Similarity, Comparability and Correlation

Helmut Schütz

Difference factor f_1, similarity factor f_2

Difference factor f_1

- Percent difference between dissolution profiles at each time point
- Measurement of the relative error between the curves.

$$f_1 = 100\left\{\sum_{t=1}^{t=n}|R_t - T_t| \Big/ \sum_{t=1}^{t=n} R_t\right\}$$

Similarity factor f_2

- Logarithmic reciprocal square root transformation of the sum of squared error.
- Measurement of the similarity in the percent dissolution between the curves.

$$f_2 = 50 \cdot \log\left\{100 \cdot \left[1 \Big/ \sqrt{1 + \frac{1}{n}\sum_{t=1}^{t=n}(R_t - T_t)^2}\right]\right\}$$

Difference factor f_1, similarity factor f_2

Simple example

n	3
$\Sigma (R_t - T_t)$	10
$\Sigma \lvert R_t - T_t \rvert$	10
$\Sigma (R_t - T_t)^2$	38
ΣR_t	258
f_2	71.6
f_2	3.9

t (min)	R_t (%)	T_t (%)	$\Delta (R_t - T_t)$	$\Delta \lvert R_t - T_t \rvert$	Δ^2
15	83	78	5	5	25
30	85	83	2	2	4
45	90	87	3	3	9

Difference factor f_1, similarity factor f_2

Certain conditions must be fullfilled for the application of f_2.

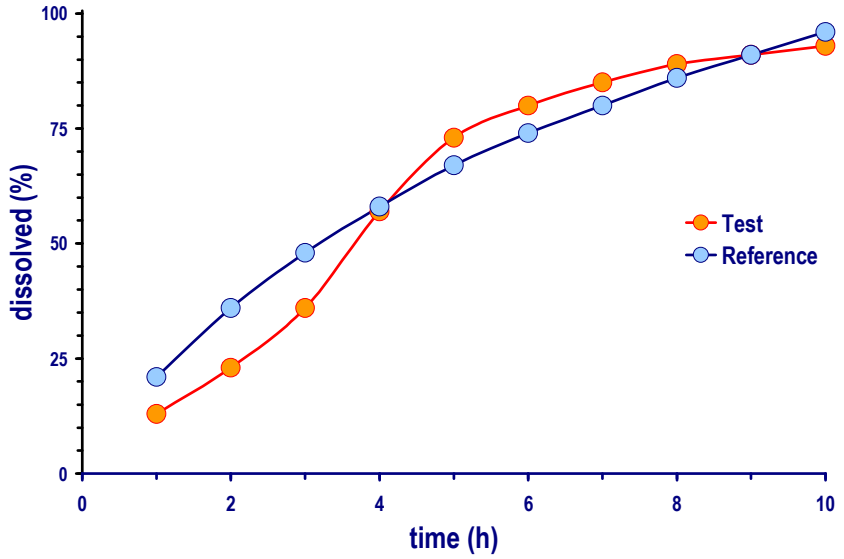
- *f_2 not required* if product releases ≥85% in all three media.
- 12 units of test and reference product.
  R_t and T_t are their arithmetic means.
- *CV* should not be >20% at ≤15 minutes.
- *CV* should not be >10% at other time points.
- Sampling time points after 85% release.
  - FDA: Only one measurement included for test product.
  - EMA: Not more than one mean value of >85% dissolved for each formulation.
  - WHO: Maximum of one time-point should be considered after 85% dissolution of the comparator (Brand/Reference/Innovator) product has been reached.

Difference factor f_1, similarity factor f_2

Different release characteristics

- Cave: Although f_1 (2.1) and f_2 (57.7) suggest similarity, the comparison is not suitable because the profiles display different release kinetics.

t (h)	R_t (%)	T_t (%)	$\Delta (R_t - T_t)$	$\Delta \lvert R_t - T_t \rvert$	Δ^2
1	21	13	8	8	64
2	36	23	13	13	169
3	48	36	12	12	144
4	58	57	1	1	1
5	67	73	-6	6	36
6	74	80	-6	6	36
7	80	85	-5	5	25
8	86	89	-3	3	9
9	91	91			
10	96	93			



Reference: Zero order?

Test: Sigmoidal (Hill or Weibull?)

Vivian Gray, *Dissolution Workshop*. 10 December 2010.

Alternatives?

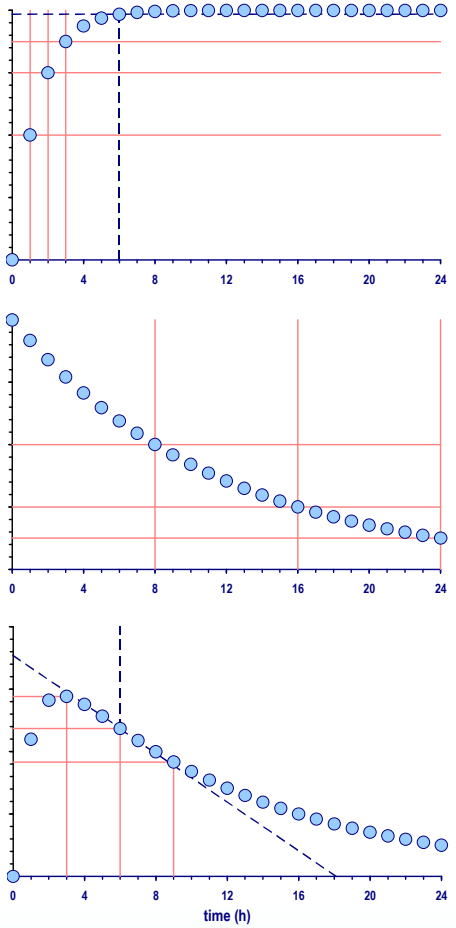
Suggested if variability (especially in early time points) is high

- Multivariate statistical distance (MSD)
  - MSD is estimated
    - Its 90% confidence interval calculated.
    - The upper limit compared to the similarity limit.
  - A subset of MSD is the Mahalanobis' Distance (MD).
    - Currently explored by the EMA's Biostatistical Working Party.
- Model-dependent approaches
  - Select a suitable model (quadratic, logistic, probit, Hill, Weibull, …).
  - Similarity region is specified based on the variability.
  - Calculate MSD and CI as above.

A(D)ME

In vivo curve can be described by absorption (A) and elimination (metabolization + excretion)

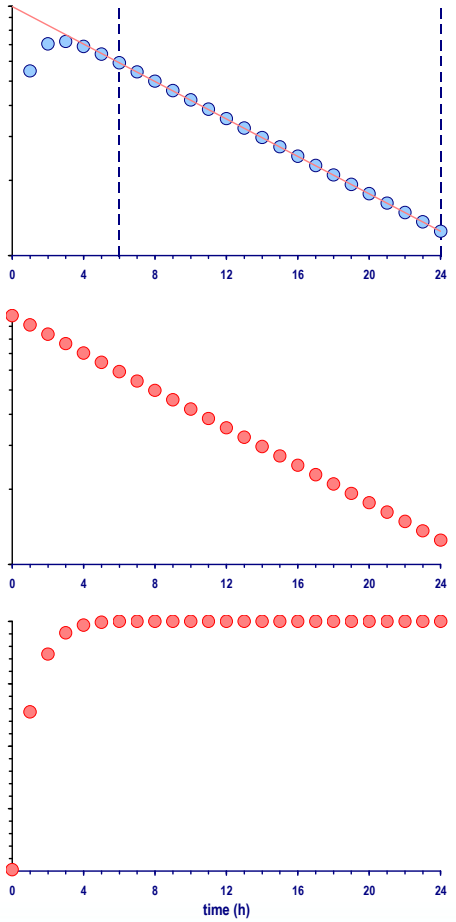
- One-compartment model does not have D (distribution).
  - Example: $t_{½a}$ 1 h, $t_{½e}$ 8 h
    - After 3×$t_{½a}$ (3 h) 87.5% are absorbed.
    - After 3×$t_{½e}$ (24 h) 87.5% are eliminated.
    - In the *in vivo* curve the inflection point (where the curve changes from concave to convex) is seen at 2×t_{max} (6 h).
      At this time absorption is essentially complete (98.44%) and the *in vivo* curve practically represents elimination only.
- We can get *in vivo* absorption by subtracting the estimated elimination.



A(D)ME

Reconstructing *in vivo* absorption (residual method)

- Fit elimination (λ_z from $2\times t_{max}$ or later to t_z).
- Predict *in vivo* elimination.
- *In vivo* absorption is the *in vivo* curve minus the predicted elimination.



Different other methods exist.

- One-compartment model
  - Wagner-Nelson

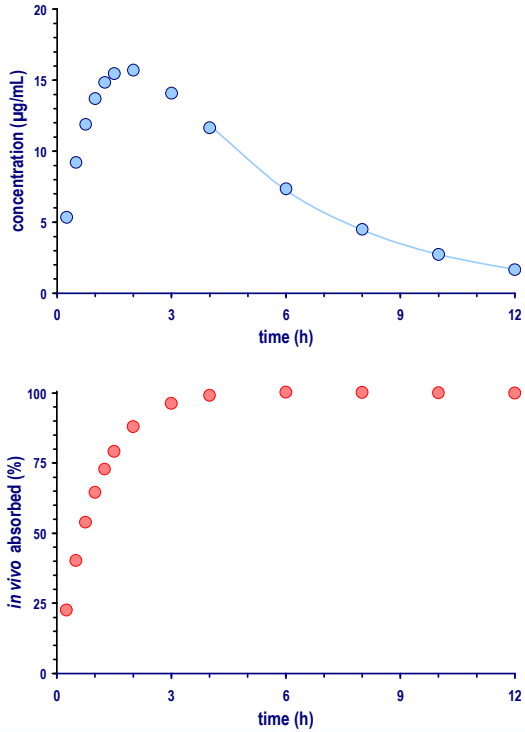
$$abs(\%) = 100\frac{C_t + k_{el} \cdot AUC_{0-t}}{k_{el} \cdot AUC_{0-\infty}}$$

- Two-compartment model
  - Loo-Riegelman (needs true elimination from iv); the distribution phase is reconstructed.

Wagner-Nelson

D 100 mg, V 4 L, F 1, k_a 1 h^{-1} ($t_{½}$ 0.69 h), k_{el} 0.25 h^{-1} ($t_{½}$ 2.77 h)

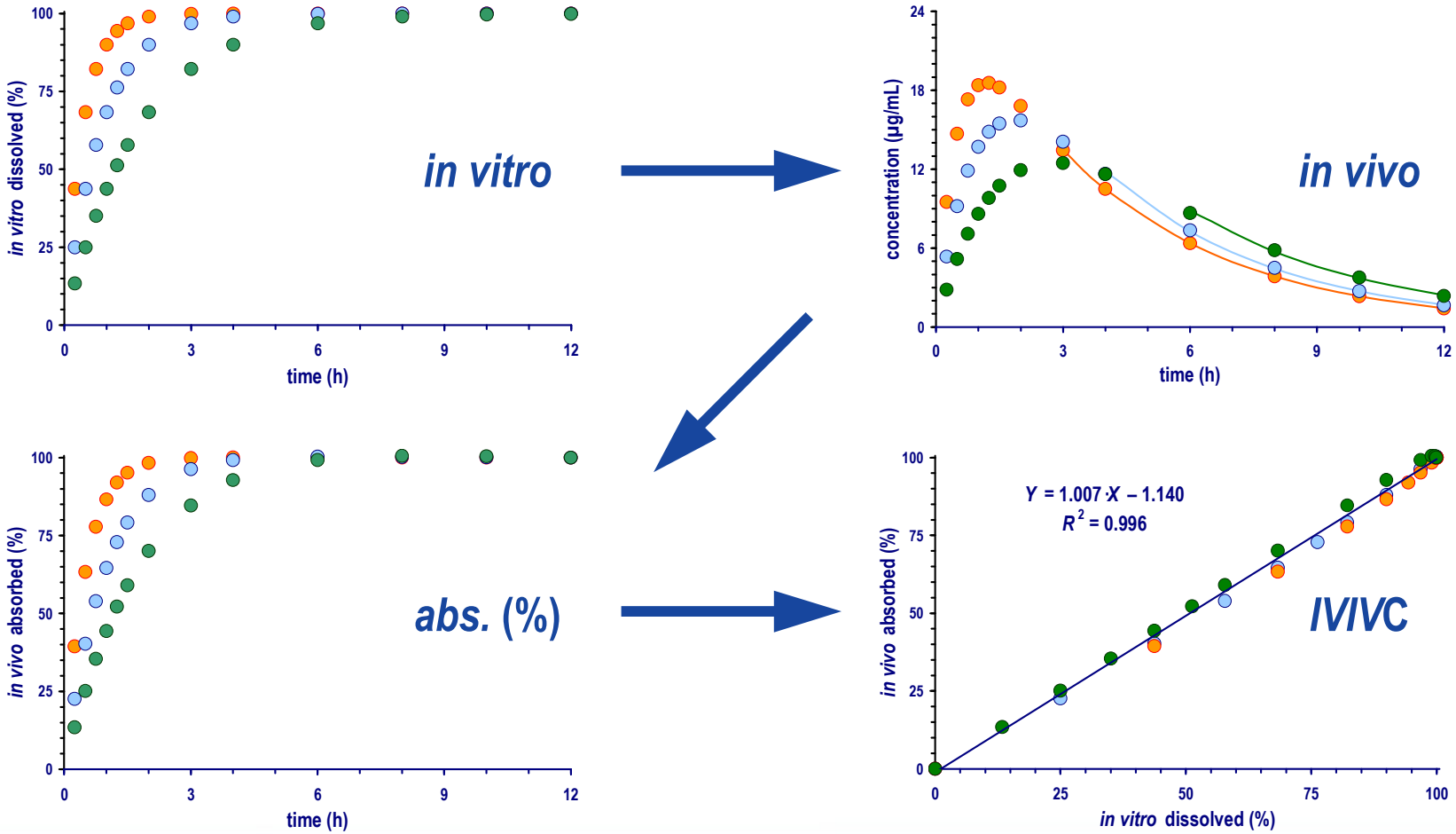
- Lin-up/log-down trapezoidal method for $AUC_{0–t}$.
- λ_z (estimated from 4 to 12 hours) = 0.2444.
- $AUC_{0–\infty} = AUC_{0–12} + C_{12} / \lambda_z = 99.68$.



t (h)	C (mg/mL)	$AUC_{0–t}$	abs (%)
0.00	BQL	–	–
0.25	5.35	0.67	22.63
0.50	9.20	2.49	40.26
0.75	11.89	5.12	53.94
1.00	13.70	8.32	64.58
1.25	14.84	11.89	72.84
1.50	15.47	15.68	79.22
2.00	15.71	23.47	88.03
3.00	14.09	38.36	96.31
4.00	11.65	51.19	99.17
6.00	7.36	69.87	100.31
8.00	4.50	81.50	100.23
10.00	2.73	88.88	100.08
12.00	1.66	92.68	100.00

IVIVC (Level A)

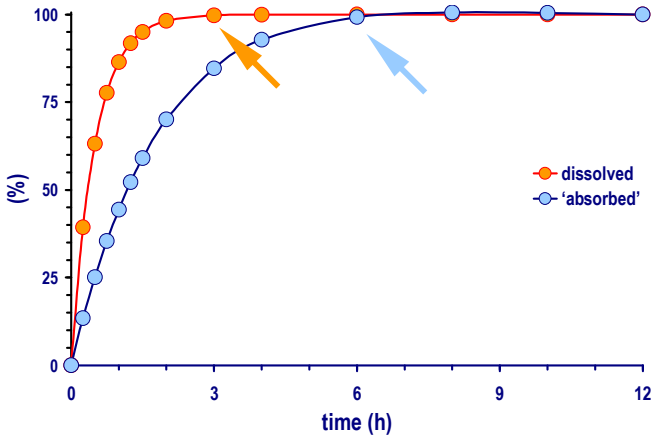
Three candidate formulations (fast, intermediate, slow)

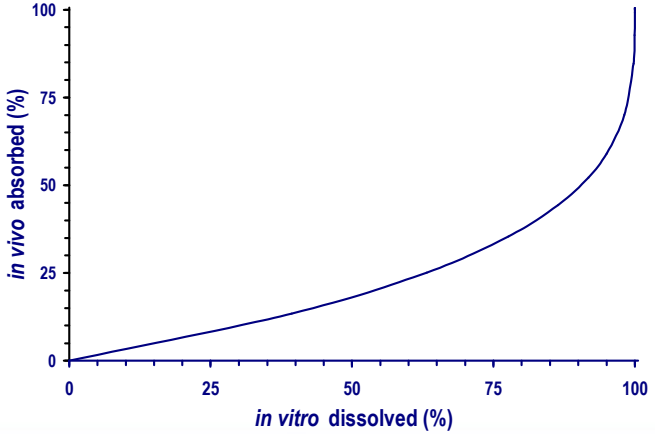


IVIVC (Level A)

Different rates *in vitro* / *in vivo*

- Not suitable for IVIVC (nonlinear relationship)



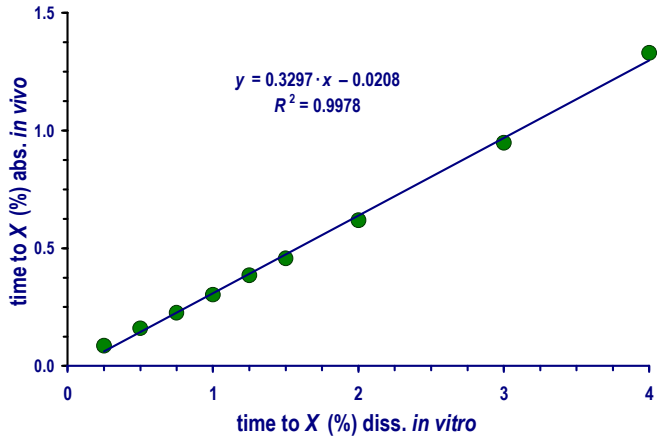


t (h)	*diss* (%)	*abs* (%)
0.00	0.00	0.00
0.25	39.35	13.44
0.50	63.21	25.14
0.75	77.69	35.44
1.00	86.47	44.37
1.25	91.79	52.22
1.50	95.02	59.04
2.00	98.17	70.10
3.00	99.75	84.66
4.00	99.97	92.82
6.00	100.00	99.27
8.00	100.00	100.57
10.00	100.00	100.43
12.00	100.00	100.00

IVIVC (Level A)

Different rates *in vitro* / *in vivo*

- Modify the dissolution method (*e.g.*, less agitation) to get a better match.
- Establish a Levy plot (time to get % dissolved or absorbed). Use interpolation to find dissolution times which match absorption.



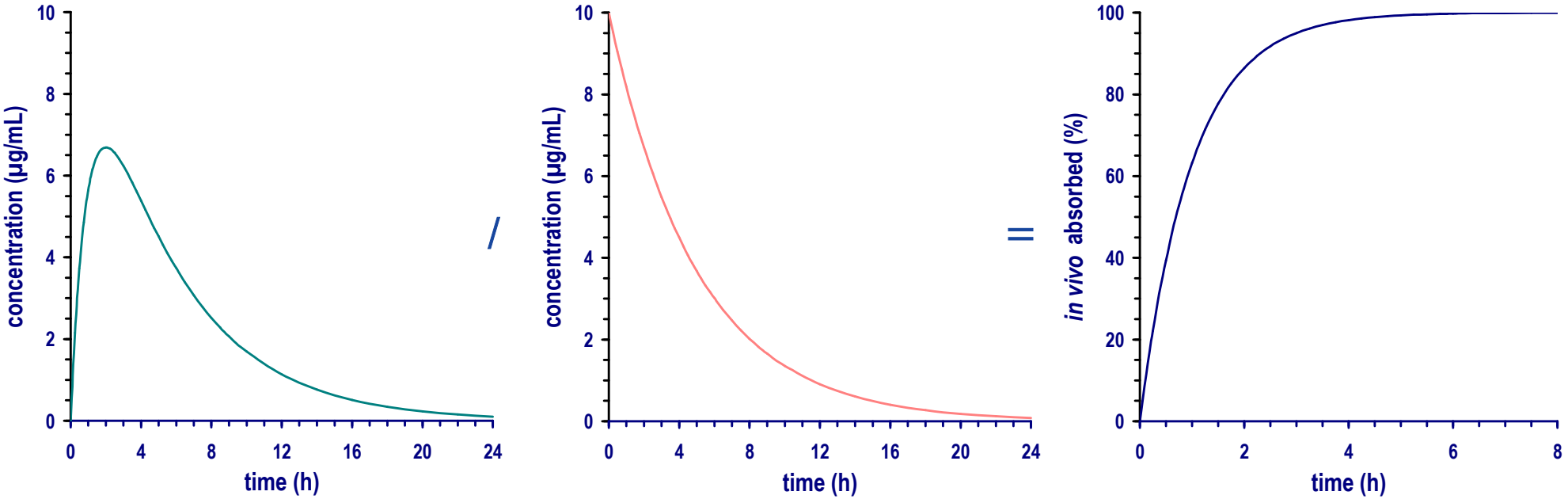
- Calculate new *in vitro* sampling times.
  $t_{in\ vitro} = t_{in\ vivo} \times 0.3297 - 0.0208.$

in vivo		*diss. time*	
t (h)	*abs* (%)	(h)	(h:mm)
0.00	0.00	0.00	0:00
0.25	13.44	0.06	0:03
0.50	25.14	0.14	0:08
0.75	35.44	0.23	0:13
1.00	44.37	0.31	0:18
1.25	52.22	0.39	0:23
1.50	59.04	0.47	0:28
2.00	70.10	0.64	0:38
3.00	84.66	0.97	0:58
4.00	92.82	1.30	1:17
6.00	99.27	1.96	1:57

IVIVC (Level A)

Alternative to Wagner-Nelson and Loo-Riegelman

- **Deconvolution:** Derive *in vivo* input curve from *in vivo* profile. Only method which is can be applied if there are more than two compartments. Notation: $f = g / h$

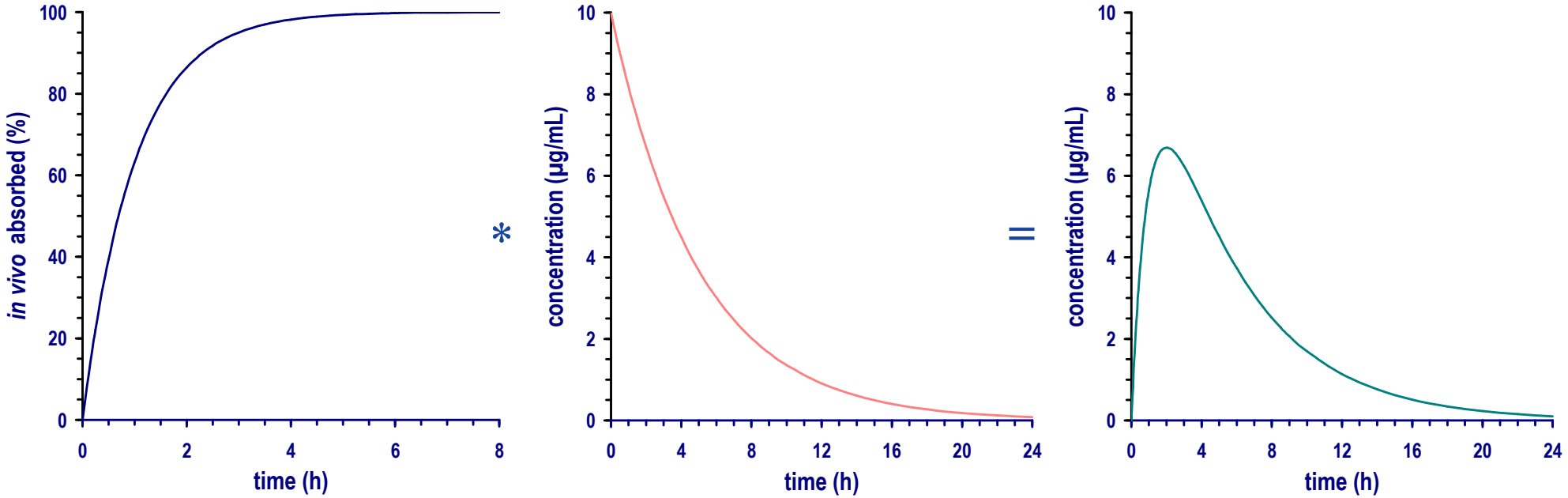


Jean-Michel Cardot. *IVIVC Workshop*. Mumbai, 27 – 29 January 2012.

IVIVC (Level A)

Alternative to Wagner-Nelson and Loo-Riegelman

- **Convolution:** Derive *in vivo* profile from simulated *in vivo* input curve (obtained by IVIVC). Notation: $f = g * h$



Jean-Michel Cardot. *IVIVC Workshop*. Mumbai, 27 – 29 January 2012.

IVIVC (Level A)

Deconvolution / Convolution

- Already mathematically demanding for continous functions – even more complicated if only data-pairs are available.
  - Numeric methods require equidistant supporting points. Must interpolate / impute data.
  - Requires additionally to % absorbed the rate of absorption *dA* / *dt* (method by Vaughan, Denis 1978).
  - Requires between six and ten sampling points in the absorption phase ($\leq 2 \times t_{max}$).

Jean-Michel Cardot. *IVIVC Workshop*. Mumbai, 27 – 29 January 2012.

IVIVC (Levels B and C)

Level B

- Correlation of statistical moments describing *in vitro* and *in vivo* profiles.
  - Mean dissolution time (*MDT*) with mean residence time and mean absorption time (*MRT*, *MAT*).
    Problem: *MRT* of *in vivo* profiles depend to a large part on distribution / elimination. Needs iv (or at least solution) data to obtain *MAT*.

Level C

- Correlation of single-point metrics.
  - % dissolved (at least 80%) up to an certain time point with a PK metrics (*e.g.*, C_{max}, truncated *AUC*).
  - Few 'working' examples (*e.g.*, glibenclamide).

Jean-Michel Cardot. *IVIVC Workshop*. Mumbai, 27 – 29 January 2012.

IVIVC

Quite often what one thinks to be 'different' (based on a QC dissolution method) turns out to be similar *in vivo*.

- **Modify formulations, perform *in vivo* pilot studies until you see a difference *there*.**
  - **Then (!) develop a discriminatory *in vitro* method (Session 8) which is able to predict *in vivo* absorption**
    - **Try different agitation speeds, use surfactants, change the apparatus, if nothing helps – explore biorelevant media.**
    - **The final *in vitro* method likely has nothing in common with the one used in QC.**
      If Earl Grey with a sip of milk is predictive, use it! **(Jean-Michel Cardot)**
- **Once you found a discriminatory method, modify formulations to find one which matches the reference.**
  - **This does not guarantee that the reference will behaves *in vivo* like your best candidate.**
    Another pilot (T *vs.* R) makes sense (to estimate *CV* and *GMR*).

Similarity, Comparability and Correlation

Thank You!

Open Questions?

Helmut Schütz

BEBAC

Consultancy Services for
Bioequivalence and Bioavailability Studies
1070 Vienna, Austria

helmut.schuetz@bebac.at