Partial Area Under Curve (pAUC): Product-Specific Guidance Development

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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.

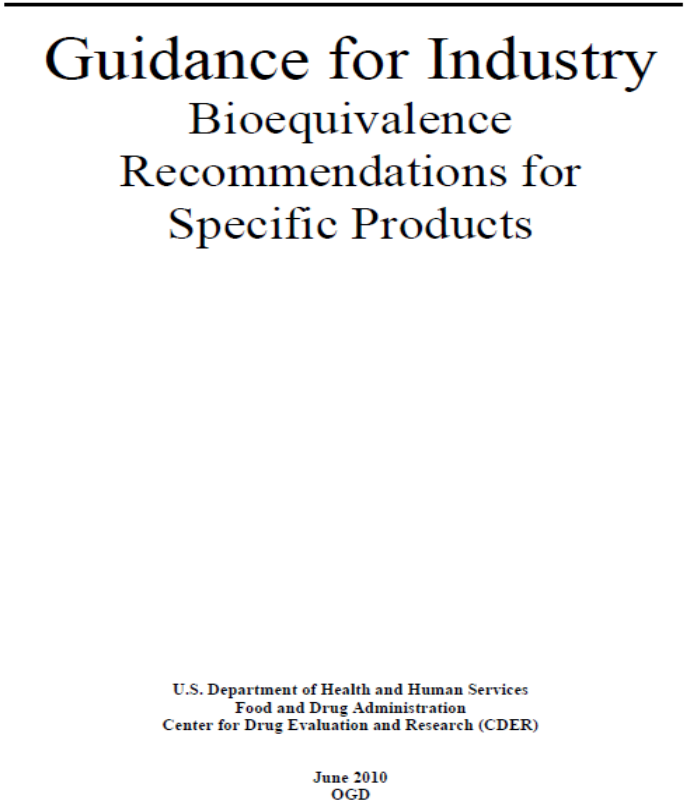
- For some products with complex pharmacokinetic (PK) profiles, the traditional metrics of AUC and Cmax may not be sufficient to ensure therapeutic equivalence.

- 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- Year 2013 FDA draft guidance "Bioequivalence Studies with PK Endpoints for Drugs Submitted Under an ANDA" and Year 2019 draft guidance "Bioavailability Studies Submitted in NDAs or INDs: General Considerations"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
- Product-Specific Guidances (PSGs) for generic drug development recommending pAUC
- Year 2018: Initiation of CDER-wide efforts regarding pAUC

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 product and reference standard~~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

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

Framework: pAUC in BE Evaluation

1. Clinical relevance of proposed pAUC
   i. Quick onset of drug effect (e.g., Naloxone HCl nasal spray)
   ii. Shape of the PK profile affects the clinical performance (e.g., Methylphenidate HCl ER capsules)

2. Product formulation-related characteristics
   i. Multi-phasic release characteristics (e.g., Zolpidem ER tablets, long-acting injectables)
   ii. Abuse-deterrent formulation (e.g., Hydrocodone bitartrate ER tablets)
   iii. Locally-acting drug products where systemic PK serves as a surrogate of local drug delivery (e.g., Mesalamine ER capsules)

3. Other considerations
   i. Multiple indications with different dosing frequencies (e.g., Scopolamine TDS)

ER: extended release; TDS: transdermal delivery system

White paper: Fang, et al, Use of Partial Area Under the Curve (pAUC) in Bioavailability or Bioequivalence Assessments: a Regulatory Perspective. Clinical Pharmacology & Therapeutics. 110. 10.1002/cpt.2174.

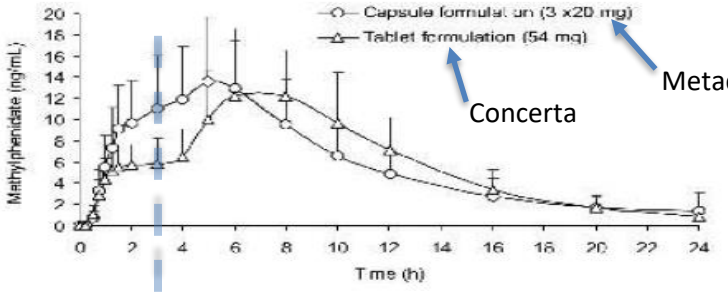
Example PSGs

- Highlight representative PSGs to explain the rationale of recommending pAUCs
  - Methylphenidate (MPH) extended-release (ER) products
  - Long-acting injectable (LAI) products
  - Mesalamine ER capsules

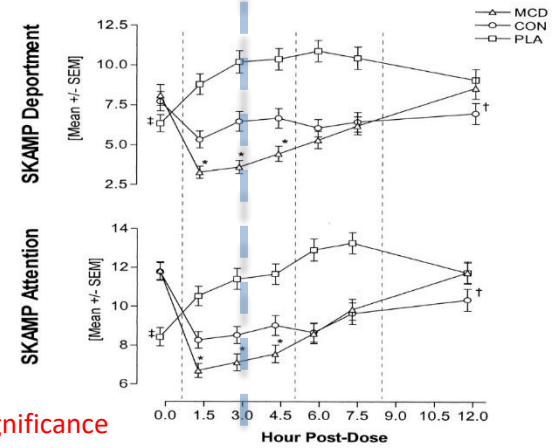
Shape of PK Profile: MPH ER

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

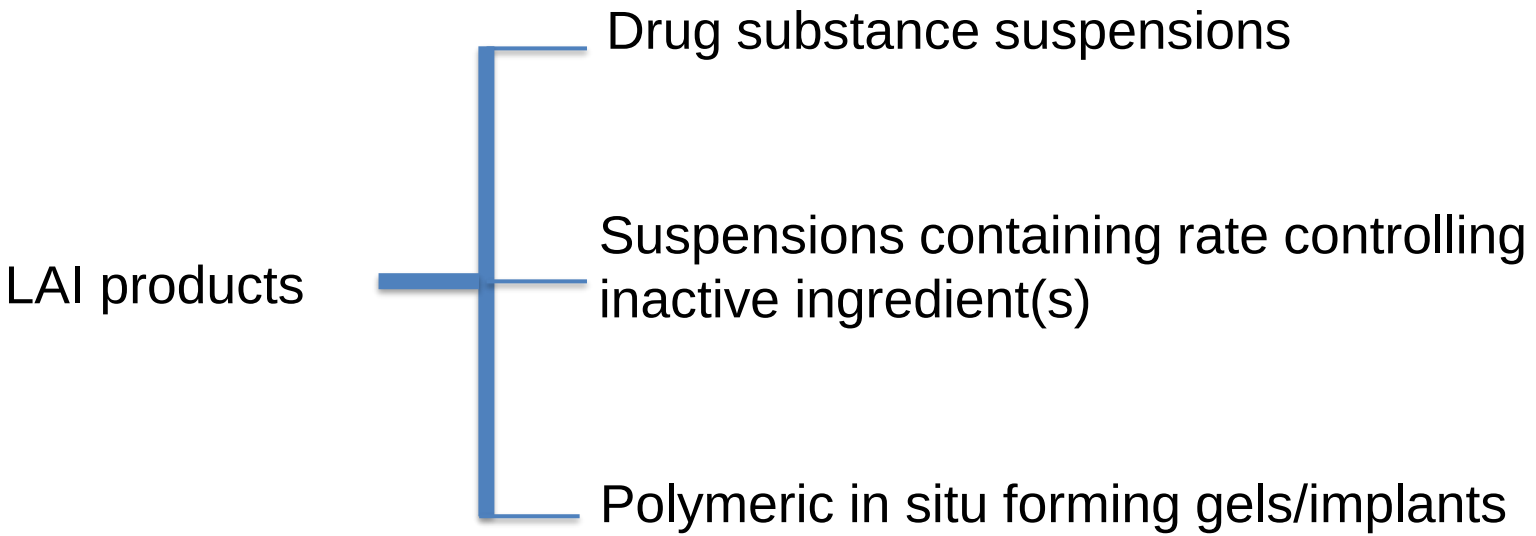
PSG for MPH ER Tablets

- 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

Long-Acting Injectable (LAI) Products

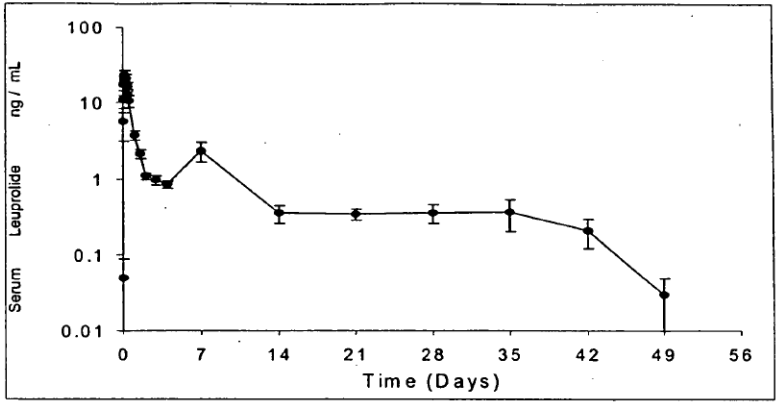
Long-acting drug products for injection, implantation, and insertion are formulated to achieve sustained drug release and action for extended time from days to years.



Pharmacokinetics (PK)

- The PK curve for the drug product (Eligard® 7.5 mg) is characterized by two main phases which include an initial burst release of drug product followed by a sustained-release "plateau" phase for several days.
- The initial burst release from Eligard formulation is complete within the first 2-3 days.
- The plateau phase lasts from 1-6 months based on strength.

Figure 1. Serum Leuprolide Concentrations (Mean, SEM) Following a Single SC Injection of ELIGARD™ 7.5 mg in 8 Orchiectomized Subjects (Study AGL 9802).



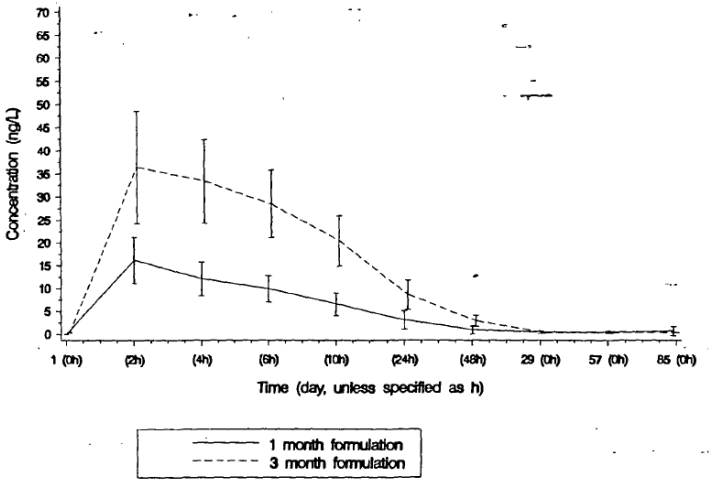


Fig 2. Comparison of serum triptorelin concentrations following first IM injection of 1-month vs 3-month formulations

Figure source: Clinical Pharmacology and Biopharmaceutics review document from Drugs@FDA for ELIGARD KIT (NDA 021343) and TRELSTAR

Reasons for pAUC Recommendation

Formulation and PK consideration:

- PK curve is characterized by a large initial peak due to high burst release which constitutes a significant portion of the total AUC. By day 7, this initial release is completed.

- The sustained release portion of the PK profile from day 7-t is the most relevant period to compare rate and extent of absorption of drug released from test product and reference standard ~~products~~.

Reasons for pAUC Recommendation

Clinical relevance:

- Transient increase in clinical signs and symptoms of puberty (because of a transient stimulatory effect of the drug) may be observed during the first weeks of therapy.
- Mean testosterone levels increased above baseline during the first week following the initial injection, declining thereafter to baseline levels or below by the end of the second week of treatment.
- AUC Day 7-t parameter is clinically relevant based on the mode of action. The sustained release portion impacts clinical performance.
  - The plateau part of PK is associated with suppressed serum level of testosterone is < 50 ng/dL (associated with surgical castration).

Leuprolide PSG

- Leuprolide injectable is gonadotropin-releasing hormone (GnRH) agonist
  - Transient stimulatory effect in the first week followed by subsequent suppressive effect on testosterone production
  - AUC Day 7-t parameter is clinically relevant based on the mode of action

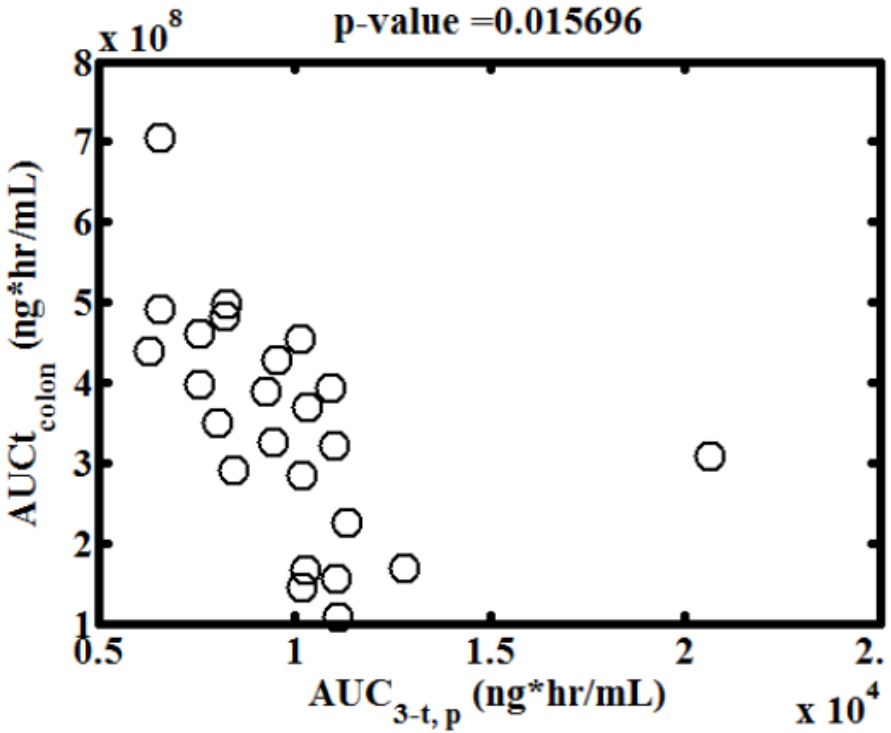
- pAUC recommendation: Day 7-t

- Day 7-t represents sustained release phase or plateau phase of PK profile

Mesalamine ER Capsules

- Indicated for the maintenance of remission of ulcerative colitis in adults.
- Mechanism of action of mesalamine (5-ASA) is believed to be **local** to the intestinal mucosa rather than systemic.
- It takes about 3 hours for the drug to reach the target region of gastrointestinal (GI) tract.
  - Local equivalence (particularly drug delivery to the colon) is important.

Predicted Colon Availability Correlates with Systemic Exposure Post 3 Hours



Slides courtesy: Xinyuan (Susie) Zhang, Ph.D.

PSG for Mesalamine ER Capsules

- PK endpoint study is a reasonable surrogate to reflect GI local delivery/availability
  - Colon drug exposures correlate with systemic $pAUC_{3\text{-}t}$

- pAUC Recommendation: Applicants should submit pAUCs (e.g., $AUC_{0\text{-}3hr}$ and $AUC_{3hr\text{-}t}$) as supportive data

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Mesalamine_draft_Oral%20cap%20ER_RLD%2020049_RC10-17.pdf

Summary

- CDER has created a center-wide framework to increase coordination between offices for the standards applied to new drug and generic drug approval
  - Case examples provided

- 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

- FDA strives to provide harmonized and consistent pAUC recommendations applicable to both new and generic drugs

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