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Criteria to Decide Whether pAUCs Are Appropriate BE Metrics and Alternatives When They Are Not

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Financial Disclosure

- I do paid consulting work for many companies, some of which might have economic interests in regulatory standards involving pAUC criteria.
- Due to contractual confidentiality restrictions, I cannot disclose which companies I work for or the products that they may have economic interests in.
- I am Chairperson of the Board and Treasurer of Scientists Advancing Affordable Medicines, Inc. a 501(c)(6) non-profit organization.

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Motivation for requiring pAUC metrics for BE

- Systemically-acting drug products
  - C_{max}, AUC may not always ensure comparable clinical effect over time
  - Broadly speaking, want similar PK profile shape when PK profile is complex
  - pAUCs typically employed where strong, direct PK/PD link exists
- Locally-acting GI drugs (typically at distal GI intestinal wall or lumen)
  - Plasma drug conc. may not directly reflect conc. at site of action
  - Complex relationship between plasma conc. and distal GI drug conc.
  - Indirect, sometimes inverse PK/PD link
  - Ensure similar timing of drug delivery along GI tract
- Different objectives for systemically- vs. locally-acting drug products

Systemically-acting drug products

- pAUC criteria have been applied to:
  - Oral modified-release [often mixed-mode (IR + ER)] formulations
  - Inhalation products requiring quick onset of action
  - Long-acting injectables
  - Abuse-deterrent oral products
  - Some transdermal delivery systems
- pAUC expected to control one or more of the following:
  - Time-to-onset of clinical effect (T_{onset})
  - Time-to-offset of clinical effect (T_{offset})
  - Duration of clinical effect ($T_{offset} - T_{onset}$)
  - Ensure comparable plasma drug conc. during certain post-dose timeframes

$AUC_{0-\infty}$

- Absorption
  - $AUC_{0-\infty}$ is a measure of the amount of drug absorbed:

$$AUC_{0-\infty} = \frac{D * F_{abs}}{k * V_d}$$

(assumes no pre-systemic metabolism)

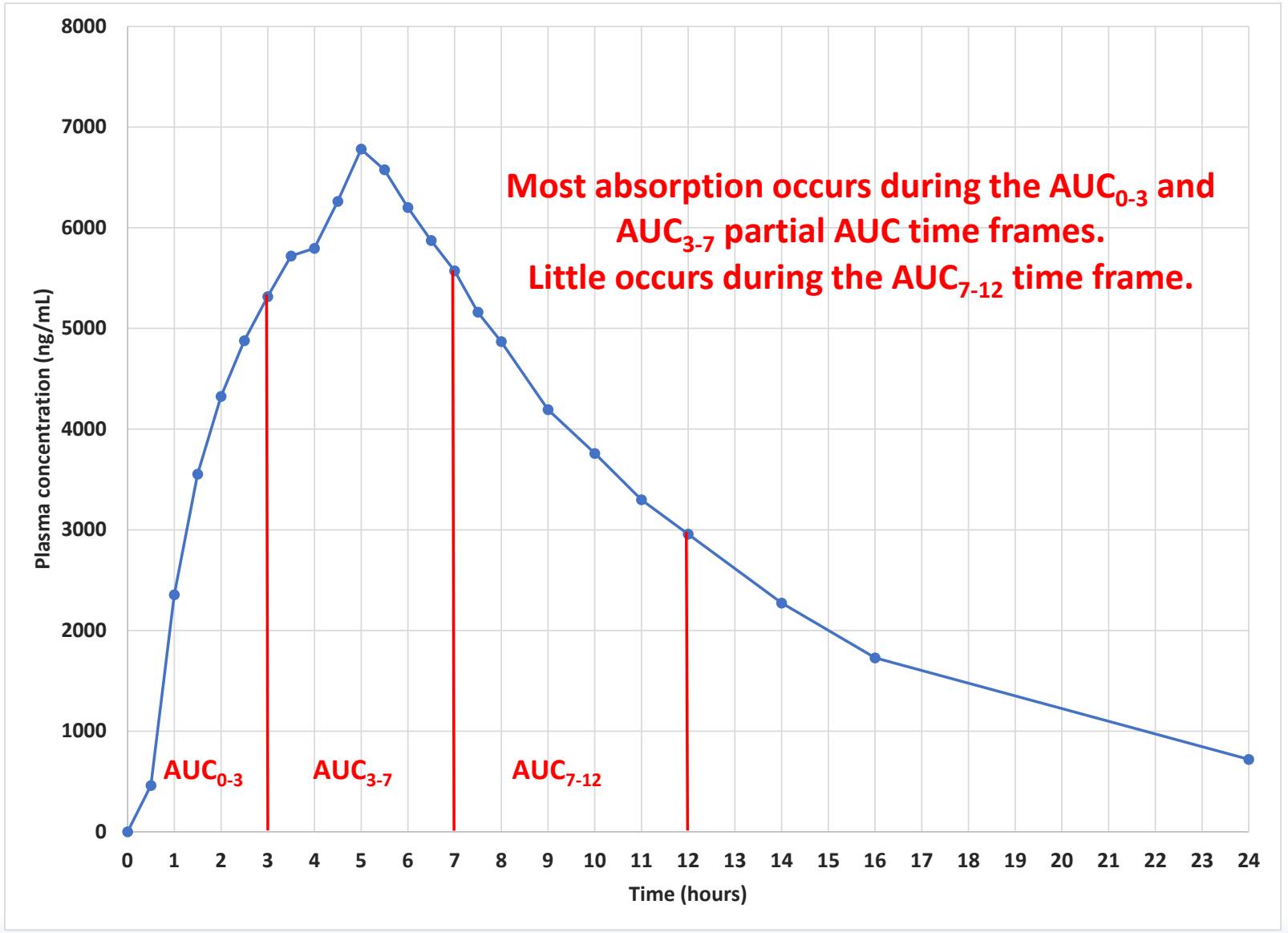
  - Used to calculate bioavailability:

$$BA_{rel} = \left(\frac{AUC_{non-IV}}{AUC_{IV}}\right) * \left(\frac{Dose_{IV}}{Dose_{non-IV}}\right)$$

- Drug exposure
  - $AUC_{0-\infty}$ is a measure of drug exposure

pAUC

- Absorption
  - pAUC does NOT reflect the amount of drug absorbed over its defined time interval
  - e.g. late pAUCs mostly reflect drug previously absorbed
- Exposure
  - pAUC is a measure of drug exposure over its defined time interval



FDA Methylphenidate study T product (ref 1)

Properties of the pAUC metric

- pAUC reflects the average concentration (C_{avg}) over its defined time interval

$$C_{avg(a-b)} = \frac{AUC_{a-b}}{(b-a)}$$

  - Note that a, b are constants for a given pAUC
  - Comparing $AUC_{a\text{-}b}$ across PK profiles is identical to comparing $C_{avg(a\text{-}b)}$ over those PK profiles

- $C_{avg(a\text{-}b)}$ is a weighted average of the individual plasma concentrations from a to b (linear trapezoidal rule):

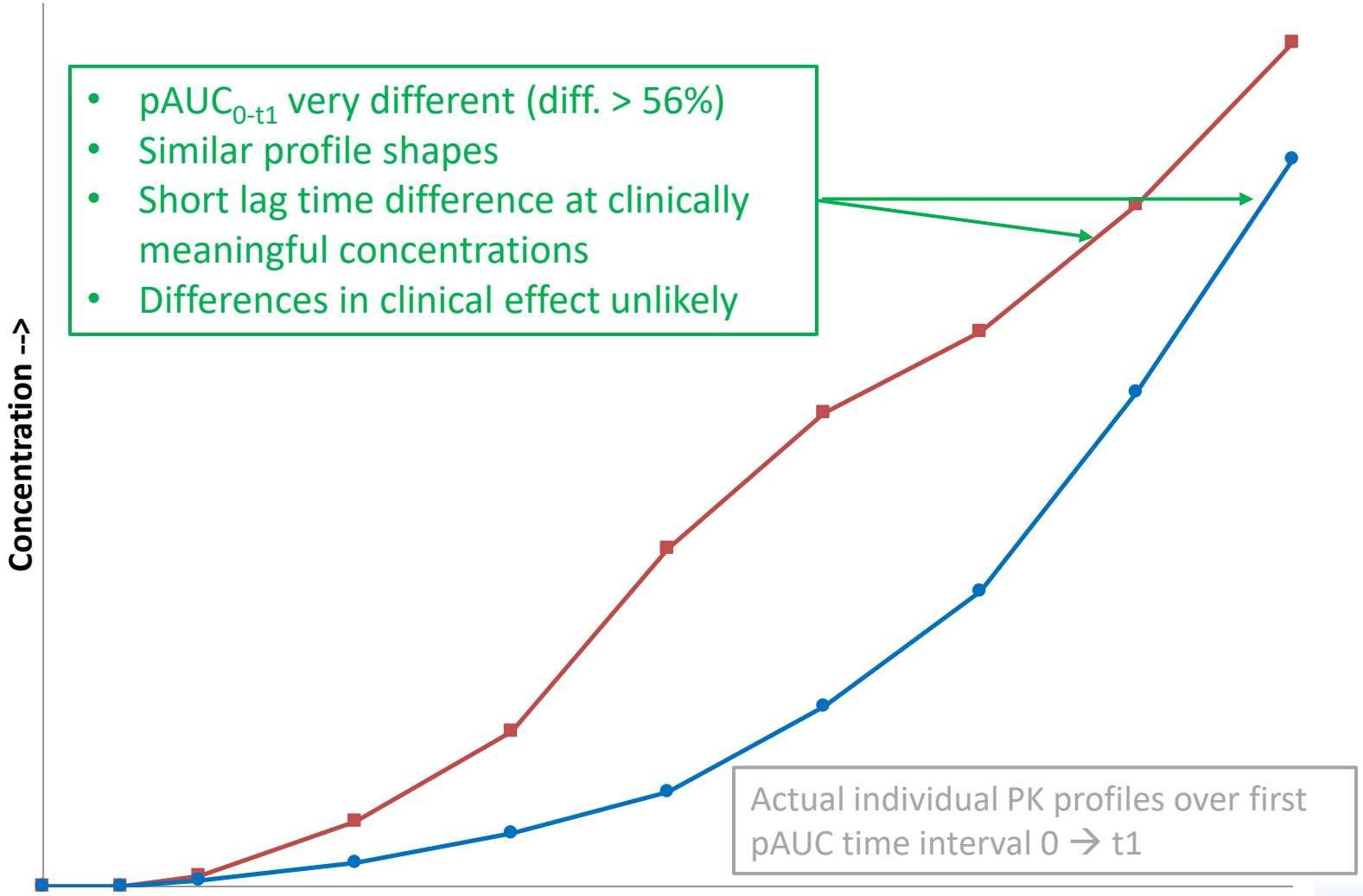
$$C_{avg(t_1-t_n)} = \frac{AUC_{t_1-t_n}}{t_n - t_1} = \frac{C_1(t_2 - t_1) + \sum_{k=2}^{n-1} C_k(t_{k+1} - t_{k-1}) - C_n(t_n - t_{n-1})}{2 * (t_n - t_1)}$$

where t_1 (=a) through t_n (=b) are the individual sampling times across the pAUC interval, and C_1 through C_n are the corresponding concentrations

Problems with the pAUC metric

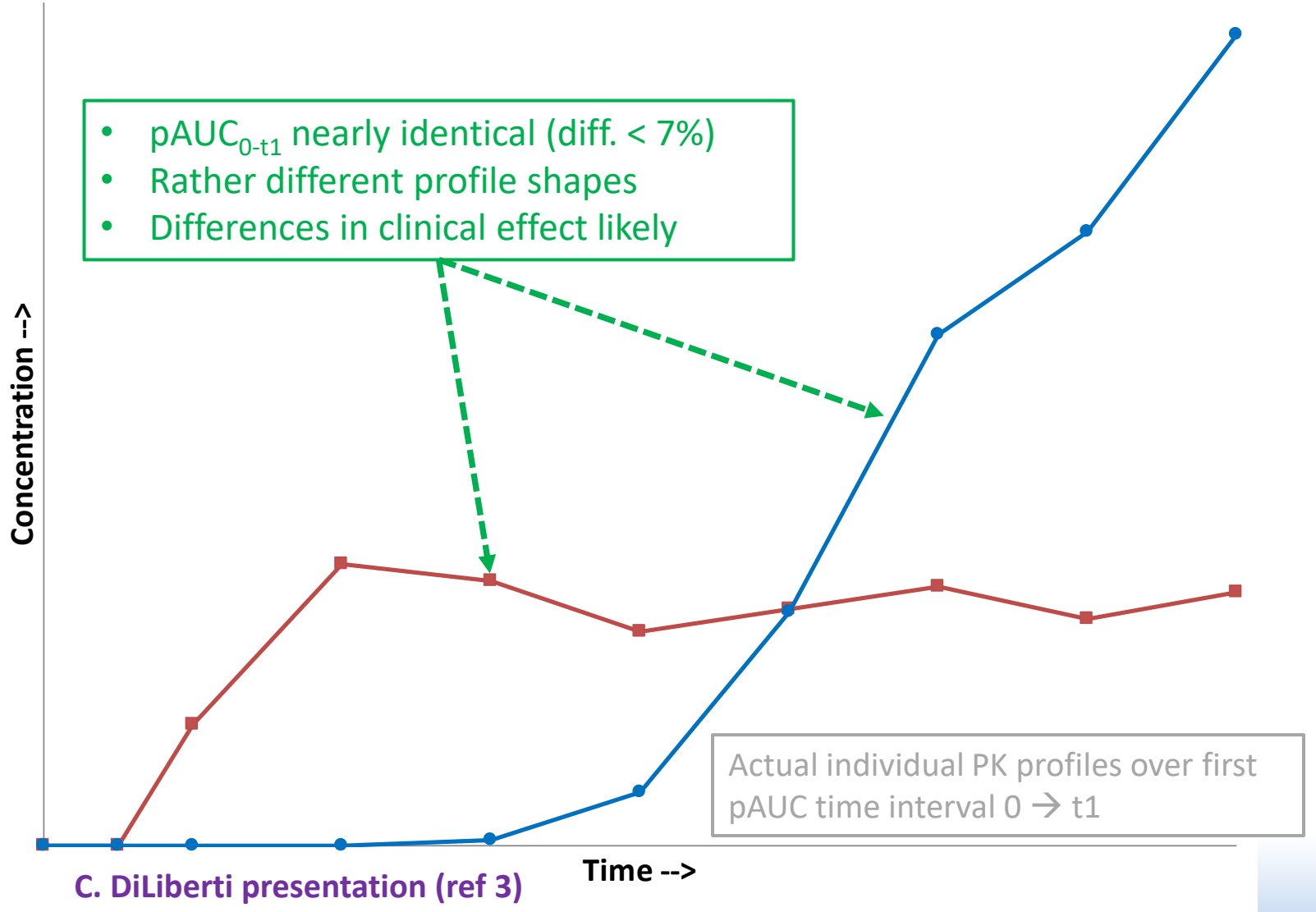
- If goal is to control when a PK profile feature occurs (i.e., time dimension), then pAUC controls the wrong (concentration) dimension
- Questionable clinical relevance of concentrations from which pAUCs are derived:
  - May be highly variable within-profile
  - May have steep within-profile slopes
    - Concentration varies sharply with small time shifts – overly sensitive
  - May include sub-therapeutic concentrations
  - Clinical meaning of C_{avg} under these circumstances ???
- pAUC may have questionable clinical relevance due to:
  - High intrasubject (ISCV), e.g., CV ≈ 65% for $AUC_{0\text{-}1.5}$ for zolpidem ER tabs (ref 2)
  - High between-lot variability within RLD (e.g., 2 RLD lots in same study with GMR = 129%, p=0.008) (ref 3)
- Poor choice of time intervals for some mid-pAUCs

Conventional pAUC metrics may be overly sensitive toward small, clinically insignificant shifts in time course of PK profile



C. DiLiberti presentation (ref 3)

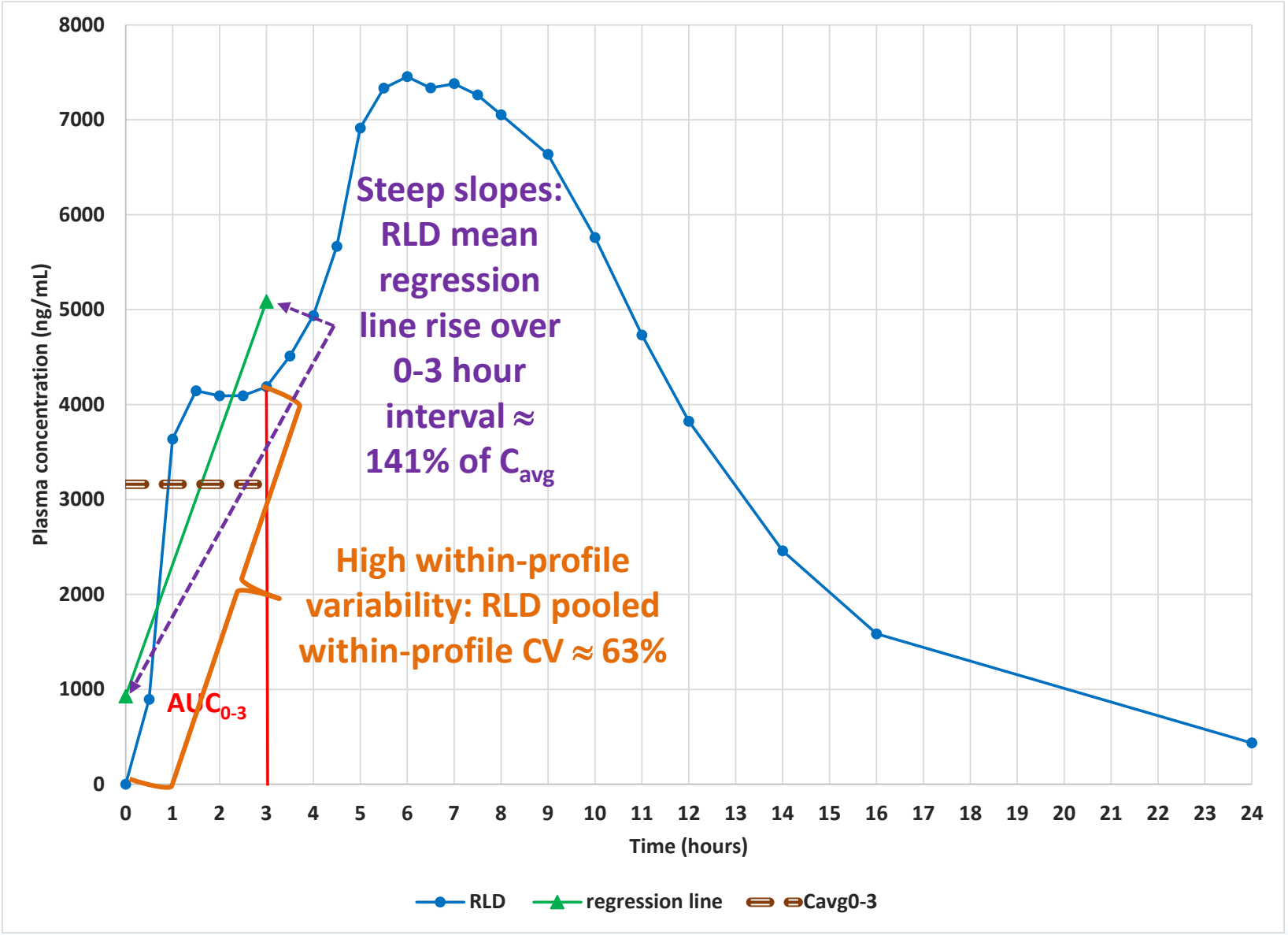
Conventional pAUC metrics may not control clinically meaningful differences in PK profile shape



C. DiLiberti presentation (ref 3)

Within-profile concentrations

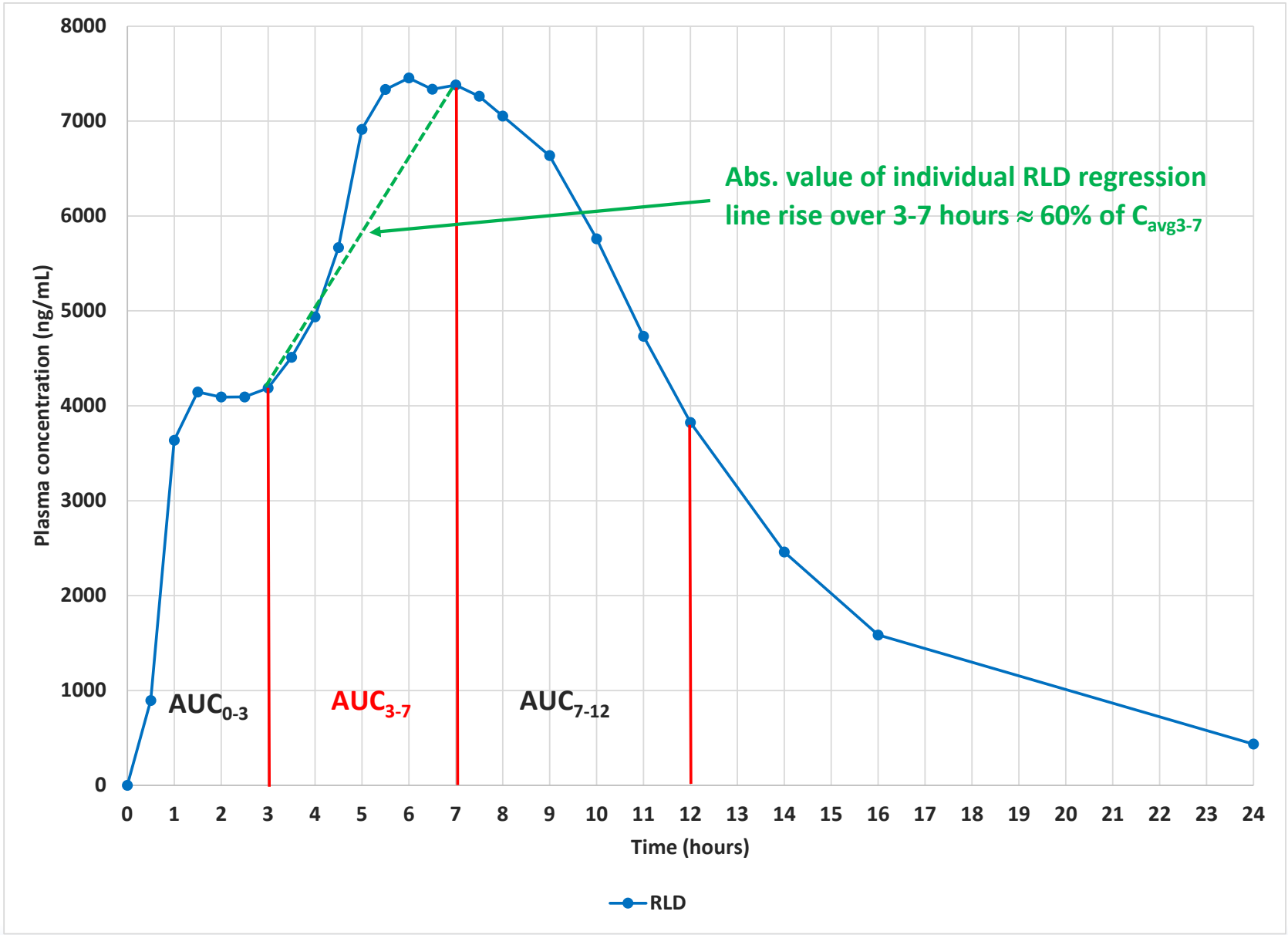
- May have highly variable within-profile concentrations
- May have steep slopes
- Clinical meaning of C_{avg} under these circumstances???



FDA Methylphenidate study R product (ref 1)

Suboptimal choice of middle pAUC?

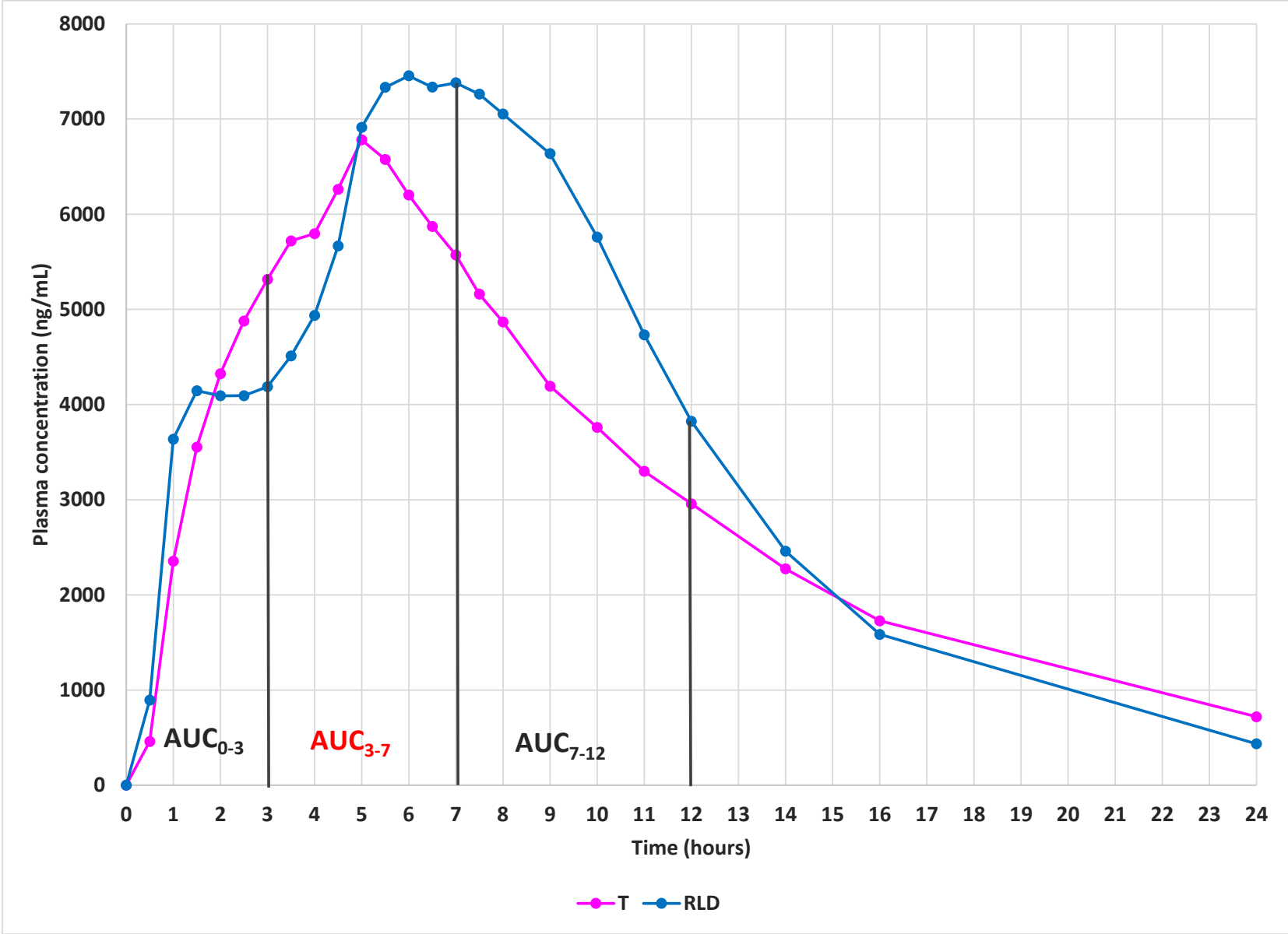
- Methylphenidate ER tabs (Concerta®) – fasting study PSG:
  - Early $AUC_{0\text{-}3}$
  - Middle $AUC_{3\text{-}7}$
  - Late $AUC_{7\text{-}12}$
- Middle $AUC_{3\text{-}7}$ shows steep upslope for RLD
- Clinical relevance of $C_{avg3\text{-}7}$ given steep upslope?



FDA Methylphenidate study R product (ref 1)

Suboptimal choice of middle pAUC?

- Other shapes could yield similar C_{avg3-7}, e.g. test product in this study
- AUC_{3-7} T/R GMR = 96.1%
- AUC_{3-7} may not be very discriminating
- 3 and 7 hour boundaries chosen more for early and late pAUCs?



FDA Methylphenidate study (ref 1)

pAUC performance characteristics essential for systemically-acting drugs

- Low to moderate pAUC ISCV (i.e., not highly variable)
- Consistency among different lots of RLD
- Concentrations over the time interval defining the pAUC metric:
  - Not highly variable, not steeply sloped, no/few subtherapeutic concentrations
- pAUC should not cover too short a time interval
- pAUC should detect clinically meaningful differences, not just differences
- pAUC metrics should only include a time frame where RLD concentrations are fairly high, and likely to be therapeutically effective
- If PK study was conducted before pAUC recommendation was made, then should allow for linear interpolation between time points to estimate pAUC to specified time points

Systemically-acting products for which pAUC metrics make sense

- pAUC performance objective: to ensure comparable average drug concentrations within clinically important time intervals
- Drugs with a long duration of action and slowly varying drug concentrations:
  - Long-acting injectables, e.g., exenatide, leuprolide, goserelin
  - Transdermal patches, e.g., scopolamine, dextroamphetamine
- Possibly the middle (plateau) phase of some mixed-mode (IR/ER) formulations, e.g., amphetamines, methylphenidate

Systemically-acting products for which pAUC metrics do not make sense

- pAUC performance objective: to ensure comparable onset, offset times and/or duration of action
- Drugs with a short duration of action (< 24h) and rapidly varying drug concentrations:
  - Short-acting inhalation products, e.g., naloxone, loxapine, nalmefene
  - Assessing onset, offset, duration of action for oral products with clinically important time-to-onset, time-to-offset, and/or duration of action properties, e.g., methylphenidate, amphetamines, zolpidem
  - Probably abuse deterrent formulations, e.g., opioids

Many PK metrics proposed

- Outlined at April 13, 2010 Advisory Committee for Pharmaceutical Science and Clinical Pharmacology Meeting
- Metrics derived from PK curve first, then compared:
  - Time based: T_{max}, C_{max}/AUC_{inf}, $C_{max}/pAUC_{0\text{-}Tmax}$, Mean Residence Time (MRT), Peak Occupancy Time (POT-25), T_{apical}, Half Value Duration (HVD)
  - Concentration based: C_{apical}
  - Exposure (AUC, conc*time) based: $pAUC_{0\text{-}Tmax}$, $pAUC_{0\text{-ind Tmax}}$, $pAUC_{t1\text{-}t2}$, AUC_{apical}
  - Moment (conc*time^2) based: Area under the moment curve (AUMC)
  - Conc/time based: C_{max}/T_{max}
- Direct (point-by-point) comparison of PK curves:
  - F1, F2, DCC Rescigno Index, DCC absolute difference, DCC squared difference, DCC Chinchilli Metric (CM), DCC (ratio weighted), DCC (ratio-1 weighted)
- Cumulative AUC based: Partial AUC profile, Relative AUC profile
- Deconvolution based: Wagner-Nelson, Loo-Riegelman, CAT-model

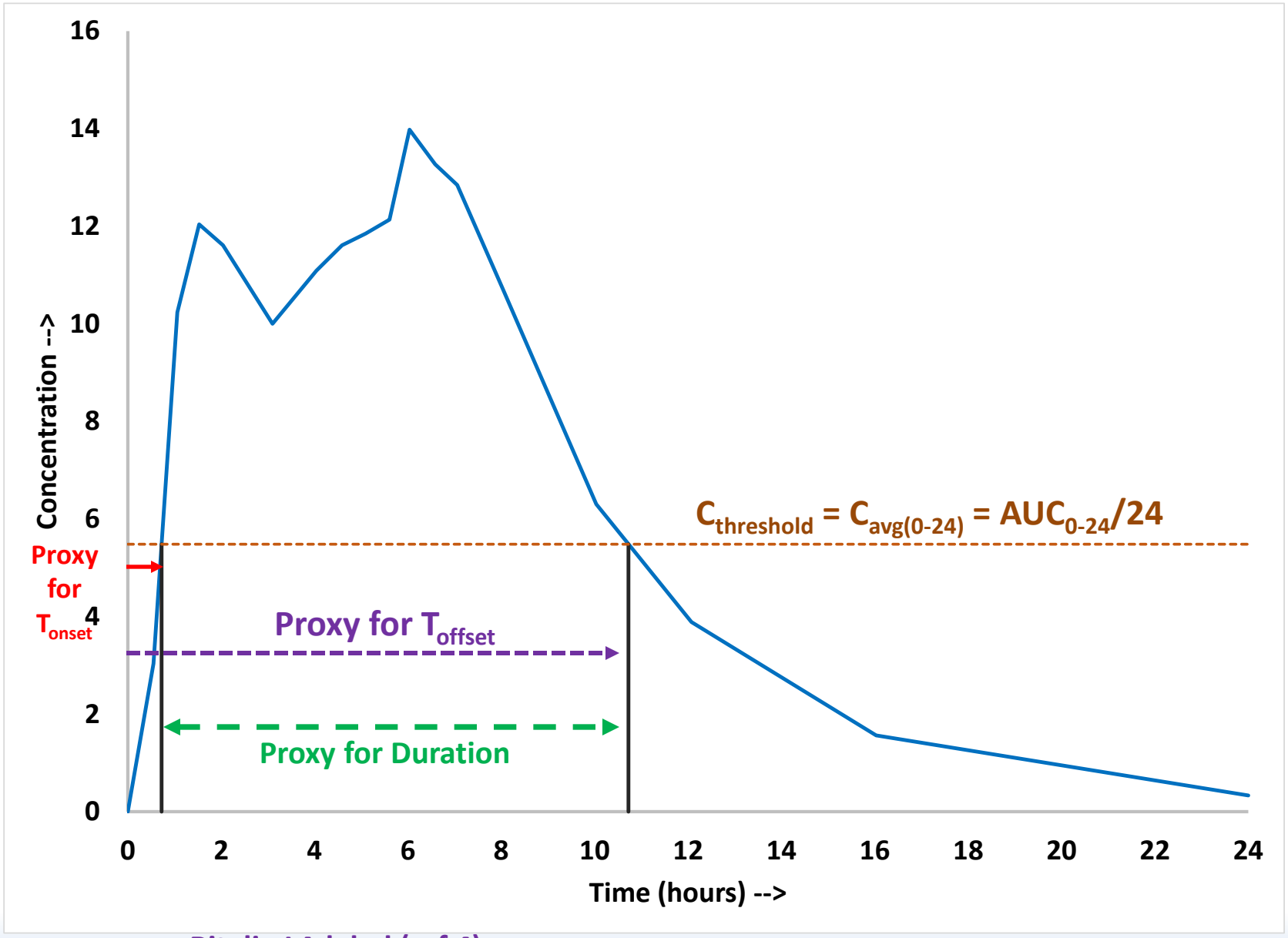
Time-based BE metrics

- Controlling the correct (time) dimension for T_{onset}, T_{offset}, dur. of action (T_{dur})
- Desirable properties of possible time-based BE metrics:
  - Time-to-$C_{threshold}$ based
  - $C_{threshold}$ not determined from fixed Minimum Effective Concentration (MEC)
    - MEC may not be known
    - Would yield erratic/undesirable results if between-subject CV is large, or for different strengths; C_{max} for some subjects might not even attain a fixed MEC
  - Not based on RLD concentrations for same subject or same study:
    - Can't do proper statistical analysis – T values not independent of R values
  - $C_{threshold}$ should scale (approximately) with AUC of same PK profile
- May need to develop clinically relevant time-based BE margins
  - 80 to 125% CI limits for GMR may not be reasonable, especially for T_{onset}

Example of proposed time-based BE metrics

- Calculate $C_{avg(0-24)} = C_{threshold} = AUC_{0-24}/24$
- Calculate (proxy for) T_{onset}, time until PK curve first crosses $C_{threshold}$
- Calculate (proxy for) T_{offset}, time when PK curve last crosses $C_{threshold}$
- If desired, calculate (proxy for) duration of action

  $T_{dur} = T_{offset} - T_{onset}$
- Use linear interpolation to estimate exact times



Ritalin LA label (ref 4)

General comments on time-based BE metrics

- Using $C_{avg(0-24)}$ as $C_{threshold}$ appears to work well for once-daily oral IR/ER formulations such as methylphenidate, dexmethylphenidate, amphetamines, zolpidem, yielding duration of action consistent with labeling
- Choice of AUC time frame to calculate C_{avg} ($C_{threshold}$)
  - May need to use different AUC time frames to calculate $C_{threshold}$ for other products, especially short-acting inhalation products
  - Regulatory agencies should choose AUC time frame to calculate $C_{threshold}$ so that t_{onset}, t_{offset}, and t_{dur} are consistent with labeling

General comments on time-based BE metrics (cont'd)

- Modeling support
  - Should seek to relate onset, offset, and duration times of PD effect to T_{onset}, T_{offset}, T_{dur} proxies calculated with the proposed time-based metric
  - Relating pAUEC to pAUC does not answer the relevant clinical questions about onset, offset, and duration of clinical effect
- For products where onset, offset, and/or duration of clinical effect is important:
  - Time-based BE metrics, not pAUC metrics, should be used to control onset, offset, and/or duration proxies in PK curves
  - If additional mid-curve control is needed, a mid (plateau) region pAUC metric could be considered, although the boundary times for it should be chosen carefully to ensure good performance characteristics as described above

pAUC metrics to control concentrations during specific times

- Regulatory agencies should choose pAUC boundary times based on clinical relevance, and to ensure good performance characteristics as described above
- Target products:
  - Long acting injectables
  - Some transdermal delivery systems
  - Middle (plateau) phase of some MR (IR/ER) products
    - Where warranted based on clinical importance
    - Where clinically relevant pAUC boundary times can be chosen so that pAUC has good performance characteristics

Locally-acting GI drugs

- Because locally-acting GI products are not designed to be well-absorbed, they often have highly variable PK, including pAUCs
  - high variability is acceptable and can be managed with RSABE
- Where possible, regulatory agencies should do the necessary modeling studies to determine appropriate pAUC boundary times
- Usually, an extensive T vs. R dissolution study is needed to support BE in addition to PK

Research priorities for systemically-acting drugs

- FDA should re-evaluate the (in)appropriateness of using pAUC criteria to supplement C_{max} and AUC BE criteria for those drug products where time-to-onset, time-to-offset, and/or duration of clinical effect are important to control
- FDA should develop suitable time-based BE criteria to supplement C_{max} and AUC, and replace early and late pAUC metrics with them
- Where possible, FDA should use time-to-PD effect (onset, offset, duration) as the benchmark for modeling to support time-based PK metrics
- FDA should re-evaluate any remaining pAUC metrics to ensure acceptable performance characteristics as described above, and modify them to improve performance where necessary
- This work should be done quickly, considering the imminent harmonization efforts on M13

References

1. Clinical Study Report No FDU-P9-178, Sponsor Protocol Number RIHSC 14-065D, *A Randomized, Fully Replicated, Single-dose, Crossover Comparative Bioavailability Study Of Two Formulations Of Methylphenidate Hydrochloride Extended-release Tablets In Healthy Subjects Under Fasting Conditions*; Sponsored by ORS/OGD/CDER/FDA https://www.regulations.gov/document/FDA-2016-N-3118-0044

2. Midha KK and McKay G, *Use of Partial Area Under the Curve for BE Assessments of Products with Complex PK Profiles; a View Point*, presentation at Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, April 13, 2010

3. DiLiberti, CE; *Partial AUCs 2.0 – Improved Metrics for Assessing Bioequivalence on Mixed Release Mode (IR/ER) Drug Products*; presented at Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review Workshop; Silver Spring, MD, 10/2/2017

4. Ritalin LA Capsules Package Insert, NDA 21-284, Supplement 027

Thank-you!