BIOEQUIVALENCE OF EARLY EXPOSURE: t_{max} & pAUC.

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BioBridges 2023

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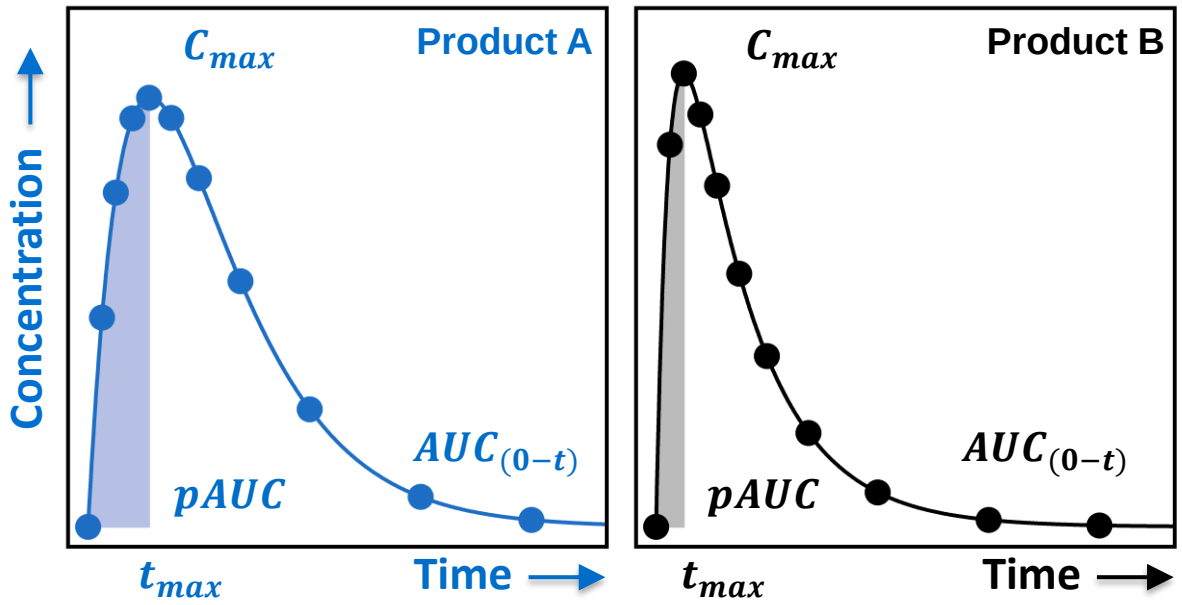
EARLY EXPOSURE: CLINICALLY RELEVANT

(…) 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/PD relationships**, the traditionally applied PK parameters of **C_{max} and AUC may be insufficient** for PK profile characterization or comparison.

Fang et al. (2021). Clin Pharmacol Ther 110(4): 880-887



$$C_{max} \cong C_{max}$$
$$AUC_{(0-t)} \cong AUC_{(0-t)}$$
$$t_{max} \neq t_{max}$$
$$pAUC \neq pAUC$$

EARLY EXPOSURE: TIME MACHINE

EU guideline [1991]

(…) a **clinically relevant claim** for rapid release or action or signs related to adverse effects. The **non-parametric 90% confidence interval** for this measure of relative bioavailability should lie within a **clinically determined range.**

Investigation of bioavailability and bioequivalence (1991); Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98)

EMEA guideline [2010]

A statistical evaluation of t_{max} is not required. However, if rapid release is claimed to be **clinically relevant** and of importance for onset of action or is related to adverse events, there should be **no apparent difference in median t_{max}** and its variability between test and reference product.

EMA Guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr)

EARLY EXPOSURE: EMA GUIDANCE

Product-specific BE guidance(s) [2018]

Requirements for bioequivalence demonstration (PKWP)	
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-x}, C_{max} and T_{max}
	90% confidence interval: 80.00–125.00% for AUC_{0-x} and C_{max}. **Comparable median and range for T_{max}.**

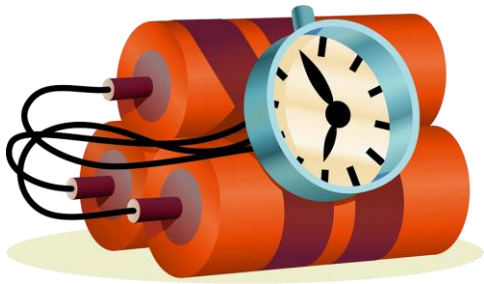
x – t for ibuprofen [EMA/CHMP/356876/2017] & paracetamol [EMA/CHMP/356877/2017], 72h for tadalafil [EMA/CHMP/315234/2014/Rev.1]

(…) simply on the **numerical comparison** of medians and ranges.

Overview of comments (EMA/CHMP/644909/2017)

(…), t_{max} should occur in the **same sampling** time or in **an adjacent one,** since the median may differ simply based on a minor imbalance.

Matji et al. (2020). Chirality 32: 185–190.



Catalent®

Article 10(1) referral [2021]

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EARLY EXPOSURE: 2023 PSBGL REVISIONS

Requirements for bioequivalence demonstration (PKWP)	
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-x}, C_{max} and T_{max}
	90% confidence interval: 80.00–125.00% for AUC_{0-x} and C_{max}. **Comparable median (≤20% difference, 80.00–125.00%) and range for T_{max}.**

x – t for ibuprofen [EMA/CHMP/356876/2017 Rev.1*] & paracetamol [EMA/CHMP/356877/2017 Rev.1*], 72h for tadalafil [EMA/CHMP/315234/2014 Rev.2*]

*This revision concerns defining what is meant by 'comparable' T_{max} as an additional main pharmacokinetic variable in the bioequivalence assessment section of the guideline.

The revision of the PSBGL intends to clarify the regulatory expectations by defining an **objective criterion to avoid arbitrations.** (…), the continued use (…) is recommended **until the BE requirements are updated with M13.**

Overview of comments (EMA/CHMP/356876/2017 Rev.1)

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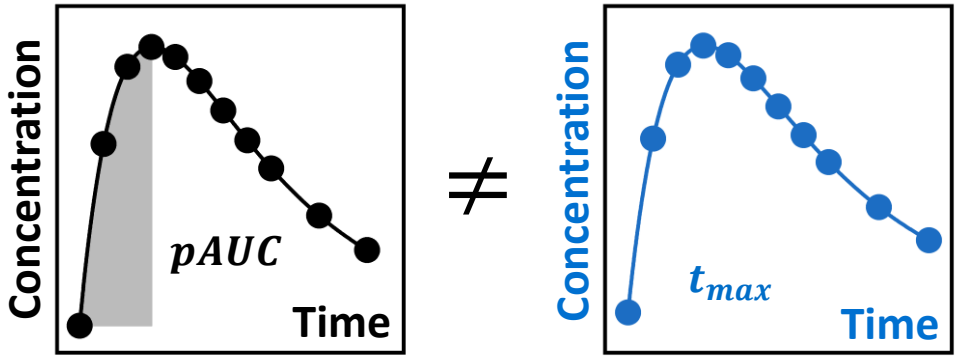
EARLY EXPOSURE: ICH M13A VS. PSBGL



2.1.8.3 Early exposure [Lines 297-305]

(…) when the early onset of action is **clinically relevant.** (…), an **additional PK parameter**, such as **area** under the concentration vs. time curve **between two specific time points (pAUC),** may be applied.

Requirements for bioequivalence demonstration (PKWP)	
Bioequivalence assessment	**Comparable median (≤20% difference, 80.00–125.00%) and range for T_{max}.**

x – t for ibuprofen [EMA/CHMP/356876/2017 Rev.1*] & paracetamol [EMA/CHMP/356877/2017 Rev.1*], 72h for tadalafil [EMA/CHMP/315234/2014 Rev.2*]

ACCEPTABLE RANGE: (≤20%, 80.00–125.00%)

World of t_{max}

t_{max} distribution, either on the original scale (or on the log-scale), rarely follows a normal distribution.

Chow & Liu (2009). Chapman & Hall/CRC, Boca Raton

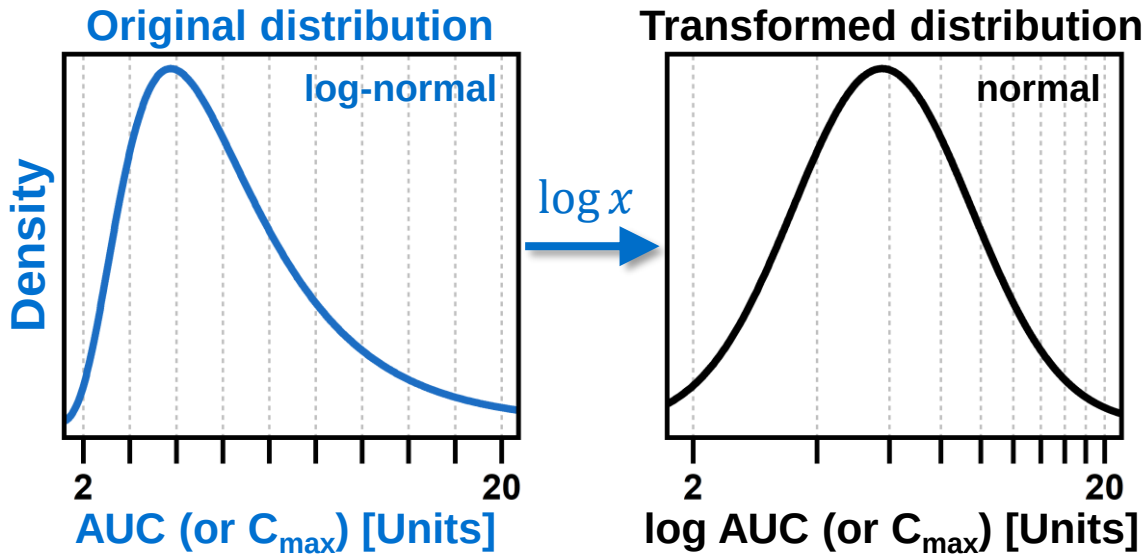
t_{max} distribution is discrete, ordinal, skewed to the right: analysis of untranformed values

$$[-20\%, +20\%] = [80.00 - 120.00\%]$$
$$[-20\%, +25\%] = [80.00 - 125.00\%]$$

World of AUC and C_{max}

The pharmacokinetic parameters under consideration (…). (…) should be transformed prior to analysis using a logarithmic transformation.

CPMP/EWP/QWP/1401/98 Rev.1/Corr



$$-\ln 0.8 = \ln 1.25 = 0.2231$$

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ACCEPTABLE RANGE: 80.00–125.00%

Nitpicker‘s corner: Why 20% is calculated if test has longer t_{max}? Rounding of limits to 2 decimals expected?

The proposed ≤20% difference should be understood as 80–125% in order to be symmetrical. (…) (i.e. the requirement that test should be equivalent to reference if and only if reference is equivalent to test)

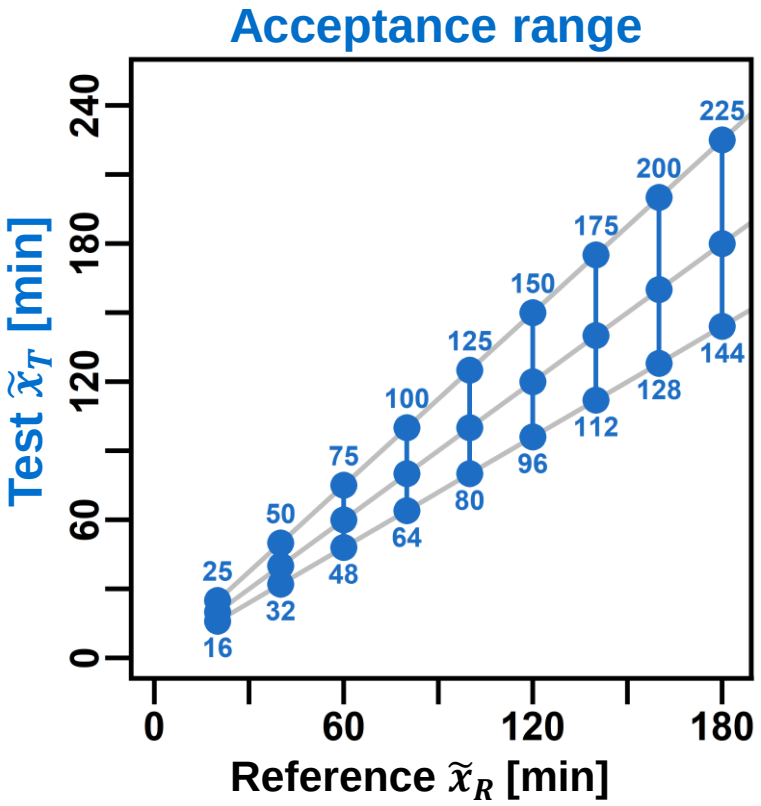
Overview of comments (EMA/CHMP/356876/2017 Rev.1)

EMA example

Reference $\tilde{x}_R = 1.50\ h$ Test $\tilde{x}_T = 1.75\ h$ $20\% = 0.300\ h\ (18')$	
Difference [%]	**Limits [h][1)]**
$\pm 20\%$	$1.200 - 1.800$
$-20\%, +25\%$	$1.200 - 1.875$

Lower: $\tilde{x}_T \geq \tilde{x}_R - 0.20\tilde{x}_R$
Upper: $\tilde{x}_T \leq \tilde{x}_R + 0.25\tilde{x}_R$

ACCEPTABLE RANGE: MEDIAN $\tilde{x}_R$ OF REFERENCE



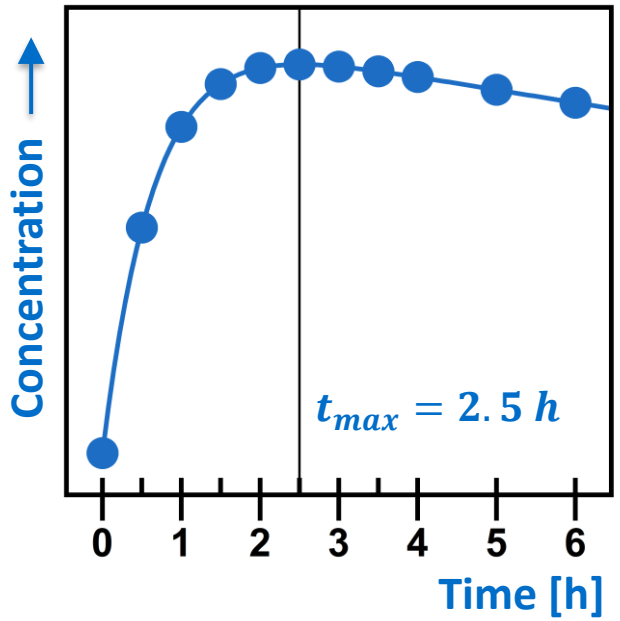
Sampling requirements	
$\tilde{x}$ [min]	Each [min]
15	3
20	4
30	6
45	9
60	12

It is agreed that **frequent sampling may be required** (…). Samples as early as 5 or 10 minutes after dosing are not infrequent. Therefore **a few more samples for a proper characterisation of T_{max} and C_{max} are not considered an ethical problem.**

Overview of comments (EMA/CHMP/356876/2017 Rev.1)

MEDIAN: INFLUENCE OF A SINGLE VALUE?

$$20\% = 0.5\ h\ (30')$$
$$[L, U] = [2.00 - 3.13\ h]$$



$$\tilde{x} = \frac{x_5 + x_6}{2}$$

All data [h]

n	T	R
1	1.0	1.0
2	1.0	1.0
3	1.0	1.0
4	1.0	1.5
5	**1.5**	**2.5**
6	**2.5**	**2.5**
7	2.5	2.5
8	2.5	3.0
9	3.0	3.0
10	3.0	3.0
$\tilde{x}$	**2.0**	**2.5**

$\tilde{x}$ comparable

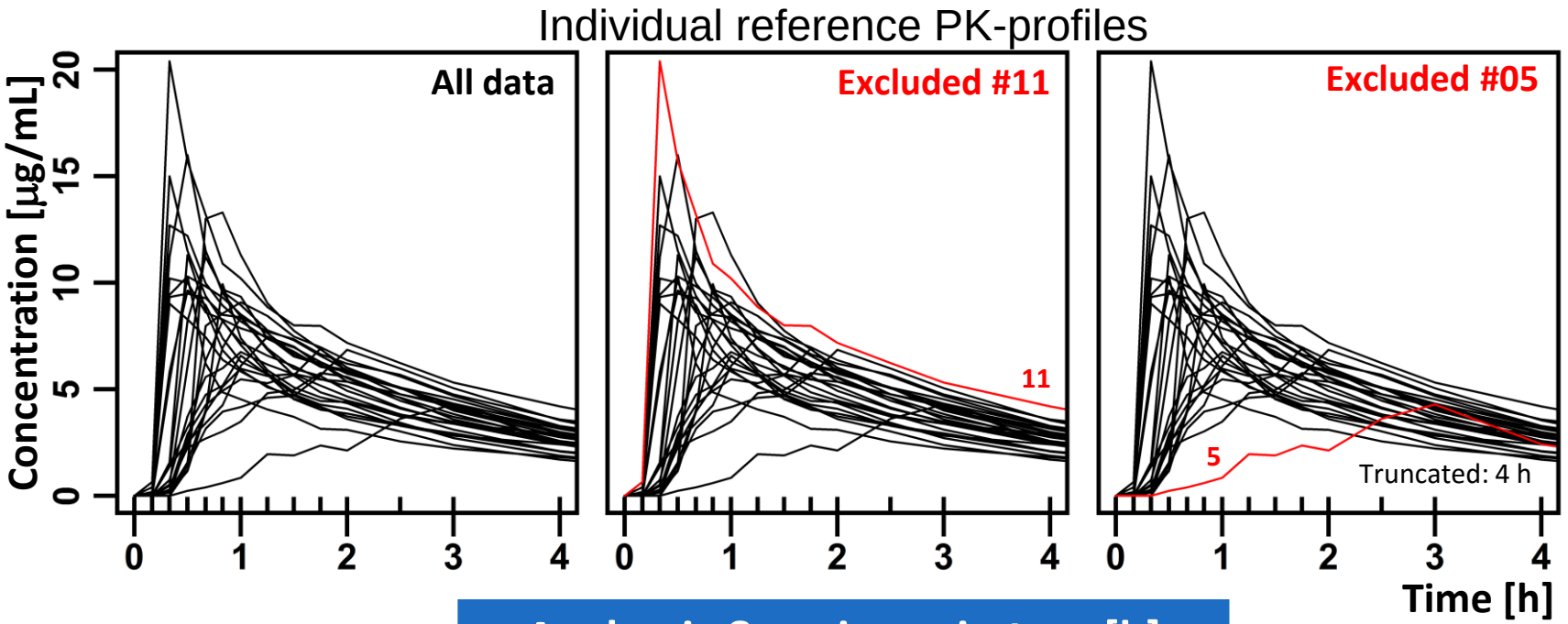
Reduced data [h]

n	T	R	
1	1.0	1.0	
2	1.0	1.0	
3	1.0	1.0	
4	1.0	1.5	
5	**1.5**	**2.5**	$\tilde{x} = x_5$
6	2.5	2.5	
7	2.5	2.5	
8	2.5	3.0	
9	3.0	3.0	
10	–	–	← **Missing**
$\tilde{x}$	**1.5**	**2.5**	

$\tilde{x}$ **not comparable**

$$[L, U] = [2.00 - 3.13\ h]$$

MEDIAN: INFLUENCE IN REAL DATA



Design of study

- Single-dose
- 2x2x2 cross-over
- Healthy subjects
- **Sample size: 26**
- Sampling: 20 [0 to 24 h]

Analgetic & antipyretic t_{max} [h]		
Data	$\tilde{x}$	**Limits [h]**[1)]
All data	0.75	$0.60 - 0.94$
Excluded #11	0.83	$0.66 - 1.04$
Excluded #05	0.67	$0.54 - 0.84$

[1)]Lower: $\tilde{x} - 20\%$; Upper: $\tilde{x} + 25\%$

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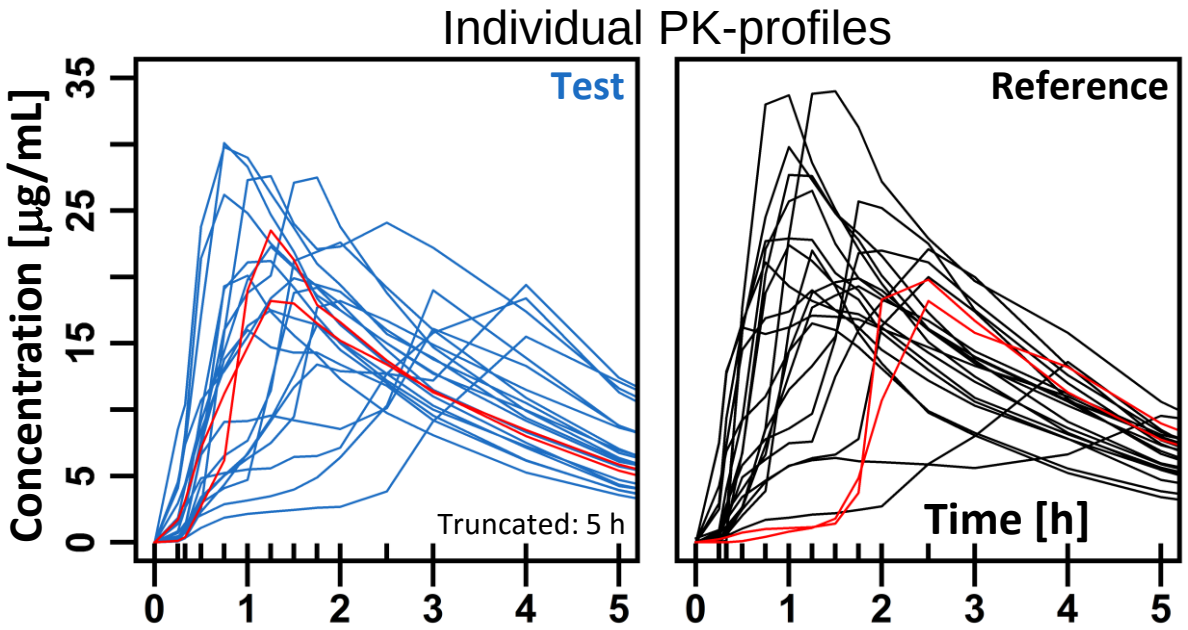
MEDIAN: INFLUENCE IN REAL DATA



Design of study

- Single-dose
- 2x2x2 cross-over
- Healthy subjects
- **Sample size: 22**
- Sampling: 18 [0 to 12 h]

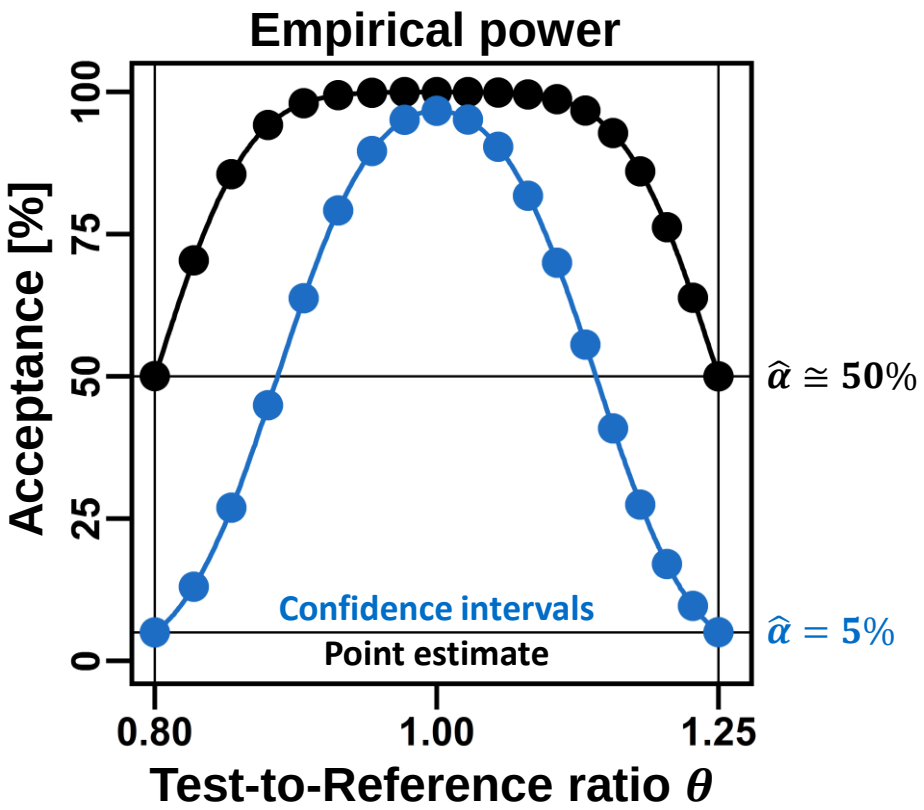
NSAID I t_{max} [h]			
Data	$\tilde{x}_T$	$\tilde{x}_R$	Limits [h][1)]
All[2)]	1.375	1.375	1.10—1.72
Reduced[3)]	1.625	1.250	1.00—1.56

[1)]Lower: $\tilde{x} - 20\%$; Upper: $\tilde{x} + 25\%$; [2)]N=22; [3)]N=20

POINT ESTIMATE: TYPE I ERROR CONTROL?

Nitpicker‘s corner: Well, a strict α-control in 2-stage designs required, or recent discussions to f_2 estimate?

World of AUC and C_{max}



Simulation settings: CV = 20%, N = 24, design: 2x2x2 cross-over, Simulations: n = 1‘000‘000 per scenario

World of t_{max} in PSBGL

It is agreed that the proposed approach is not able to preserve the type 1 error.

The comparison of the medians does not intend to preserve the type 1 error but to exclude formulations with different onset of action.

Overview of comments (EMA/CHMP/356876/2017 Rev.1)

EMA: OTHER FEEDBACK TO COMMENTS

Overview of comments (EMA/CHMP/356876/2017 Rev.1)

The **assessment of the range** is more subjective. If **all the values except one are the same,** the ranges would be considered acceptable. Therefore, only if **differences are evident** and worse for the test product, the range could be used for a regulatory decision.

Although it is agreed that the **non-parametric 90% CI** for the T_{max} difference is **more correct** methodologically, its use was discarded (…). **The definition of a clinically relevant acceptance range for each specific drug is not feasible** (...).

Even for those NSAIDs for which a PSBGL has not been issued, it can therefore be implied that the **same requirements** are applied in the assessment of **applications** if they are used **for acute pain relief.**

The present approach is not based on ratios. (…) **a straightforward numerical subtraction.**

$$\tilde{x}_T \geq \tilde{x}_R - 0.20\tilde{x}_R \qquad \tilde{x}_T \leq \tilde{x}_R + 0.25\tilde{x}_R$$

$$\tilde{x}_T \geq \tilde{x}_R(1 - 0.20) \qquad \tilde{x}_T \leq \tilde{x}_R(1 + 0.25)$$

$$\frac{\tilde{x}_T}{\tilde{x}_R} \geq 0.8 \qquad \frac{\tilde{x}_T}{\tilde{x}_R} \leq 1.25$$

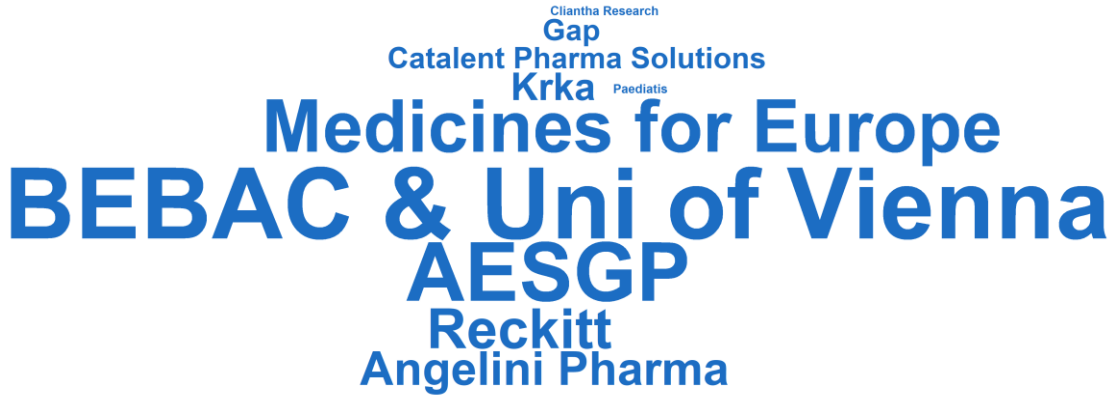
COMPARABLE MEDIAN: DRAFT TO FINAL

10 stakeholders: companies & associations

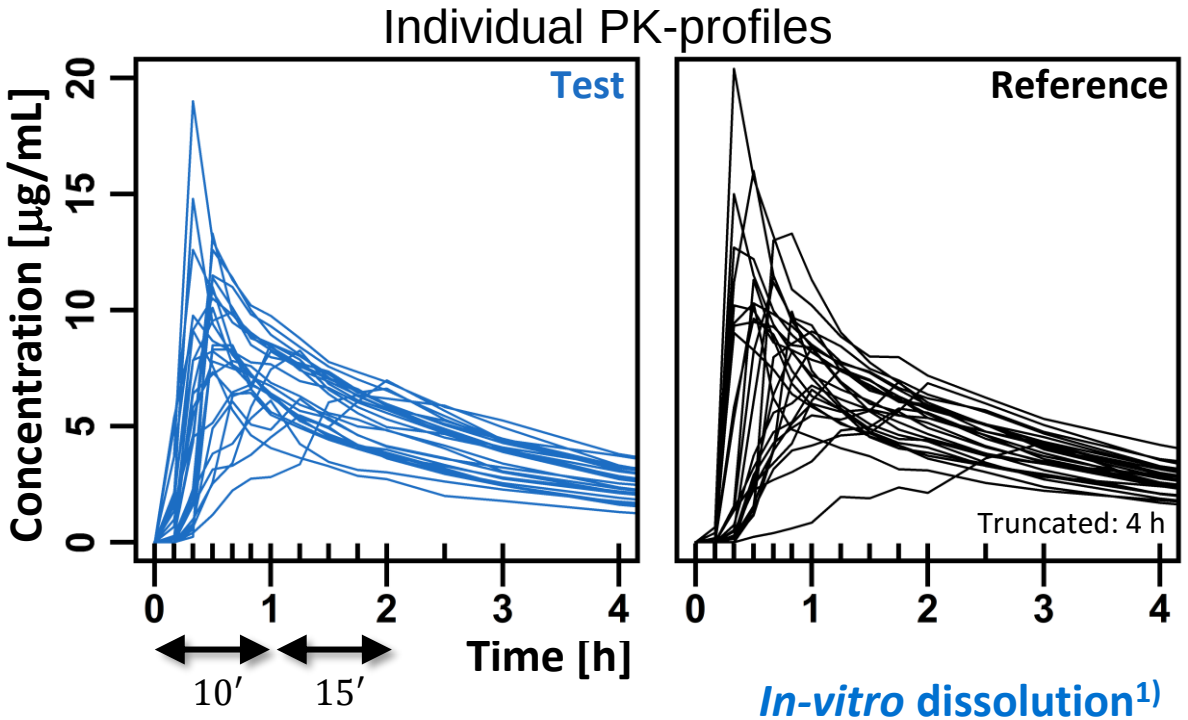
General and specific comments

Number [%] of comments[1)]		
Outcome	**General**	**Specific**
Not accepted	**6** [38%]	**29** [83%]
Partially accepted	**4** [25%]	**3** [9%]
Accepted	**3** [19%]	**3** [9%]
None (Noted)	**3** [19%]	**0** [0%]
Total	**16** [100%]	**35** [100%]

[1)]Incomplete comments published for paracetamol (only 6 pages out of 32 pages released)



CASE STUDIES: ANALGETIC & ANTIPYRETIC TABLET



Design of study

- Single-dose
- 2x2x2 cross-over
- Healthy subjects
- Sample size: 26
- Sampling: 20 [0 to 24 h]

In-vitro dissolution[1)]

Buffer	Result
pH 1.2	>85% in 15‘
pH 4.5	>85% in 15‘
pH 6.8	>85% in 15‘

[1)]biobatches, V=900 mL, 50 rpm, USP II

Analysis of t_{max} [h] (N=26)		
IMP	$\tilde{x}$	$min - max$
Test	0.50	0.33 – 2.00
Reference	0.75	0.33 – 3.00
$[L, U] = [0.60 - 0.94\ h]$		
T−R[1)]	−0.125	−0.245 – 0.000

[1)] Hodges-Lehmann with 90% non-parametric confidence interval (WMW-test p=0.2234)

Comparable median not shown. Bioequivalence of t_{max} failed. Sampling 20% rule: 9 minutes.

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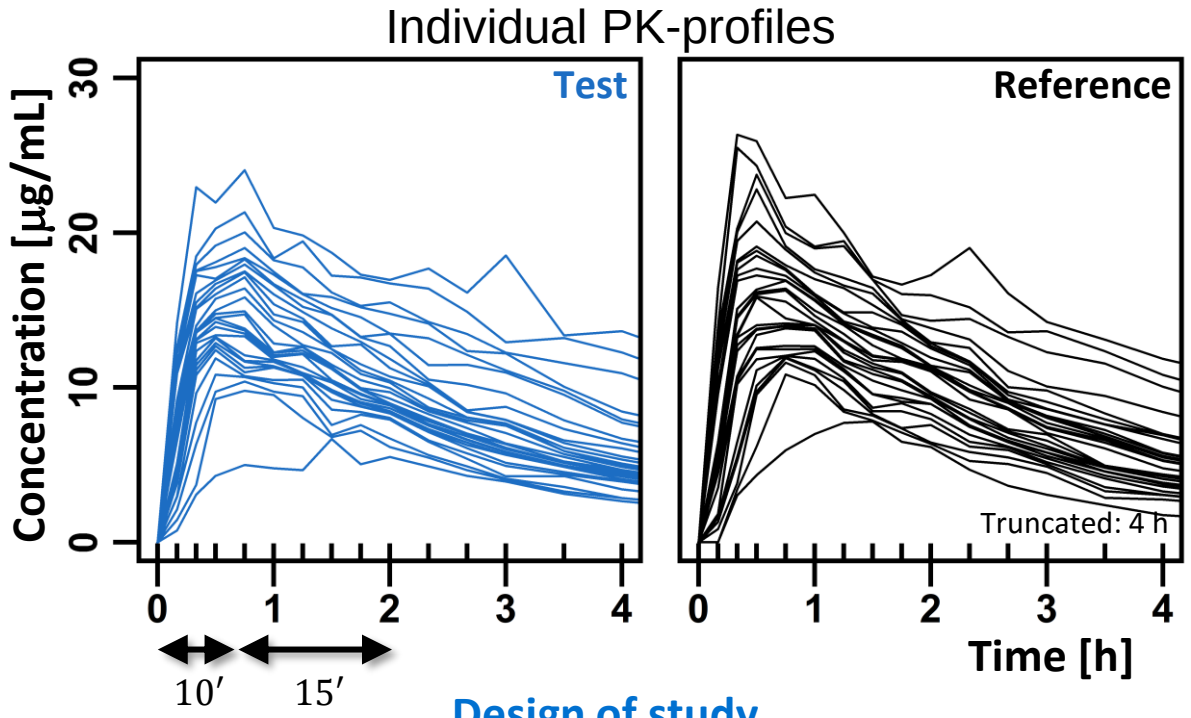
CASE STUDIES: NSAID I SUSPENSION



Design of study

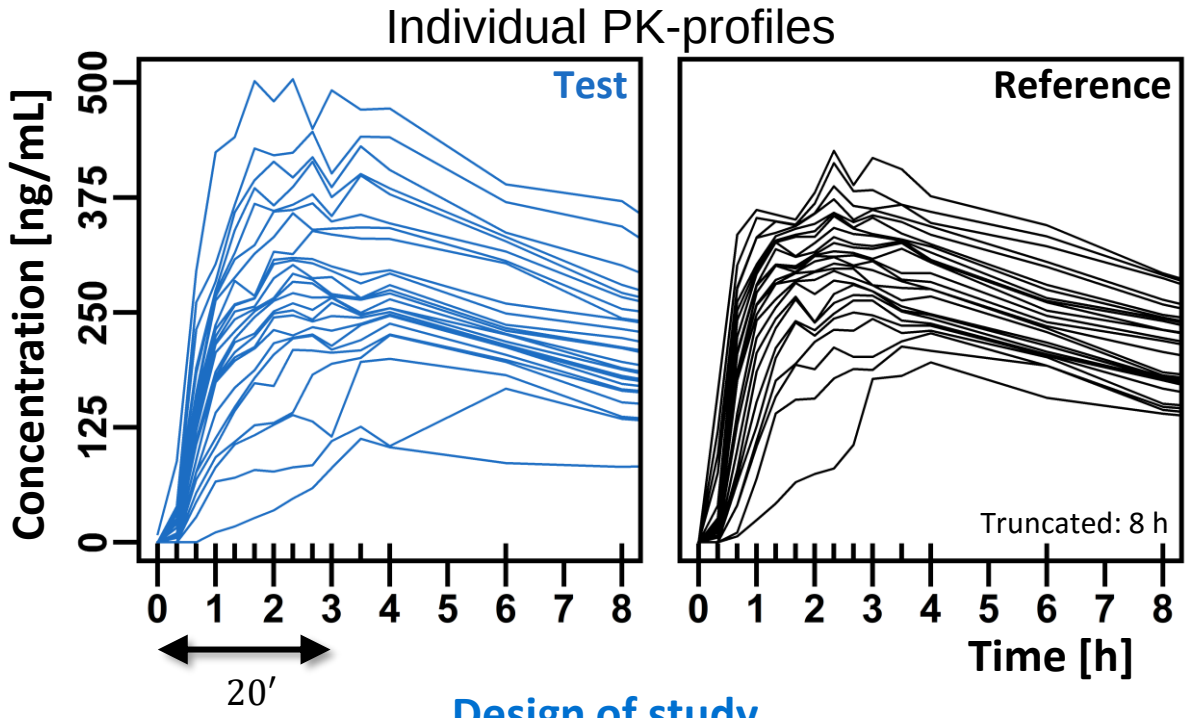
- Single-dose
- 2x2x2 cross-over
- Healthy subjects
- Sample size: 28
- Sampling: 19 [0 to 12 h]

Analysis of t_{max} [h] (N=28)		
IMP	$\tilde{x}$	$min - max$
Test	**0.75**	**0.33 – 3.00**
Reference	**0.50**	**0.33 – 2.33**
$[L, U] = [0.40 - 0.63\ h]$		
T−R[1)]	**0.042**	**−0.125 – 0.125**

[1)] Hodges-Lehmann with 90% non-parametric confidence interval (WMW-test p=0.6562)

Comparable median not shown. Bioequivalence of t_{max} failed. Sampling 20% rule: 6 minutes.

CASE STUDIES: PDE5 INHIBITOR TABLET



Analysis of t_{max} [h] (N=25)		
IMP	$\tilde{x}$	$min - max$
Test	**2.67**	**1.67 – 6.00**
Reference	**2.33**	**0.67 – 4.00**
$[L, U] = [1.87 - 2.92\ h]$		
T−R[1)]	**0.415**	**−0.080 – 0.915**

[1)] Hodges-Lehmann with 90% non-parametric confidence interval (WMW-test p=0.2295)

Design of study

- Single-dose
- 2x2x2 cross-over
- Healthy subjects
- Sample size: 26 (1 dropped)
- Sampling: 21 [0 to 72 h]

Comparable median shown. Bioequivalence of t_{max} proven. Sampling 20% rule: 28 minutes.

Comparable range?

PARTIAL AREAS: I'LL BE BACK…

Draft EMA guideline [2008]

4.1.8 Evaluation [Lines 555-557]

For products where rapid absorption is of importance, equivalence (…) **by demonstration of bioequivalence for partial AUC as a measure of early exposure.**

Keywords from comments: high variability & large sample sizes due to 80-125%, justifying a truncation time point, no retrospective application.

Draft M13A guideline [2023]

2.1.8.3 Early exposure [Lines 297-305]

(…) **when the early onset of action is clinically relevant.** (…)**, an additional PK parameter, such as area** (…) **between two specific time points (pAUC), may be applied.**

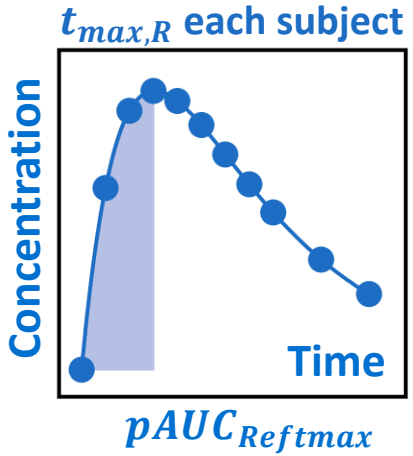
Keywords from comments: high variability & scaling not permitted, unclear cutoff values, no retrospective application.

PARTIAL AREAS: VARIABILITY

Immediate release

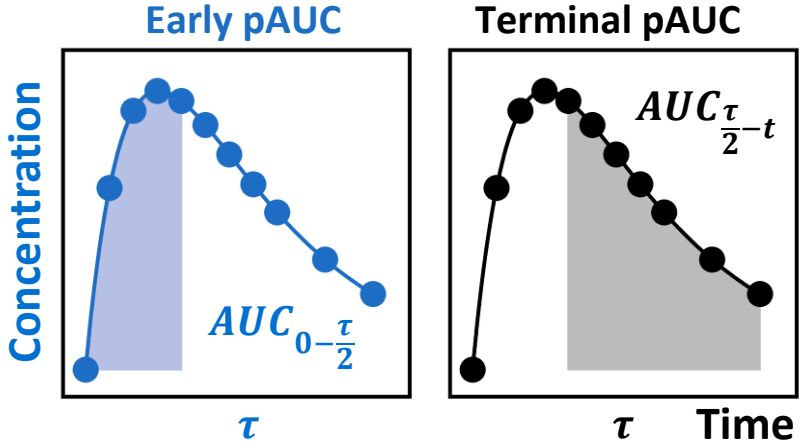
Intra-CV [%] of PK-metrics[1)]			
IMP	C_{max}	AUC_t	$pAUC$
NSAID I	11	6	30
NSAID II	10	9	44
NSAID III	11	4	67

[1)] pAUC for t_{max} in each subject ($pAUC_{Reftmax}$);
Chen et al. (2011) Pharm Res 28: 1939-1947

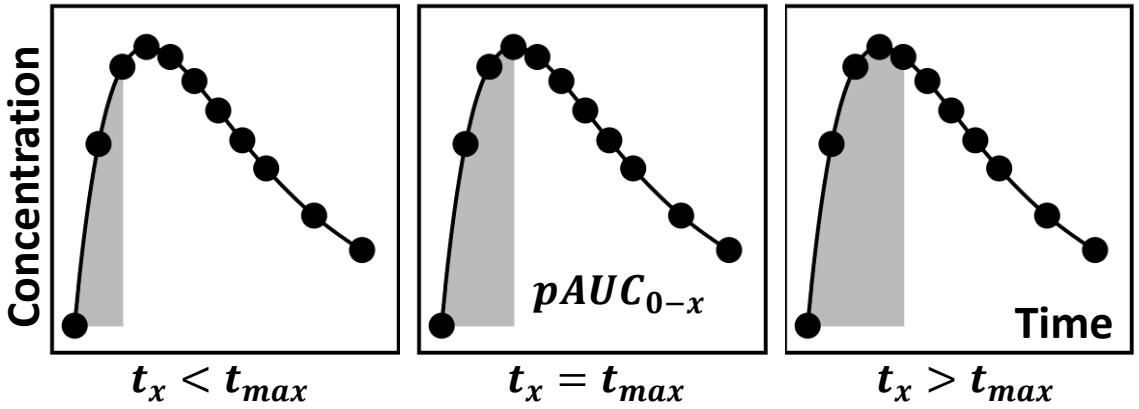


Modified-release

…, the **early pAUC** (…) appeared to be slightly more variable, (…) the **terminal pAUCs** presented a **significantly larger** difference in ISCV (…). (…) **all the pAUC parameters were more variable** than the conventional AUC parameters.
Boily et al. (2015). Eur J Pharm Sci. 66: 70-7



PARTIAL AREAS: CUTOFF $(0 - x)$?



Draft EMA guideline 2008 [Line 313-317]

The partial area can in most cases be truncated at the **population median of t_{max}** values for the reference formulation. However, an alternative time point for truncating the partial AUC can be used when clinically relevant.

Health Canada BA guideline 2023

Where the time to onset of action is important, the following parameter should also be reported: h) The area under the curve to t_{max} of the reference product, calculated **for each study subject** ($AUC_{Reftmax}$).

CASE STUDIES: PARTIAL AREAS

Analgetic & Antipyretic

Ratio & intra-CV [%][1)]		
pAUC	Ratio	CV
$pAUC^1$	102	74
$pAUC^2$	147	72
$AUC_{(0-t)}$	101	7
C_{max}	101	21

[1)] N=26

NSAID I

Ratio & intra-CV [%][1)]		
pAUC	Ratio	CV
$pAUC^1$	95	24
$pAUC^2$	106	30
$AUC_{(0-t)}$	99	8
C_{max}	92	13

[1)] N=28

PDE5 inhibitor

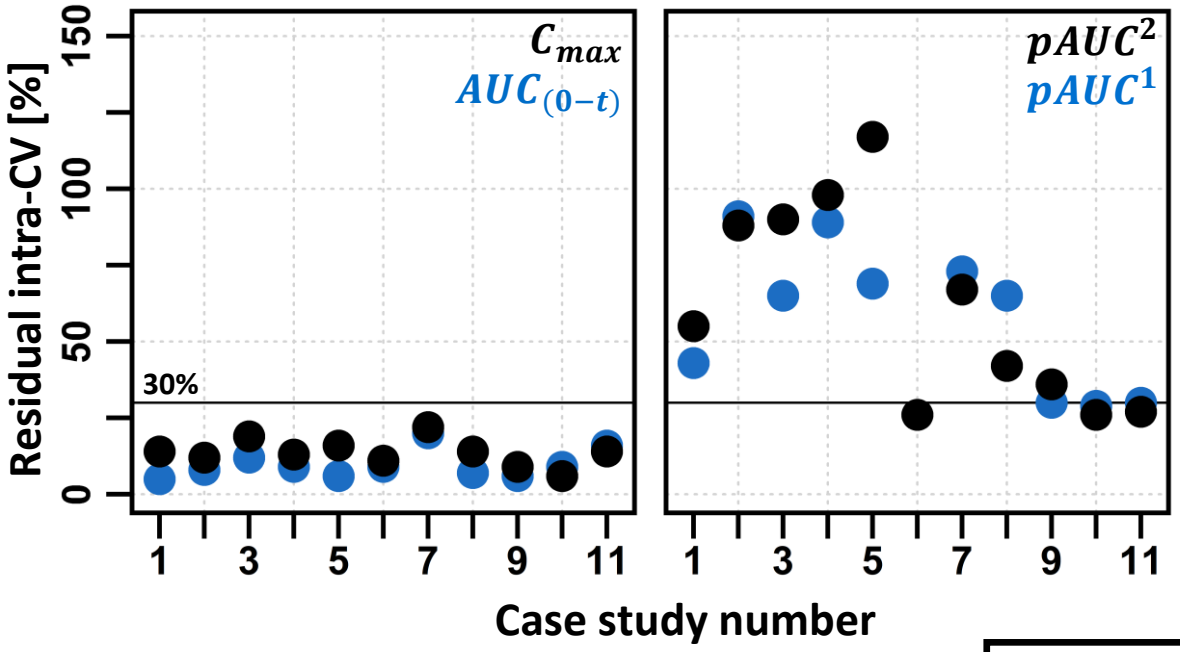
Ratio & intra-CV [%][1)]		
pAUC	Ratio	CV
$pAUC^1$	72	56
$pAUC^2$	81	57
$AUC_{(0-t)}$	99	10
C_{max}	96	15

[1)] N=25

$pAUC^1$: $t_{max,R}$ in each subject
$pAUC^2$: $t_{max,R}$ median

CASE STUDIES: VARIABILITY

Intra-subject variability



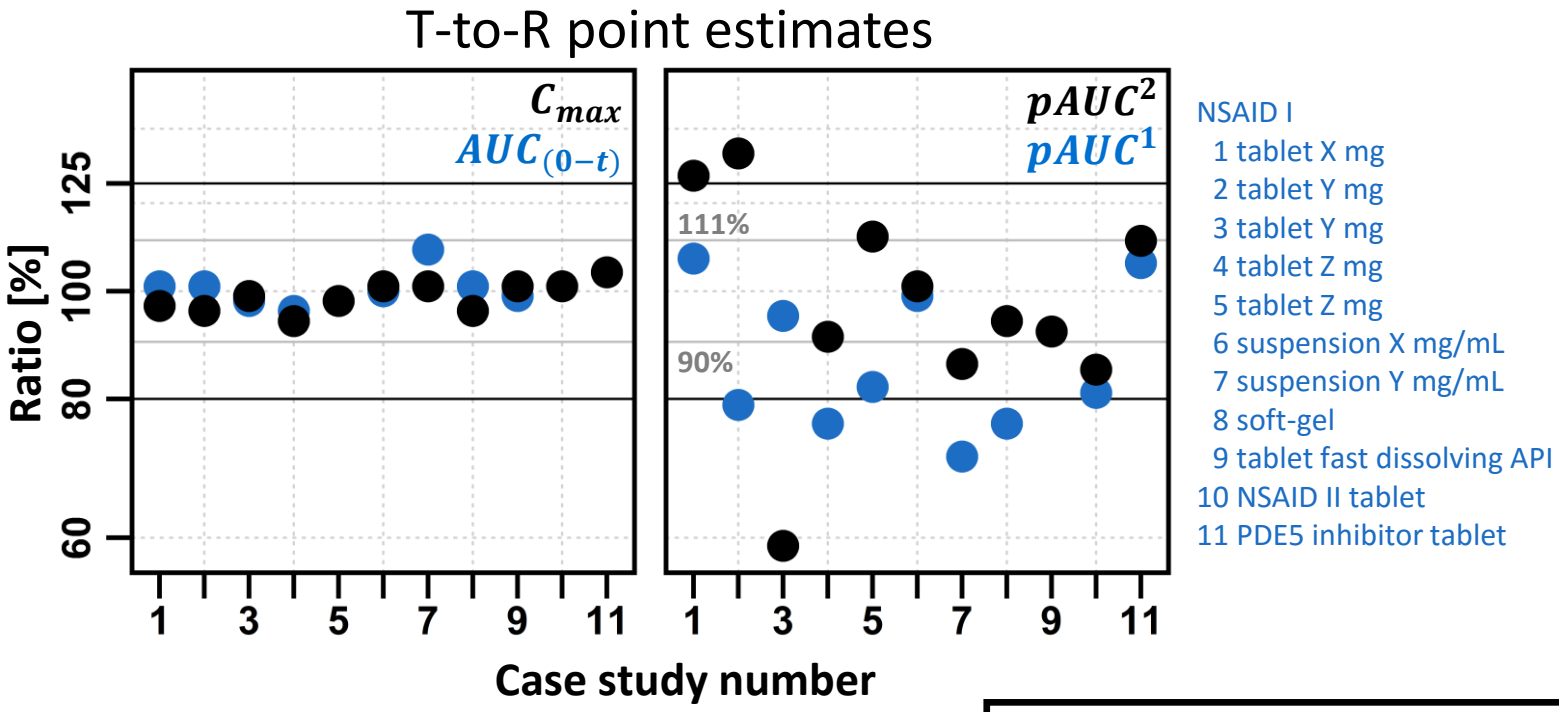
NSAID I
1 tablet X mg
2 tablet Y mg
3 tablet Y mg
4 tablet Z mg
5 tablet Z mg
6 suspension X mg/mL
7 suspension Y mg/mL
8 soft-gel
9 tablet fast dissolving API
10 NSAID II tablet
11 PDE5 inhibitor tablet

$pAUC^1$: $t_{max,R}$ in each subject
$pAUC^2$: $t_{max,R}$ median

pAUC are substantially more variable [average: 4- and 7-fold] compared to classical PK-metrics: C_{max} and AUC_{0-t}.

Designs: 2x2x2 cross-over, single-dose, in healthy volunteers

CASE STUDIES: RATIOS



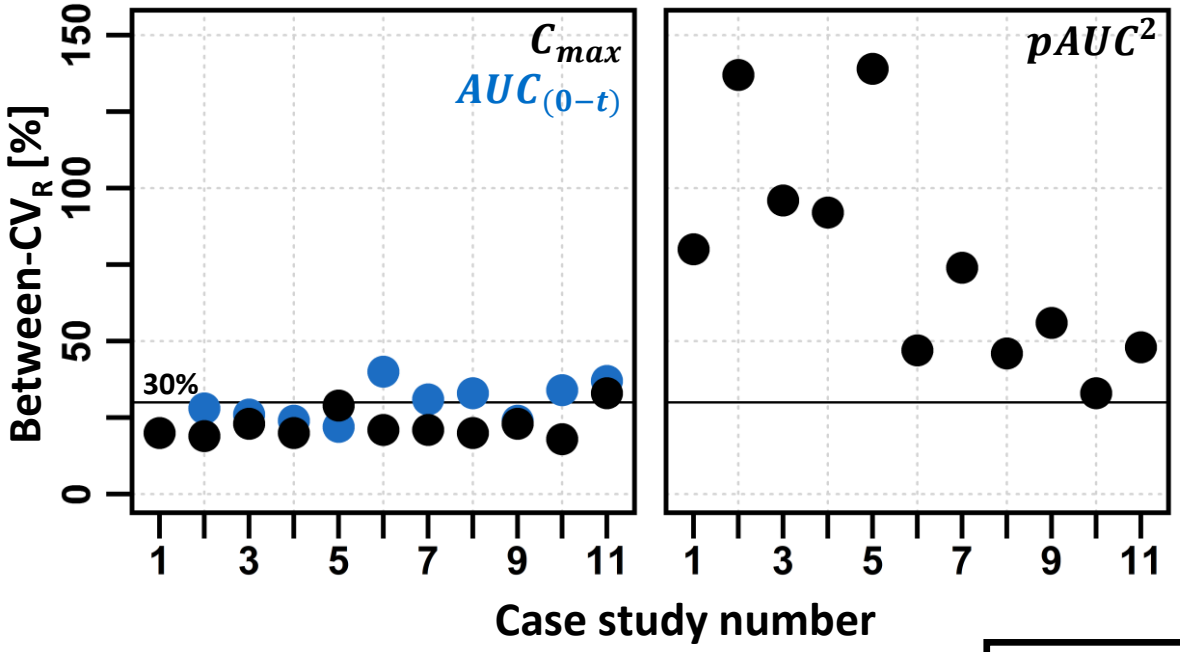
pAUC[1]: $t_{max,R}$ in each subject
pAUC[2]: $t_{max,R}$ median

Point estimates of pAUC are unstable compared compared to classical PK-metrics: C_{max} and AUC_{0-t}.

Designs: 2x2x2 cross-over, single-dose, in healthy volunteers

CASE STUDIES: REFERENCE VS. REFERENCE

Between-subject variability

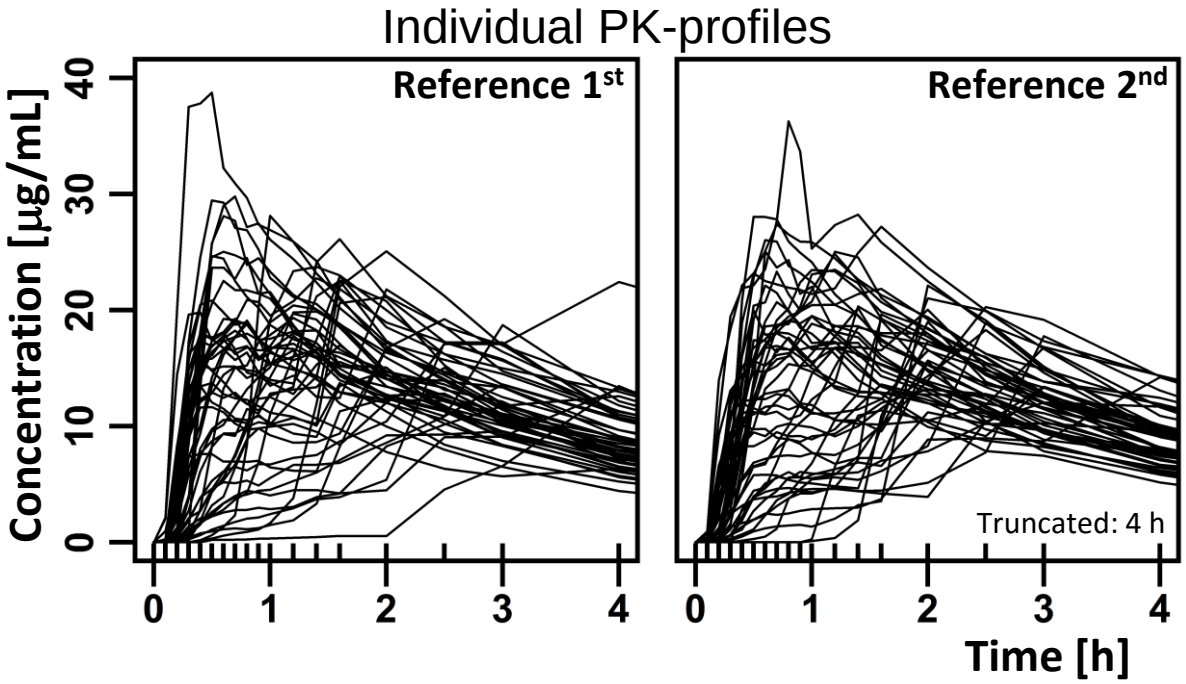


NSAID I
1 tablet X mg
2 tablet Y mg
3 tablet Y mg
4 tablet Z mg
5 tablet Z mg
6 suspension X mg/mL
7 suspension Y mg/mL
8 soft-gel
9 tablet fast dissolving API
10 NSAID II tablet
11 PDE5 inhibitor tablet

$pAUC^2$: $t_{max,R}$ median

Comparison between study periods (P_2 vs. P_1) reveals high variability of pAUC for reference product alone.

CASE STUDIES: REFERENCE VS. REFERENCE



NSAID I[1)]

Intra-CV_R [%][2)]	
Metric	**CV**
$pAUC^2$	**58**
$AUC_{(0-t)}$	**8**
C_{max}	**16**

[1)]fixed-dose combo with α_1-agonist; [2)] reference only

$pAUC^2$: $t_{max,R}$ median

A replicated cross-over study reveals high variability of pAUC for reference product alone.

Design: 2x2x4 cross-over, single-dose, in healthy volunteers

SUMMARY & QUESTIONS

80-125% of $\tilde{x}_R$ t_{max}: statistically flawed & not appropriate	Non-parametric CI with clinical range as alternative?
Stakeholder comments to PSBGL were essentially dismissed	Scientific arguments not sufficient? Do we understand each other?
Studies before 2023: not compliant with PSBGL & ICH M13?	Expiry date on studies done before 2023?
ICH M13 & pAUC: extreme variability & unstable point estimate	What changed from 2008–2023? Do we understand variability of pAUC? Scaling not permitted? Cut-off to be used?
Clinical relevance of onset of action	Do we understand the PK/PD?

QUOTES: LIBRARY(FORTUNES)

```
> library(fortunes)
> fortunes::fortune(360)
```

Either I am misunderstanding your intent or you need another cup of coffee.

-- A Rolf Turner (in response to a user who did not understand his advice) R-help (November 2013)

```
> library(fortunes)
> fortunes::fortune(354)
```

Well, the biggest room in the world is the room for improvement :)

-- Soren Hojsgaard (in reply to a suggestion to make pbkrtest and lme4 more robust) R-SIG-Mixed-Models (August 2013)

R Core Team (2023). https://www.R-project.org/