine aspartate, Amphetamine sulfate, Dextroamphetamine saccharate, Dextroamphetamine sulfate	ER capsules	$AUC_{0-5hours}$, $AUC_{5hours-t}$
	Zolpidem	ER tablets	$AUC_{0-1.5hours}$, $AUC_{1.5hours-t}$
pAUC recommended for formulation characteristics/complexities			
Abuse-deterrent	Hydrocodone bitartrate	ER tablets	$AUC_{0-3hours}$, $AUC_{0-4hours}$
	Morphine sulfate	ER tablets	$AUC_{0-3hours}$, $AUC_{0-4hours}$
	Morphine sulfate; naltrexone hydrochloride	ER capsules	$AUC_{0-2hours}$
	Oxycodone	ER capsules	$AUC_{0-3hours}$, $AUC_{0-4hours}$
	Oxycodone HCl	IR tablets and ER tablets	$AUC_{0-3hours}$, $AUC_{0-4hours}$
Long-acting injectable	Naltrexone	ER suspension	$AUC_{1-10days}$, $AUC_{10-28days}$
	Leuprolide acetate	Injectable and injectable depot	$AUC_{7days-t}$
	Leuprolide acetate, Norethindrone acetate	Injectable depot / tablet	$AUC_{7days-t}$
	Triptorelin pamoate	Injectable	$AUC_{7days-t}$
	Buprenorphine	Injectable	$AUC_{3-4weeks}$
	Octreotide acetate	Injectable	$AUC_{0-28days}$, $AUC_{28-56days}$
GI locally acting	Budesonide	ER tablets	$AUC_{8-48\ hours}$
		ER capsules	$AUC_{0-4hours}$, AUC_{4-t}
	Mesalamine	ER capsules	$AUC_{3hours-t}$
		DR capsules and tablets	$AUC_{8-48hours}$
Other considerations			
Multiple indications with different dosing frequencies	Scopolamine	Transdermal, film ER	$AUC_{0-36hours}$

AUC, area under the concentration-time curve; BE, bioequivalence; DR, delayed-release; ER, extended-release; FDA, US Food and Drug Administration; GI, gastrointestinal; IR, immediate-release; pAUC, partial area under the concentration-time curve; PD, pharmacodynamic; PK, pharmacokinetic; PSG, product-specific guidance.

multiphasic modified-release formulation designed to achieve both rapid onset of activity and sustained activity for the intended duration. Recommendations are as follows: ($pAUC_{0-3hours}$) for the first pAUC time window, to ensure comparable early onset of response to both test and reference products; ($pAUC_{3-7hours}$) for the second pAUC time window, to ensure efficacy from after lunch through the end of the school day; and ($pAUC_{7-12hours}$) for the third pAUC time window, to ensure comparable sustained therapeutic response for the intended duration.[8] A fed state prolongs the release of drug product by 1 hour. To account for this change, recommendations of pAUCs under a fed study are: $pAUC_{0-4hours}$, $pAUC_{4-8hours}$, and $pAUC_{8-12hours}$.[8] The 90% CIs of the geometric

mean test/reference (T/R) ratios for the metrics C_{max}, $AUC_{0-\infty}$, and above-mentioned pAUCs should fall within the limits of 80.00–125.00%.

Partial AUC recommended for unique formulation characteristics

Another important consideration is product-related or formulation-related characteristics, which are critical to the overall performance and substitutability of generic drugs.

A product with an abuse-deterrent formulation. Addiction, abuse, and misuse of prescription opioid analgesics continues to be a major public health challenge in the United States. As one way to address it, the FDA has supported development of opioid formulations with abuse-deterrent (AD) properties.[22] HYSINGLA ER (hydrocodone bitartrate ER tablet), for example, has been approved for the "management of pain that is severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate."[23,24] It has been demonstrated to have physical and chemical properties expected to deter abuse through parenteral, oral (chewable), or nasal routes, and is considered to have AD properties.[22,24]

To assist prospective applicants developing generic versions of AD opioid products, the FDA published the general guidance "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products" in November 2017.[25] It recommends conducting studies to demonstrate that a proposed generic product has no fewer AD properties than the reference listed drug with respect to all potential routes of abuse. For comparative human nasal and oral PK studies, the recommended PK parameters include C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, and pAUCs. In this case, pAUC should be related to a clinically relevant PD measure (e.g., drug likability or take drug again). In a comprehensive PK/PD analysis, early systemic exposure to opioids was shown to be a good predictor of abuse by recreational opioid users who received a single dose of oral or nasal intact or manipulated opioid AD formulations.[26] Based on these findings, the FDA recommends early pAUCs (e.g., $AUC_{0-3hours}$ and $AUC_{0-4hours}$) as supportive PK metrics for the assessment of AD properties of generic products, such as the hydrocodone bitartrate ER tablet.[23] As supportive evidence, there is no specific recommendation that the 90% CIs of the geometric mean T/R ratios for the early pAUCs should fall within the limits of 80.00–125.00%, but an upper limit greater than 125.00% may be concerning.

A long-acting injectable product. Long-acting injectable products are designed to provide sustained drug release during a long dosing interval, thus reducing the frequency of drug administration. Buprenorphine HCl ER solution is a long-acting injectable product approved for administration each month for the treatment of moderate-to-severe opioid use disorder.[27] The PK profile for this drug product is characterized by two main phases, which include an initial release of drug product followed by a sustained-release plateau phase for several days.[27] Results from the opioid blockade clinical study in subjects with moderate-to-severe opioid use disorder showed an overall increasing trend of clinical response (i.e., reduced drug liking) with increases in buprenorphine concentration, based on the comparison between buprenorphine concentration and the placebo-corrected drug liking visual analog scale score.[28] Thus, having a comparable PK profile for a generic drug was considered important for ensuring therapeutic equivalence.

C_{max}, in combination with T_{max}, is considered adequate for ensuring a comparable PK profile during the initial absorption phase.[29] In addition, maintenance of average plasma minimum concentration (C_{min}) in the plateau phase is considered important to ensure comparable clinical efficacy for a potential generic formulation. Due to inherent variability leading to the difficulties of BE assessment on C_{min}, the PSG recommends pAUC from 3 to 4 weeks, which represents an average plasma concentration for the last 1-week time period after dosing.[29] With the control of initial (C_{max} and T_{max}) and later phases ($pAUC_{3-4weeks}$) of PK profiles, as well as the extent of drug absorption reflected by total AUCs, failure modes for the comparable performance of the test product are minimized; and hence recommendation for other pAUCs in the plateau phase of the PK profile were not considered necessary for this product. The 90% CIs of the geometric mean T/R ratios for the above-mentioned $pAUC_{3-4weeks}$ should fall within the limits of 80.00–125.00%.

A locally acting drug product intended to deliver drug to a specific region of the GI tract. APRISO (mesalamine ER capsules) is a locally acting aminosalicylate product approved for once-daily administration and indicated for the maintenance of ulcerative colitis remission in adults.[30] The mechanism of action of mesalamine is not completely understood but its effect is considered to be local to the intestinal mucosa rather than systemic[30]; therefore, it is considered a locally acting GI drug.[31] Because mesalamine is rapidly and thoroughly absorbed in the stomach and small intestine,[32] the development of modified-release formulations is necessary to ensure adequate drug delivery to the site of action (i.e., the colon).

Mesalamine ER capsules contain granules formulated with a pH-sensitive polymer that controls the drug release at pH values greater than six. Mesalamine ER capsules have been found to reach the site of action (i.e., the ileocecal region), around 3.31 ± 1.03 (mean ± SD) hours after administration.[33] A GI intubation clinical study, which measured local mesalamine levels after administration of mesalamine ER capsules, reported the appearance of large quantities of mesalamine in the distal jejunum by 3 hours and limited release in earlier regions, such as the duodenum.[31] Mesalamine has a short half-life after intravenous administration (about 42 minutes)[34] and drug exposures during different time windows following oral administration can provide information as to the local GI availability of mesalamine. The FDA performed physiologically-based PK (PBPK) modeling and simulation for mesalamine ER capsules have at the fasting state, and the results showed that systemic pAUC from 3 hours to the last measurable timepoint correlated with predicted exposure to mesalamine in the colon.[35] Therefore, the systemic PK exposures during different time windows can serve as a reasonable surrogate to reflect GI local delivery/availability. As such, $pAUC_{3-t}$ is recommended in

Table 2 Case examples of pAUC recommendations based on modeling approaches

No.	Products	Modeling approach	Application
1	Methylphenidate and zolpidem ER tablet	PK/PD modeling	PK/PD modeling established the linkage between exposure and clinical response at specific time window of interest
2	Hydrocodone bitartrate ER tablet	PK/PD modeling	PK/PD modeling showed that early systemic exposure of opioids is a good predictor of the abuse potential response in recreational opioid users.
3	Mesalamine ER Capsule	PBPK Modeling	PBPK modeling showed that systemic $pAUC_{3hours\text{-}t}$ correlated with predicted exposure to mesalamine in the colon
4	Buprenorphine HCl ER injection	Exposure-response analysis	Exploratory exposure-response analysis suggested an overall trend of increasing clinical response with increases in buprenorphine concentration

ER, extended-release; pAUC, partial area under the concentration-time curve; $pAUC_{3hours-t}$, partial area under the concentration-time curve from 3 hours to the last measurable time point; PBPK, physiologically-based pharmacokinetic; PD, pharmacodynamic.

the PSG for mesalamine ER capsules as supportive evidence for BE assessment.[36]

Partial AUC recommended for other considerations

Partial AUC has been recommended for BA or BE assessment for other products: for instance, products with multiple clinical indications having different dosing frequencies. One such product, scopolamine transdermal system, is used to prevent nausea and vomiting after anesthesia, narcotic pain medicines, surgery, as well as to prevent nausea and vomiting caused by motion sickness. However, the drug application times for the 2 indications are ~ 36 and 72 hours, respectively. To ensure BE and therapeutic equivalence for both indications, the FDA PSG recommends both early ($pAUC_{0-36hours}$) and total AUCs for BE assessments of scopolamine transdermal system products, correlated to the dosing intervals for the two indications, respectively.[37]

CHALLENGES IN THE USE OF PAUC FOR BE ASSESSMENTS

Well-characterized PK/PD relationships are the scientific foundation for recommending the use of pAUC in BE assessments. As stated in the FDA guidances, the time to truncate the partial area should be related to a clinically relevant PD or clinical end point measure, and sufficient quantifiable samples should be collected to enable adequate estimation of the partial area.[1,2,36] Specifically, the FDA communicates to the public its current scientific thinking through individual PSGs, in which pAUC is incorporated as an additional PK metric on an individual product basis.[38] Modeling and simulation approaches are valuable aids in

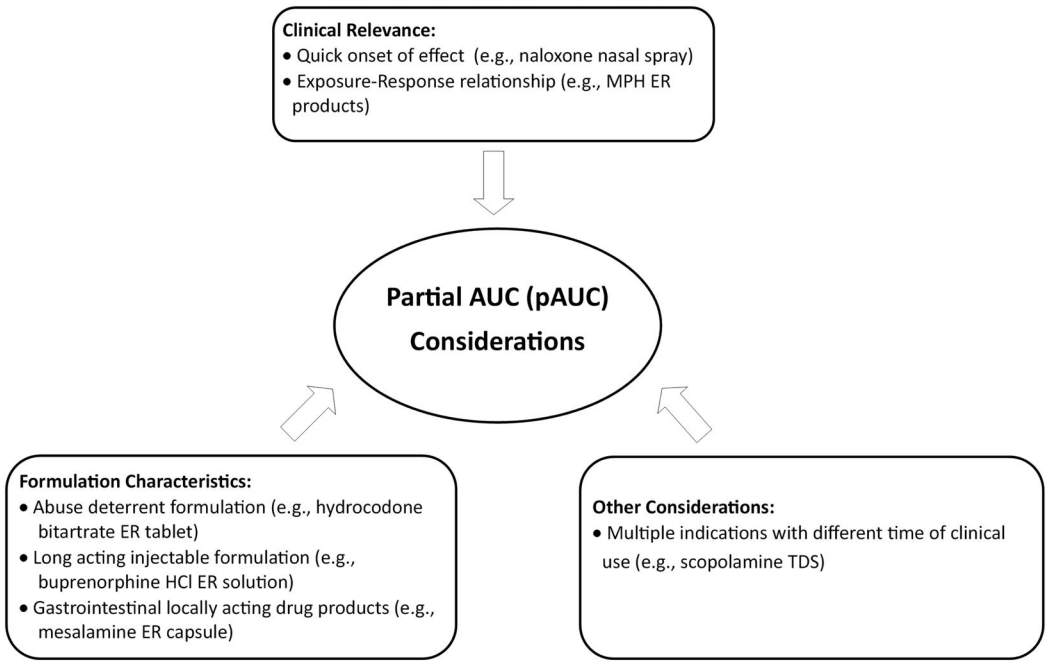

Figure 2 General framework for recommending pAUC(s) as additional bioequivalence metrics. MPH, methylphenidate; ER, extended-release; TDS, transdermal delivery system.

understanding the need for pAUC measures and proper pAUC truncation times.[15–17] As illustrated in **Table 2**, PK/PD and PBPK modeling approaches have informed identification of the time windows for pAUC recommendations.

However, for many drug products, data for characterizing the PK/PD relationship may not always be available to the FDA, and the identification of clinically relevant pAUC(s) in those cases could be challenging. From the product lifecycle management perspective, it is crucial that innovative drug development commits to defining PK/PD relationships for efficacy and safety. We should leverage different modeling approaches, such as PBPK and mechanism-based PK/PD frameworks, throughout translational/early/late drug development stages to thoroughly interrogate the PK drivers of drug effects, which will guide the BE strategy based on the totality of evidence. Additionally, pAUCs generally are associated with higher variability than overall AUC and C_{max}.[39] Consequently, the sample size needed to demonstrate BE for pAUC could be larger than those for C_{max} and AUC.

FDA CDER-WIDE EFFORTS ON PAUC RECOMMENDATIONS

Numerous citizen petitions (https://www.regulations.gov/) have requested that the FDA apply pAUC as a BE criterion to both new and generic drugs such as MYDAYIS (mixed-amphetamine ER capsule, FDA-2017-P-6922), INVEGA SUSTENNA (paliperidone palmitate ER injectable suspension, FDA-2013-P-0608), and RISPERDAL CONSTA (risperidone long-acting injection, FDA-2011-P-0086). Given the challenges in qualifying pAUC assessment in product lifecycle management, CDER has undertaken efforts to harmonize practices and enhance consistency in the use of pAUC. These efforts have had several goals: (i) the development of a science-based and risk-based regulatory approach to determining when and how to use appropriate pAUC metrics for BE assessment based on relevant information from new drug development programs, such as PK/PD relationships. This supports timely development of PSGs; (ii) the establishment of a consistent process for resolving key pAUC-related scientific and regulatory issues raised from regulatory submissions, such as citizen petitions, new drug applications, and ANDA submissions in a transparent and consistent manner; and (iii) the creation of a knowledge base of products for which pAUC assessment is considered as an additional metric for BE determination.

The pAUC working group developed a general question-based framework to help the FDA reviewers gauge the need for pAUC assessment (**Figure 2**). It emphasizes the clinical relevance of the proposed pAUC metric (i.e., whether a quick onset of drug effects is important, and whether the shape of the PK profile affects the clinical performance based on PK/PD and exposure-response relationships). The framework also takes into consideration product-related or formulation-related characteristics critical to the overall performance and substitutability of generic drugs, including but not limited to products with long-acting injectable formulation, GI locally acting formulation, and AD properties. This framework serves as a general guideline and is updated continuously as more experience and knowledge is gained.

CONCLUSION

Partial AUC constitutes a key feature of PK profiles that can be clinically relevant. The recommendations on the need to include pAUC as an additional metric to ensure BE are drug-specific and product-specific, including multifactorial considerations of PK/PD, clinical indications, and product release characteristics. Clinically relevant pAUC recommendations can critically complement conventional BE metrics, such as C_{max} and AUC, to assess product performance in humans and ensure therapeutic equivalence.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

DISCLAIMER

The opinions expressed in this white paper are those of the authors and should not be interpreted as the position of the US Food and Drug Administration.

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