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Partial AUCs 2.0 – Improved Metrics for Assessing Bioequivalence on Mixed Release Mode (IR/ER) Drug Products

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Background

- Conventional C_{max} and AUC pharmacokinetic (PK) metrics might not be adequate to ensure bioequivalence for some products with complex PK profiles, notably mixed-mode (e.g., IR + ER) formulations
- Numerous additional PK metrics have been proposed over the past few decades
- FDA introduced partial AUC to the median t_{max} of the reference product as a possible PK metric into its draft BA/BE guidance in March 2003
- Implementation has been slow and limited, starting with Zolpidem ER tablet product-specific BE guidance (finalized October 2011)
- pAUC BE criteria were later added to guidances for modified-release methylphenidate, dexmethylphenidate, mixed amphetamine salts, mesalamine, and budesonide products
- pAUC metrics intended to provide additional controls over the time course of the PK profile, often the onset and cessation (offset) of drug effect, where such timing is clinically important

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Scope of discussion

- Focus on products:
  - Typically dosed once daily
  - Complex PK profiles designed to provide early onset of action, prolonged effect, conveniently timed offset of action, and rest/recovery interval before subsequent dose
  - Little or no meaningful accumulation
  - e.g., zolpidem, methylphenidate, dexmethylphenidate, mixed amphetamine salts, etc.
- Could adapt new metrics to other products with complex PK profiles that undergo accumulation on chronic administration
- Conventional pAUC metrics also used to provide assurance that drug products with some degree of local action within the GI tract are not absorbed too early, so that adequate drug remains available for local delivery to the ileum/colon (e.g., mesalamine, budesonide products) but such products are outside the scope of today's discussion

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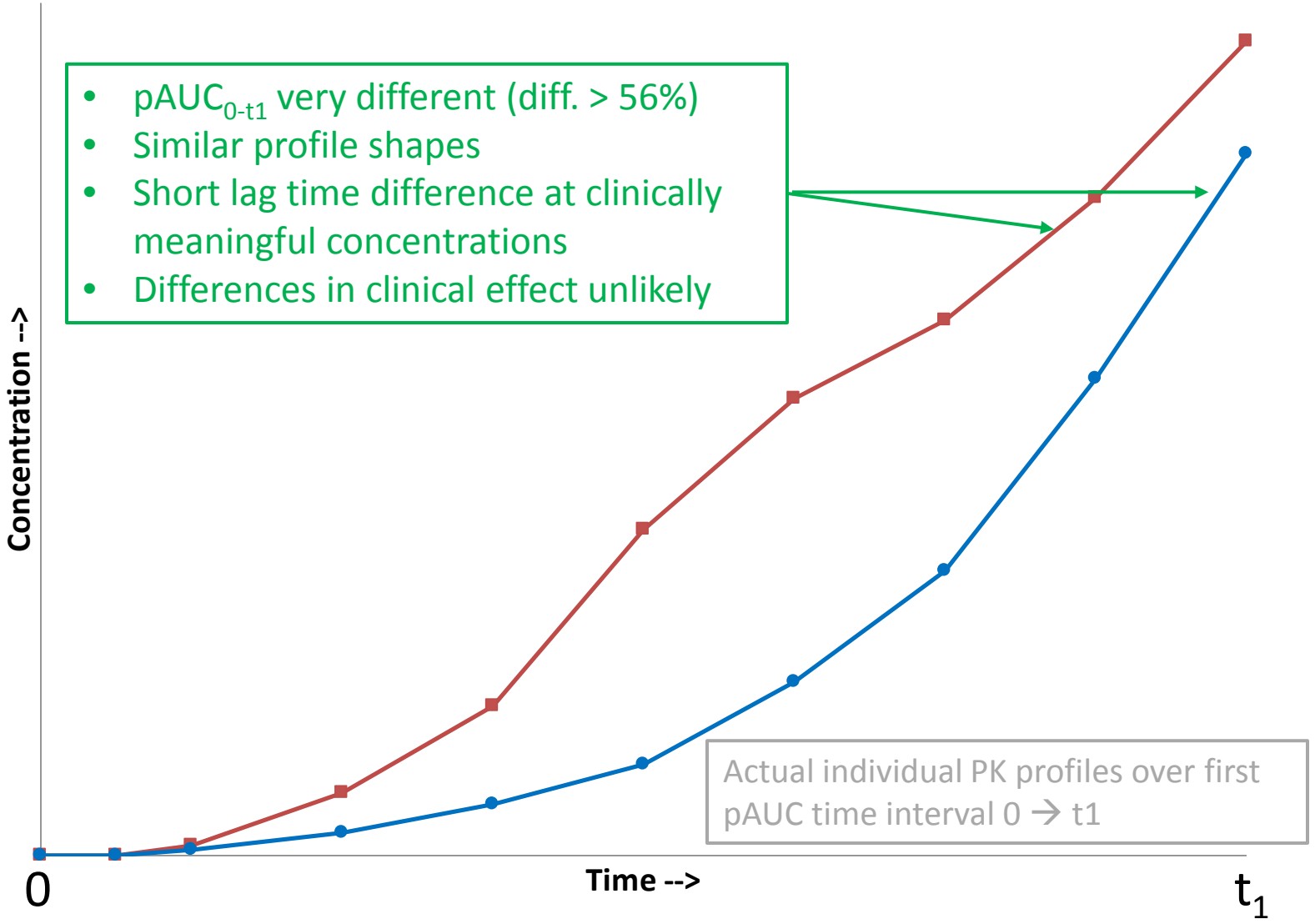
Performance issues with pAUCs

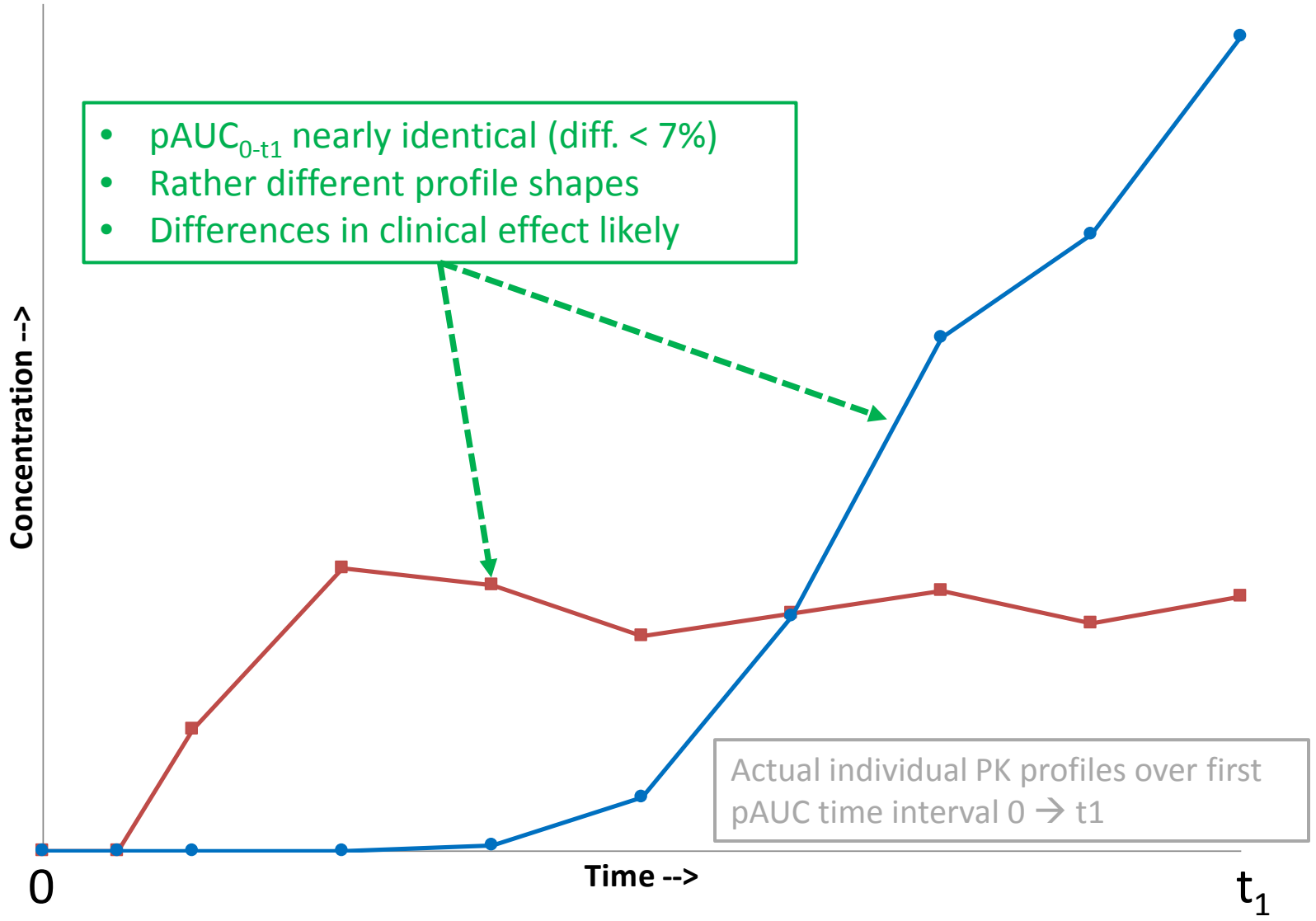
- pAUCs are sometimes prone to high within-subject variability:
  - Issue noted by multiple authors over the span of decades
  - e.g., Zolpidem ER tablets (intrasubject CV = 65% in 72 subject originator crossover design study)*
  - High intrasubject CV is an indication that the PK metric is not closely linked to safety/efficacy (not clinically discriminating) – same argument used to justify RSABE
  - Applying reference-scaled average bioequivalence method helps BE studies pass, but does not address this underlying issue
- pAUCs are sometimes overly discriminating (e.g., causing different lots of originator product to be declared inequivalent)
  - In recent PK study (data on file), two lots of originator product differed dramatically (GMR = 129%, p = 0.008) with respect to a pAUC metric specified in the corresponding product-specific BE guidance, despite superimposable *in vitro* dissolution profiles

*KK Midha and G McKay, "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

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



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



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Why do these performance issues exist?

- Fixed boundary times between which partial AUCs are calculated cause the following:
  - pAUCs to be “brittle” (not robust) toward inherent variability in timing of events within the GI tract
  - Small changes in the time course of the PK profile can have inordinately large effects on pAUCs
- Undue influence of clinically insignificant regions of PK curve (where drug concentrations are too low to have meaningful efficacy) on pAUCs

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Rethinking pAUCs – objectives and desirable properties of improved metric

- Objective: control time course of PK profiles for complex formulations to ensure comparable *in vivo* effects:
  - Note that C_{max} and AUC control size of PK profile well, but not necessarily its shape
  - Improved metric should be sensitive toward T/R differences in PK profile shape likely to affect safety/efficacy:
    - Implies that intrasubject CV for improved metric must be relatively low
  - Improved metric should be insensitive toward T/R differences in PK profile shape not likely to affect safety/efficacy:
    - Implies that two different lots of originator product should have a high likelihood of meeting BE criteria when tested with improved metric
- Objective: focus on regions of PK profile with concentrations likely to be in the therapeutically effective range:
  - Improved metric should be sensitive towards T/R differences in regions of the PK curve where concentrations are relatively high
  - Improved metric should be relatively insensitive toward T/R differences in regions of the PK curve where concentrations are relatively low

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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

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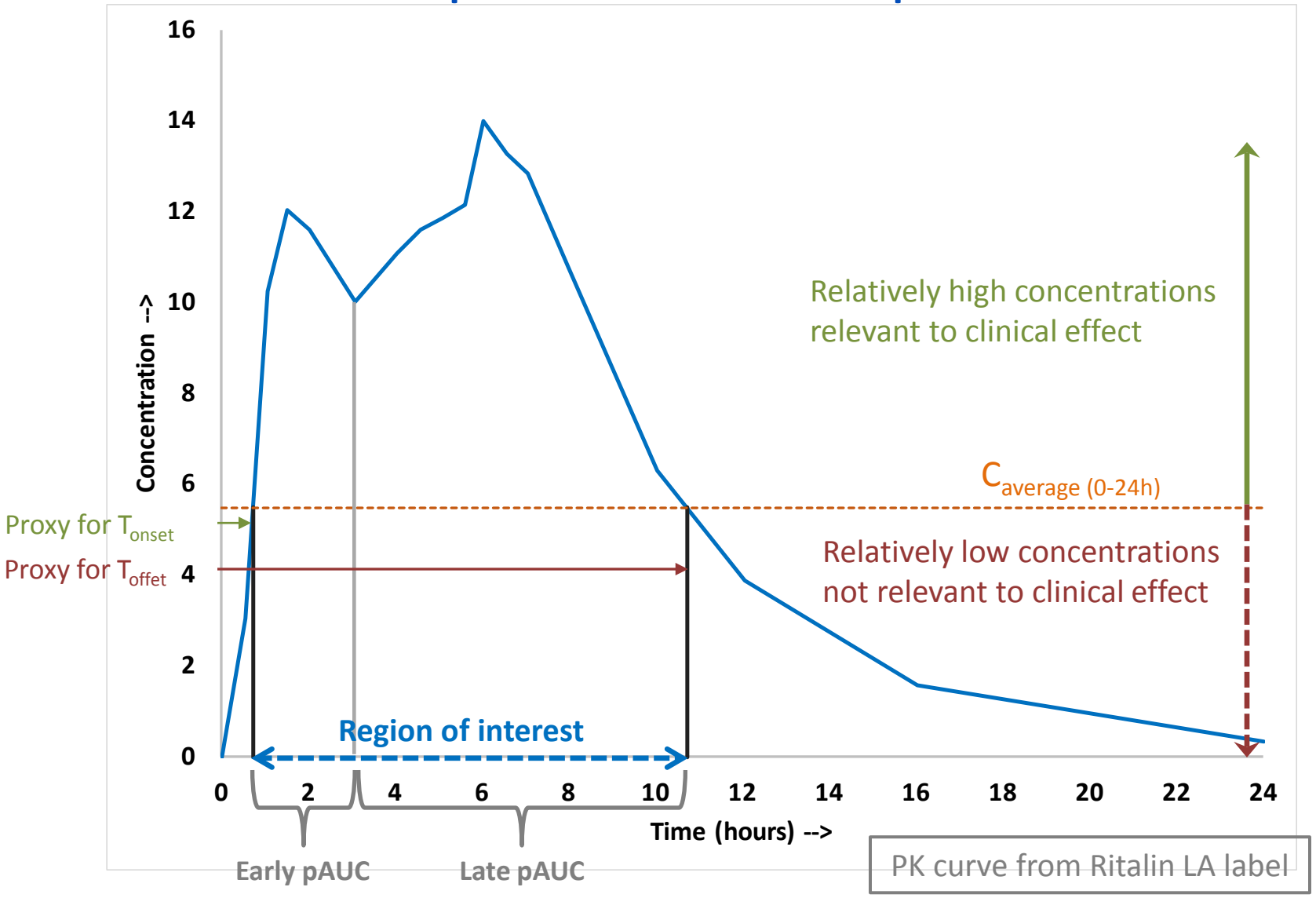
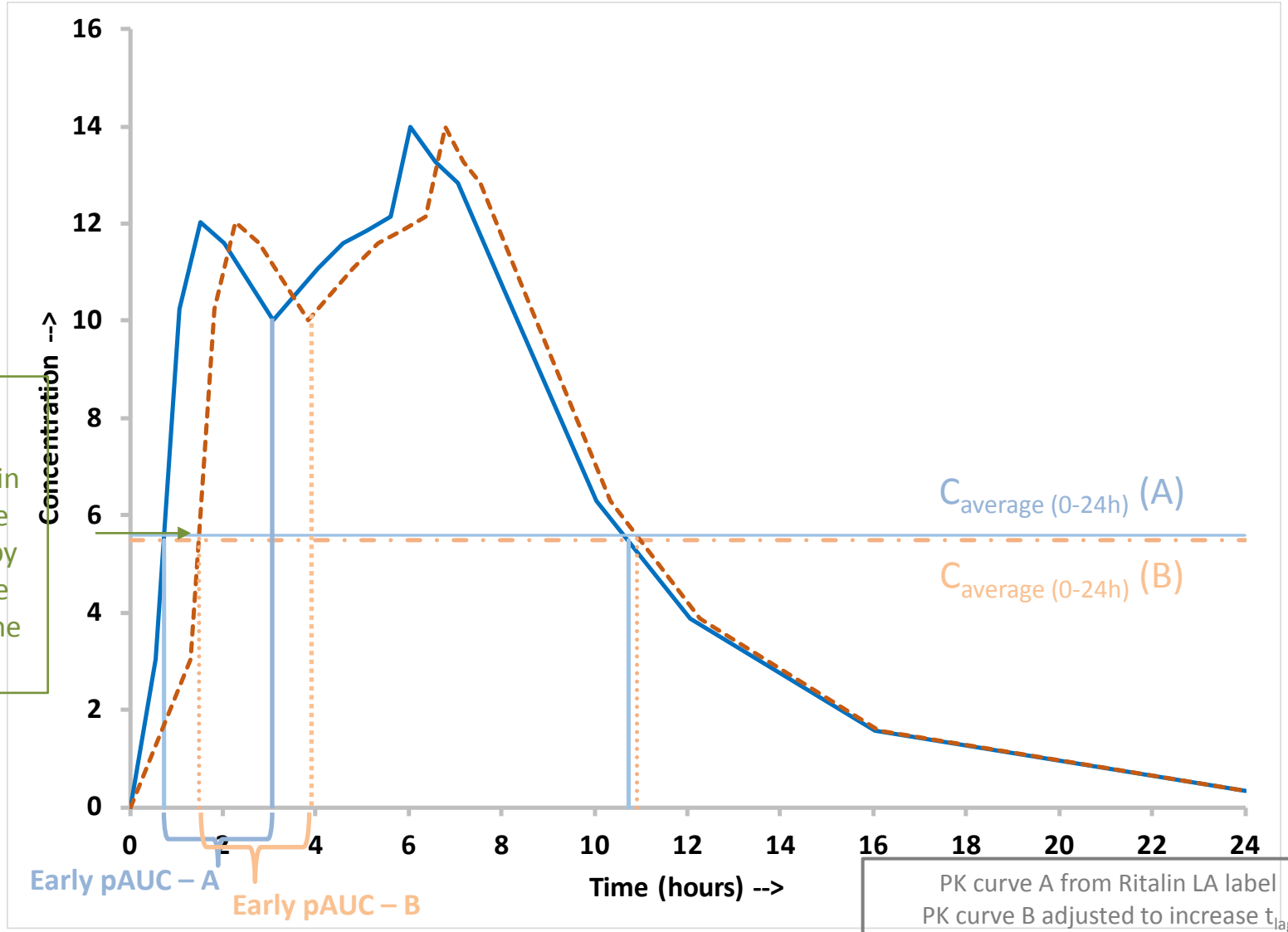
Improving upon pAUC concept – "pAUCs 2.0"

- Keep pAUC concept, but introduce flexibility (robustness) toward normal biological variation in time course of PK profiles
- Calculate pAUCs, but over time intervals defined on a per-profile basis
- Ideally, early pAUC metric would start at onset of clinical effect and late pAUC metric would end at cessation of clinical effect, (spanning the region of interest), but these concentrations and corresponding times are impossible to link precisely to clinical effects
- Nevertheless, operationally, we could define start and end boundary times for a "region of interest" for pAUC calculations in various ways:
  - Where concentrations exceed a particular level
  - Based on T_{max} of reference product for same subject
  - Based on fraction of C_{max} (e.g., 50%)
  - These values may be variable, however
- Prefer defining region of interest based on $AUC_{0\text{-}24}/24$ (i.e., $C_{average}$ over the 24-hour dosing interval)

Defining “region of interest” to be partitioned into pAUCs



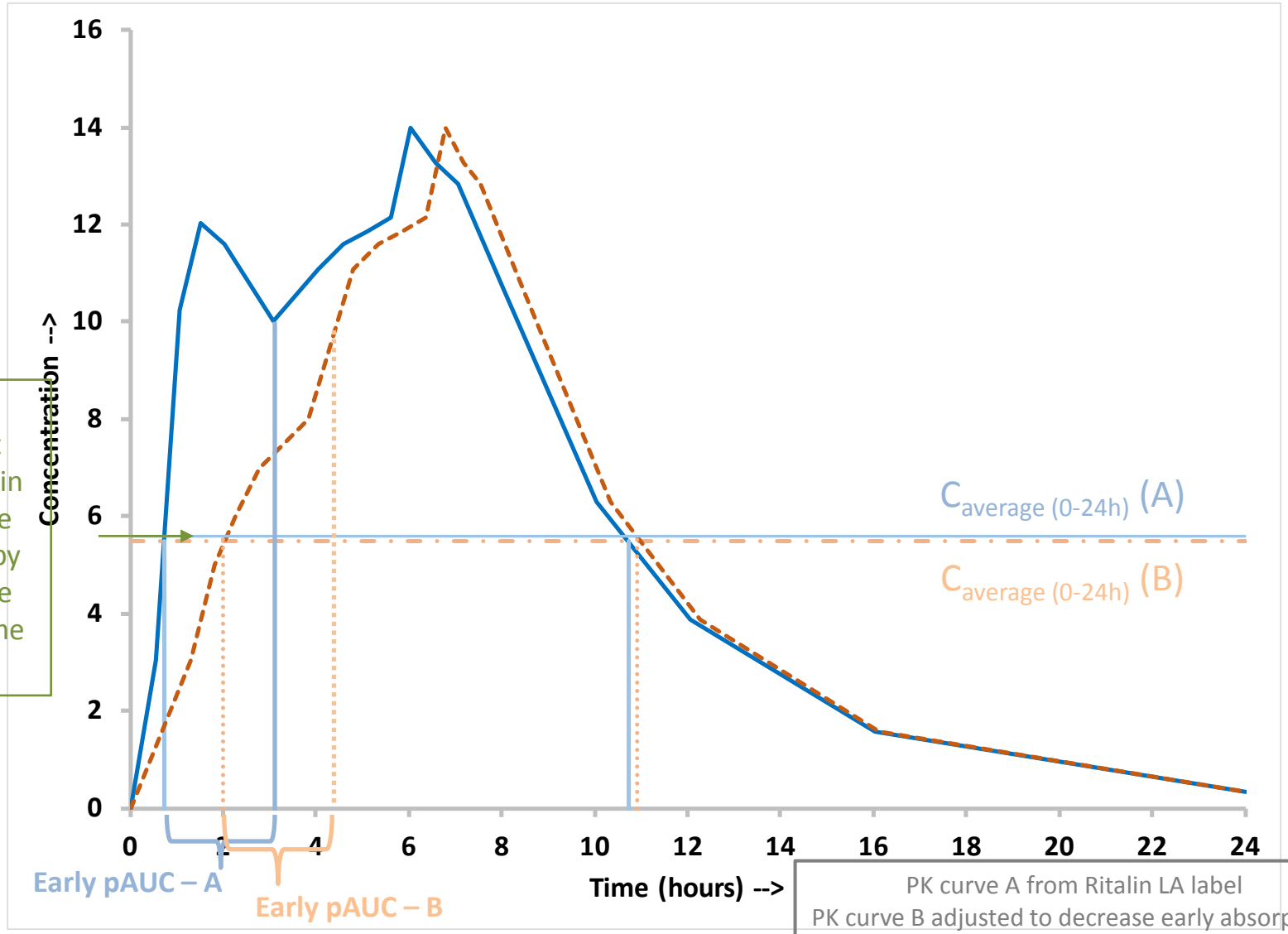
Flexibility along time axis allows for more reasonable comparisons when small shifts in time course exist



Clinically important differences in time course controlled by appropriate limits on time to C_{avg}

PK curve A from Ritalin LA label
PK curve B adjusted to increase t_{lag}

Improved pAUC metric is sensitive toward clinically meaningful differences in PK profile shape



Clinically important differences in time course controlled by appropriate limits on time to C_{avg}

PK curve A from Ritalin LA label
PK curve B adjusted to decrease early absorption

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How to select partition point(s)

- Determine average T_{onset} and T_{offset} for reference product from BE study being analyzed
- Set partition point(s) so that average T_1 (and T_2 if applicable) for reference product in the study equal(s) the corresponding time(s) in the current FDA BE guidance
- For example, if the current guidance specifies a $pAUC_{0-3h}$ and the observed mean T_{onset} and T_{offset} for the reference product in the study are 0.7 h and 10.3 h, respectively, then the region of interest would be partitioned at:

  $(3\ h - 0.7\ h)/(10.3\ h - 0.7\ h) = 0.2396$

- In other words, each individual profile (for both test and reference products) in the study would be partitioned at 23.96% of the distance from the T_{onset} to T_{offset} observed in that individual profile
- Continuing this example, if a particular PK profile in this same study had observed values for T_{onset} and T_{offset} of 0.5 h and 10.5 h, respectively, then the relevant partial AUC and C_{avg} values for that profile would be evaluated over the time interval from T_{onset} to

  $0.5\ h + 0.2396 * (10.5\ h - 0.5\ h) = 2.896\ h\ (T_1)$, i.e.,

  calculate $AUC_{(Tonset - 2.896\ h)}$ and $Cavg_{(Tonset - 2.896\ h)}$

  If appropriate, $AUC_{(2.896\ h\ -\ Toffset)}$ and $Cavg_{(2.896\ h\ -\ Toffset)}$ could also be calculated
- On average, the time at which the partitioning occurs for the reference product in the study will then be exactly equal to the pAUC time(s), e.g., T_1 (T_2) specified in the product-specific BE guidance

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Final adjustments

- Because the durations over which pAUCs are calculated will differ for each PK profile, must adjust for these differences:

$$pAUC_{(T1 - T2)}/(T_2 - T_1) = C_{avg(T1 - T2)}$$

- In effect, we are comparing average drug concentration over the early phase of Product A with the average drug concentration over the early phase of Product B:
  - Allows for small, clinically unimportant time shifts among PK profiles, improving robustness
  - Retains selectivity against differences in PK profile shape
  - Comparing average drug concentrations is easily understood and clinically relevant
- Apply similar logic for middle and/or late phases as needed

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pAUCs 2.0 summary

- All calculations done on individual PK profiles
- Calculate $C_{average\ (0 – 24h)}$
- Find time at which PK profile first attains $C_{average}$ and designate (loosely) as T_{onset}
- Find time at which PK profile is last at $C_{average}$ and designate (loosely) as T_{offset}
- Determine the fraction of the distance from T_{onset} to T_{offset} at which to partition each individual PK profile so that, on average, the reference product in the study is partitioned at the pAUC time(s) specified in the product-specific BE guidance as described earlier
- For each individual PK profile, calculate pAUCs over the resulting time segments, e.g.,

  $AUC_{(Tonset – T1)}$, $AUC_{(T1 – Toffset)}$
- For each individual PK profile, Calculate C_{avg} over the corresponding time segments, e.g.,

  $C_{avg(Tonset – T1)} = AUC_{(Tonset – T1)}/(T_1-T_{onset})$

  $C_{avg(T1 – Toffset)} = AUC_{(T1 – Toffset)}/(T_{offset} – T_1)$
- Ln-transform the resulting C_{avg} values, compare via ANOVA as for C_{max} and AUC, and apply conventional 80 – 125% BE criteria

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Criteria for T_{onset}, T_{offset}

- Although C_{avg} criteria control shape well, also want to control location along the time axis (e.g., onset and offset times)
- Suggest point estimate criterion for T/R GMR of 80 – 125% for T_{offset}
- T_{onset} typically varies considerably on a relative basis, so recommend setting fixed absolute limit (e.g., ± 1 hour) on point estimate difference in least square means [$T_{onset(test)}$ – $T_{onset(ref)}$] based on variability of originator product PK and clinical considerations

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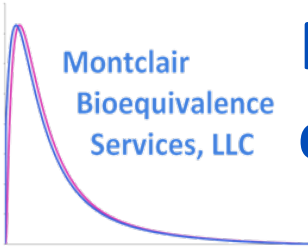
Performance of improved metrics – different lots of originator product

- Conventional pAUC metric exhibited dramatic differences between two lots of originator product (GMR = 129%, p = 0.008)
- Most extreme GMR = 104.5% (p = 0.49) for any of the corresponding improved C_{avg} metrics, max ISCV = 16%
- Delta in T_{onset} = 0.8 h, GMR T_{offset} = 100.0%



Formulations with suspected differences in clinical effects flagged by improved metrics

- Most extreme C_{avg} metric meets bioinequivalence criteria (90% CI entirely outside of 80 – 125%)

Thank-you!

Questions?