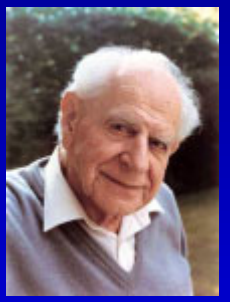
Vítejte!

Partial AUCs

Helmut Schütz
BEBAC

To bear in Remembrance...

Whenever a theory appears to you as the only possible one, take this as a sign that you have neither understood the theory nor the problem which it was intended to solve.



Karl R. Popper

Even though it's *applied* science we're dealin' with, it still is – *science!*

Leslie Z. Benet

Guidelines etc.

- Partial AUC (pAUC) in American guidances
  - 'Early Exposure'
  - Mandatory PK metric if early onset is clinically relevant (effect or AEs) – similar to t_{max} for EMA
    - US-FDA
      $AUC_{tmax,ref}$ = pAUC truncated at population median t_{max} of the reference
      90% CI of GMR within 80–125%
    - Canada-HPFB/TGD
      $AUC_{tmax,ref}$ = pAUC truncated at subject's t_{max} of the reference
      GMR within 80–125%

Assumptions…

- Main assumptions in the concept of BE
  - (1) Similar plasma concentrations →
  - (2) Similar concentrations at the effect site →
  - (3) Similar clinical efficacy and safety profile.
    If (1) and (2) hold, (3) can be waived →
    BE-study instead of therapeutic equivalence.
- Concept was empirically justified in the last three decades.
- Is it possible that with BE shown for AUC and C_{max} (t_{max}) we get therapeutic *inequivalence*?

Some Doubts…

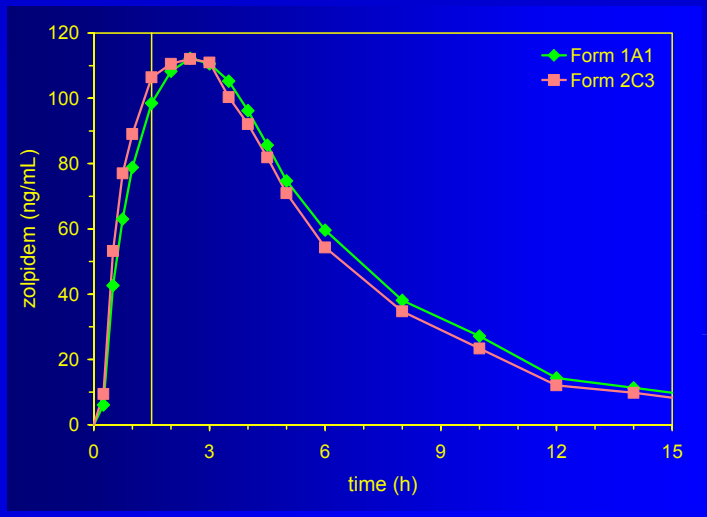
- Concept of BE was originally developed for IR formulations and later extended to MR
- Seems to ‘work’, but is it also justified for more advanced technologies?
  - Multiphasic formulations (IR + CR parts)
  - Osmotic pumps (OROS®)
  - Pulsatile formulations
  - Targeted delivery
- First doubts with CR methylphenidate → in most patients initial ‘ramp’ required for effect.

Remedies?

- Regulators have already some experience with partial AUCs ('early exposure')
- Discriminatory between formulations (which are passing AUC and C_{max})
- Open questions:
  - Cut-off time point data-driven (like 'early exposure') or set *a priori*?
  - If set in the protocol, how to justify its value?
    - Based on pharmacology (effects)
    - Based on PK (*e.g.*, visible trough between phases)
    - Different cut-offs in fasting/fed state?

Guidelines etc.

- FDA (Zolpidem ER 2009)
  - Truncated AUCs (at a time point based on clinical considerations)
  - First pAUC describes early onset, second pAUC maintenance of levels
    - $AUC_{0–1.5}$ (~ sleep onset)
    - $AUC_{1.5–t}$ (~ sleep maintenance)
    - $AUC_{0–\infty}$, C_{max}
    - pAUCs only in fasting study



FDA (Office of Generic Drugs, CDER)
Draft Guidance on Zolpidem (August 2009)
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM175029.pdf

Example Zolpidem

- FDA (Zolpidem ER 2009)
  - $pAUC_{0–1.5}$ *might be* highly variable; reference-scaling? (→ EMA's MR Draft 2013)

N	parameter	C_{max}	$pAUC_{0–1.5}$	$pAUC_{1.5–t}$	$pAUC_{1.5–\infty}$	$AUC_{0–\infty}$
72	PE 90% CI	102% 96 – 110%	122% 101 – 146%	–	96% 89 – 104%	99 92 – 106
	CV_{intra}	25%	65%	–	27%	25%
37	PE 90% CI	–	93% 85 – 103%	113% 104 – 123%	–	–
	CV_{intra}		26%	21%		

Midha KK and G McKay
Use of Partial Area Under the Curve for BE Assessment of Products with Complex PK Profiles; a View Point
Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee, April 13, 2010
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM209320.pdf

Guidelines etc.

- FDA (Methylphendiate SR/ER 2010)
  - In fasting subjects the IR's t_{max} is 2 ± 0.5 h ($\bar{x}$ ± SD)
  - Two hours is also time at which maximal response compared to placebo is achieved
  - By three hours, expected that 95% of patients should achieve maximal early onset of response (since $\bar{x}$ + 2×SD = 95% of population)
  - Food delays IR absorption by about one hour
  - Truncation time point for pAUC in fed state therefore is 3 + 2×0.5 h = 4 hours

BM Davit
Use of Partial AUC: Case Studies and BE Approaches
Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee, April 13, 2010
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM209320.pdf
FDA (Office of Generic Drugs, CDER)
*Draft Guidances on Methylphenidate (*2010–2012)

Example Methylphenidate

- Various MR formulations on the market
- Hybrid authorizations (PK + clinical data)
- Truncation time-point based on standard dosing interval of IR Ritalin (four hours)
  - Non-inferiority shown in clinical studies
  - Due to high between-subject variability of PK (high first-pass / polymorphism) and variable response dose-titration mandatory
  - Patients may be switched from *b.i.d.* IR to MR
  - Very low intra-subject CVs of PK metrics

Example Methylphenidate

- Approved formulations are *not* interchangeable; mainly differences in $pAUC_{0–4}$

study (fed state)	PE (90% CI)	CV_{intra} (%)
Ritalin LA *vs.* Medikinet retard[1]	80.4% (73.2 – 88.2%)	19.8
Equasym Retard *vs.* Medikinet retard[2]	82.9% (72.6 – 94.7%)	19.0
MPH MR *vs.* Concerta[3]	110.0% (102.1 – 119.3%)	13.6

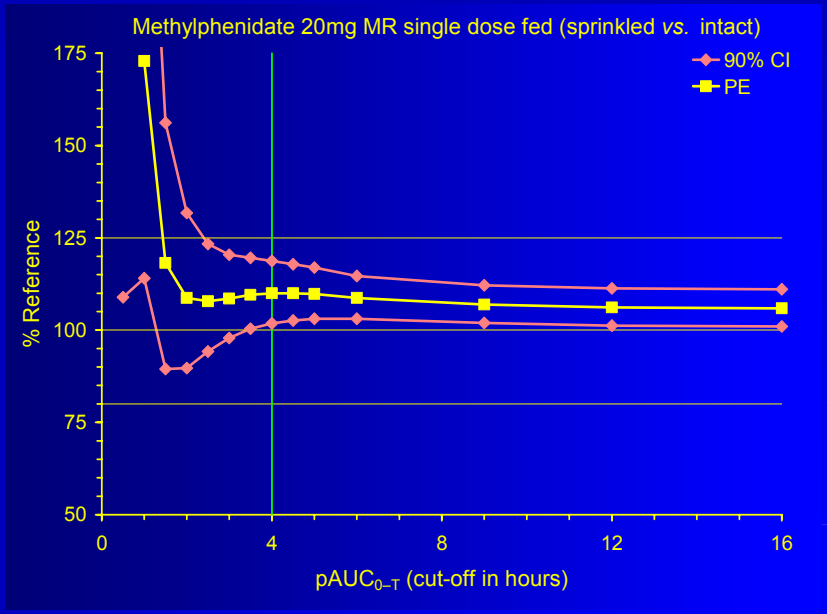
1 **Haessler F, Tracik F, Dietrich H, Stammer H, and J Klatt**
A pharmacokinetic study of two modified-release methylphenidate formulations under different food conditions in healthy volunteers
Int J Clin Pharmacol Ther 46(9), 466–76 (2008)

2 **Schütz H, Fischer R, Großmann M, Mazur D, Leis HJ, and R Ammer**
Lack of bioequivalence between two methylphenidate extended modified release formulations in healthy volunteers
Int J Clin Pharmacol Ther 47(12), 761–9 (2009)

3 *A randomized, single-center, open-label, three-way-cross-over pilot study to investigate the comparative bioavailability of two novel methylphenidate sustained-release formulations as compared to Concerta® sustained-release tablets after single oral administration in healthy male subjects (2012, unpublished)*

Example Methylphenidate

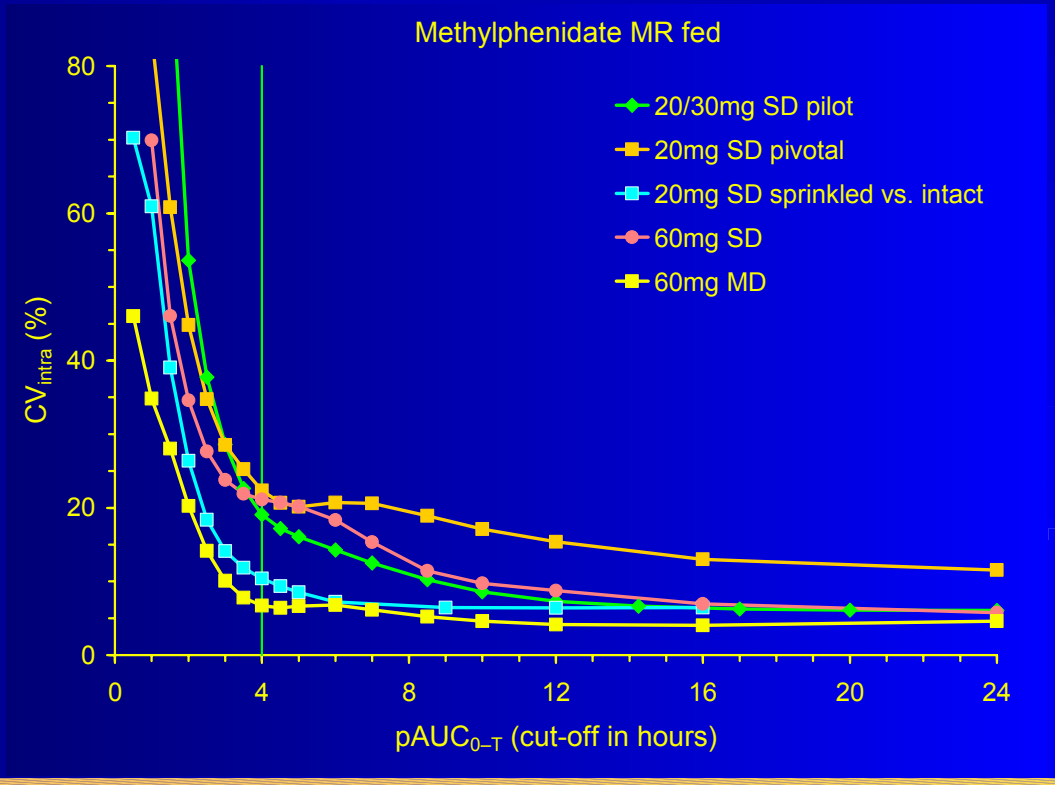
- Although bioequivalent, variability of $pAUC_{0–4}$ (CV ≈20%) higher than conventional PK metrics; typical:
  $AUC_{0–t}$ 7 – 12%
  C_{max} 10 – 15%



Fischer R, Schütz H, Grossmann M, Leis HJ, and R Ammer
Bioequivalence of a methylphenidate hydrochloride extended-release preparation: comparison of an intact capsule and an opened capsule sprinkled on applesauce
Int J Clin Pharmacol Ther 44(3), 135–41 (2006)

Example Methylphenidate

- High variability of $pAUC_{0–4}$ reproducible between studies



Guidelines etc.

- EMA Q&A Rev. 4 (Feb. 2012)
  Requirements for demonstration of bioequivalence for generics of biphasic modified release formulations for oral use
  - Phases should be separated through a cut-off time point, which needs to be pre-specified and universally applied to all subjects and for both T and R.
  - […] this cut-off time point should aim to describe the plasma concentrations in the 1st phase driven by the IR dose fraction whilst avoiding bias through an increasing contribution of the ER phase.

Guidelines etc.

- EMA Q&A Rev. 4 (Feb. 2012)
  - Equivalence needs to be shown for both extent and rate of absorption (reflecting AUC and C_{max} for conventional bioequivalence criteria), separately for both phases:
    - For the 1st phase, the assessment of equivalence should be based on the truncated AUC from t=0 until the cut-off time describing the immediate release dose fraction, and on C_{max} during the first phase.
    - For the 2nd phase, the assessment of equivalence should be based on the AUC from the cut-off time until the end of observation period, and on C_{max} during the second phase.

Guidelines etc.

- EMA Q&A Rev. 4 (Feb. 2012)
  - Unambigously BE of four PK metrics
    - $AUC_{0–T}$, $AUC_{T–t}$, $C_{max,0–T}$, $C_{max,T–t}$
  - Practically conventional PK metrics still requested
    - $AUC_{0–t}$, C_{max}
  - If early onset of clinical importance, additionally
    - $t_{max,0–T}$
  - Consequence: BE of up to seven PK metrics. Tough to meet…
  - Q&A does not give suggestions on how to select the cut-off point. Reading tea-leaves: Based on PK?

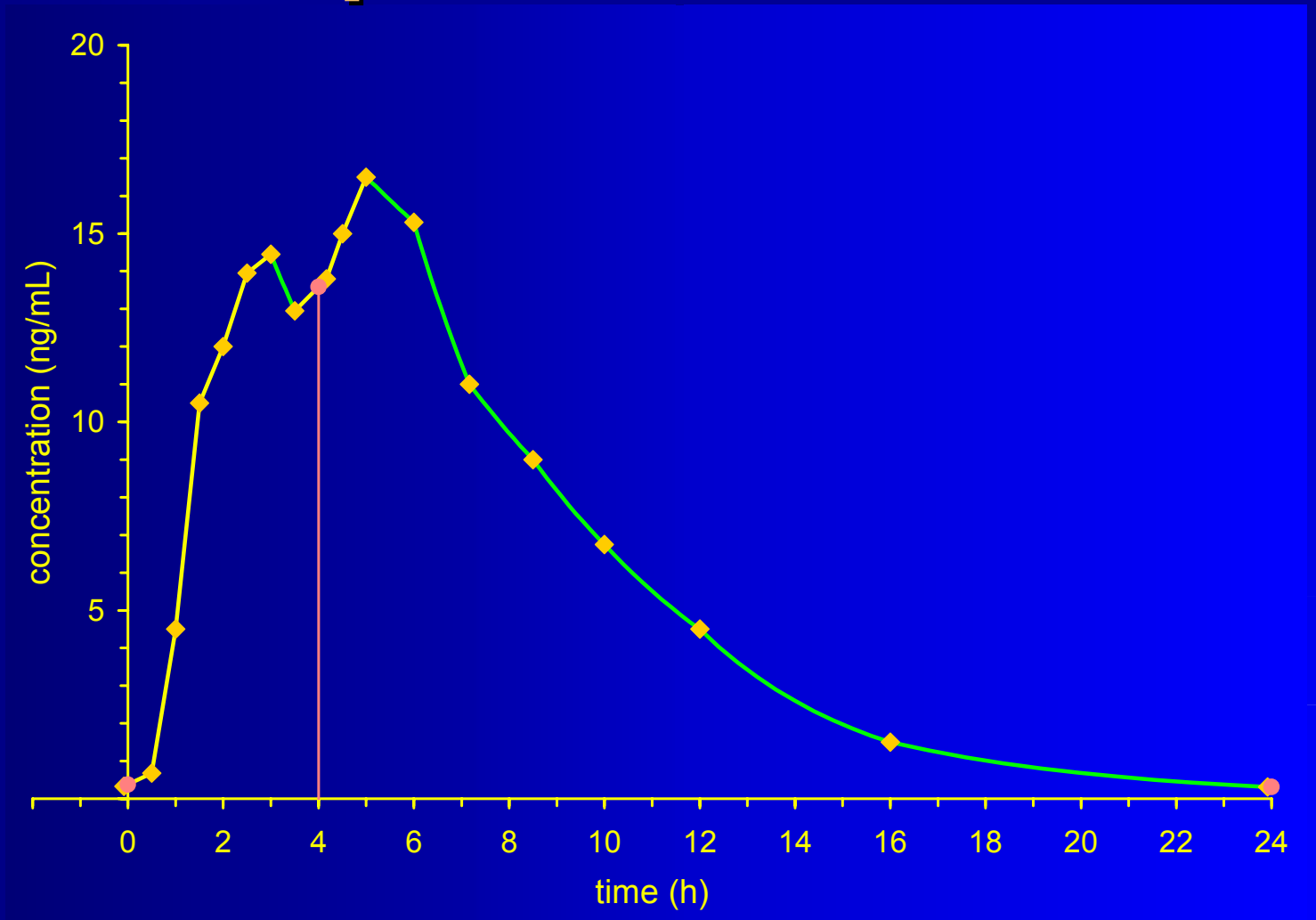
Guidelines etc.

- EMA MR Draft XXIII (March 2013)
  - Pre-specified truncation time point. Justification?
  - Descriptive up to ten PK metrics (lines 787–792)
    - AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, AUC_{0-T}, AUC_{T-t}, $C_{max,0-T}$, $C_{max,T-t}$, $t_{max,0-T}$, $t_{max,T-t}$
  - Statistical comparison (lines 800–805)
    - AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, AUC_{0-T}, AUC_{T-t}
    - Conventional acceptance range 80.00–125.00% or widening if CV_{WR} >30% (replicate design)

Pitfalls

- What to do if (due to deviations in sampling) a concentration was not measured at the scheduled truncation time point?
  - Exclude the subject from comparing the affected PK metrics. Easy & stupid.
  - Use an estimate, *i.e.*, interpolate linear in the increasing part or lin/log in the decreasing part of the profile.
    Standard in Phoenix/WinNonlin.

Interpolation at cut-off



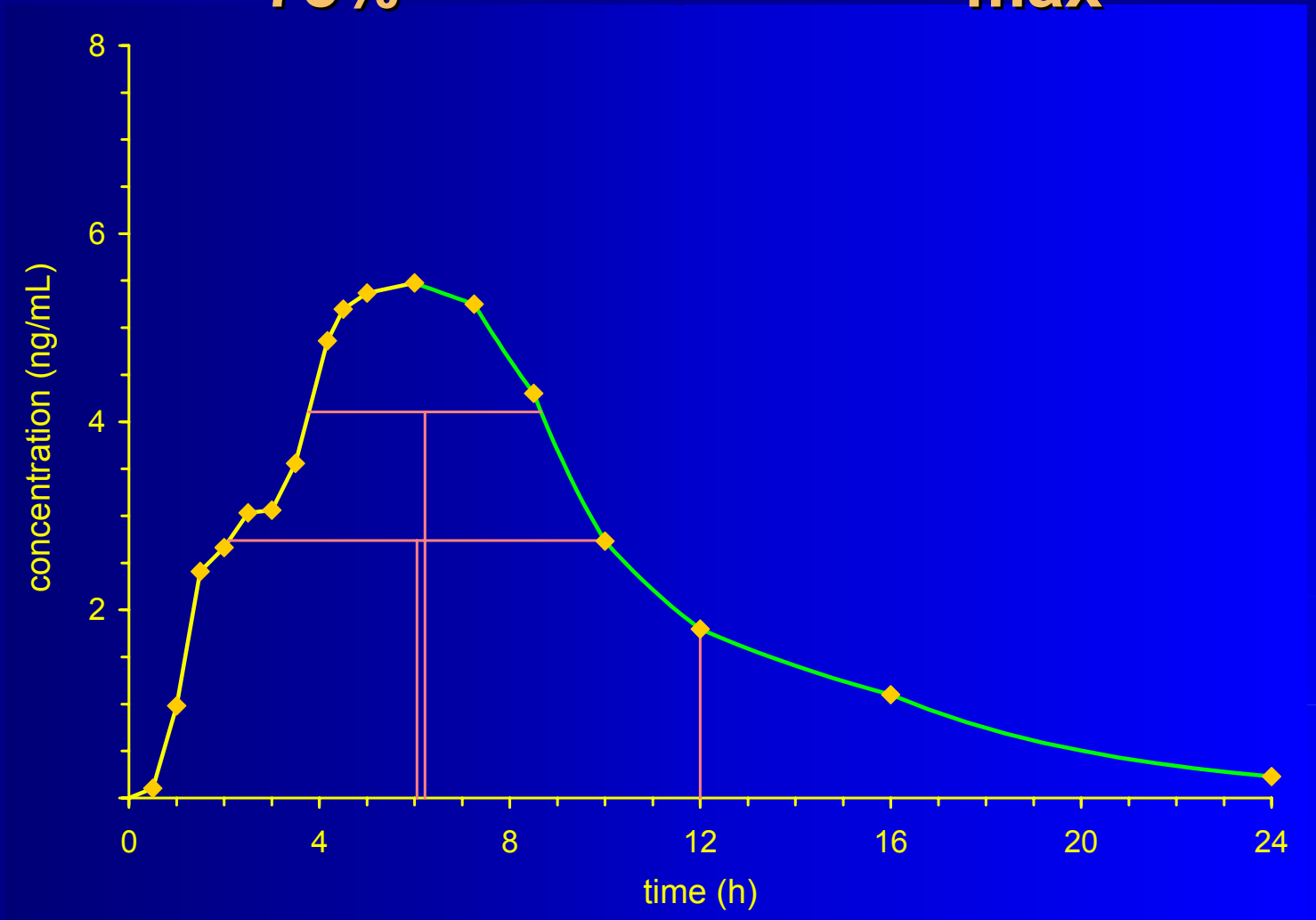
Guidelines etc.

- EMA MR Draft XXIII (March 2013)
  - Waiving of multiple dose studies of prolonged release formulations acceptable if:
    - Low accumulation (single dose $AUC_{0-\tau}$ > 90% of mean $AUC_{0-\infty}$ for both test and reference) *and*
    - BE for additional shape parameters demonstrated. 'An early $_{partial}$AUC and a terminal $_{partial}$AUC separated by a predefined time point, which is usually the half of the dosage interval are recommended, unless otherwise scientifically justified.'

Guidelines etc.

- EMA MR Draft XXIII (March 2013)
  - Waiving of MD studies of PR formulations
    - Depending on the type of formulation pAUCs might not be optimal PK metrics. Not a single publication [*sic*] about $pAUC_{0-\tau/2}$ and $pAUC_{\tau/2-\tau}$.
    - Alternatives
      - Plateau time $t_{75\%}$ (time interval where C ≥75% of C_{max}; aka Peak-Occupancy-Time POT-25)
      - Half-Value-Duration HVD (time interval where C ≥50% of C_{max}; aka Peak-Occupancy-Time POT-50)
      - pAUC of monoexponential PK truncated at the inflection point of the curve ($2 \times t_{max}$)

$t_{75\%}$ • HVD • 2×t_{max}



Thank You!

Partial AUCs

Open Questions?

Helmut Schütz
BEBAC
Consultancy Services for
Bioequivalence and Bioavailability Studies
1070 Vienna, Austria
helmut.schuetz@bebac.at

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  - Guideline on the Investigation of BE (2010)
  - Questions & Answers: Positions on specific questions addressed to the EWP therapeutic subgroup on Pharmacokinetics (2013)
  - Draft Guideline on the Pharmacokinetic and Clinical Evaluation of Modified Release Dosage Forms (2013)
- US-FDA
  - Center for Drug Evaluation and Research (CDER)
    - BA and BE Studies for Orally Administered Drug Products—General Considerations (March 2003)
    - Bioequivalence Recommendations for Specific Products (2007–2013):
      Guidance on Zolpidem (Oct 2011)
      Draft Guidances on Methylphenidate (2010–2012)
  - Docket No. FDA-2007-P-0182 – Sanofi Aventis U.S. Inc. / ANDA Suitability Petition for NDA 21-774 Ambien CR (Zolpidem tartrate), 13 Oct 2010
  - Docket No. 2004P-0139 – McNeil Consumer & Specialty Pharmaceuticals/Approval of Generic Version of Concerta (methylphenidate HCl extended-release tablets are both bio-equivalent and clinically equivlent to the innovator product), 19 Mar 2004
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  - Endrényi and Tóthfalusi
    Metrics for the Evaluation of Bioequivalence of Modified-Release Formulations
    APPS J 14(4), 321–5 (2012)
    DOI: 10.1208/s12248-012-9396-8
  - Zirkelbach JF, Jackson AJ, Wang Y, and DJ Schuirmann
    Use of Partial AUC (PAUC) to Evaluate Bioequivalence—A Case Study with Complex Absorption: Methylphenidate
    Pharm Res 30(1), 191–202 (2013)
    DOI: 10.1007/s11095-012-0862-x