IVIVC – Tricks and traps

Based on CARDOT J-M., DAVIT B.,
In vitro- in vivo correlations: Tricks and Traps,
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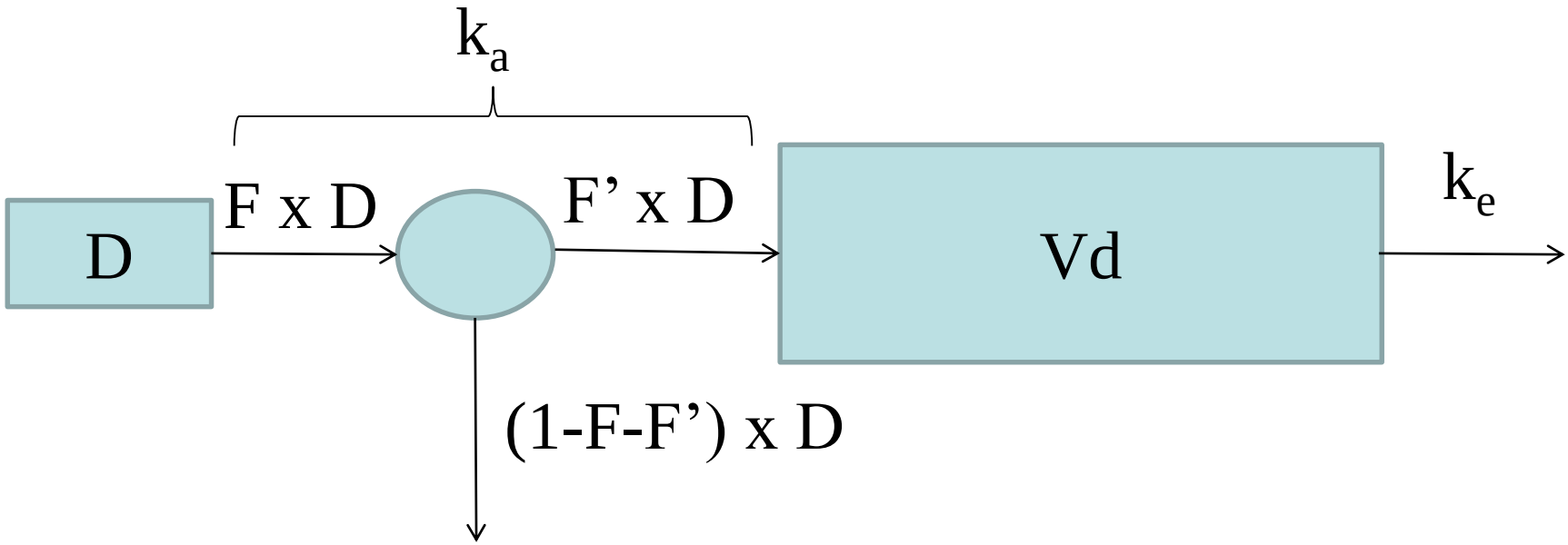
Aim

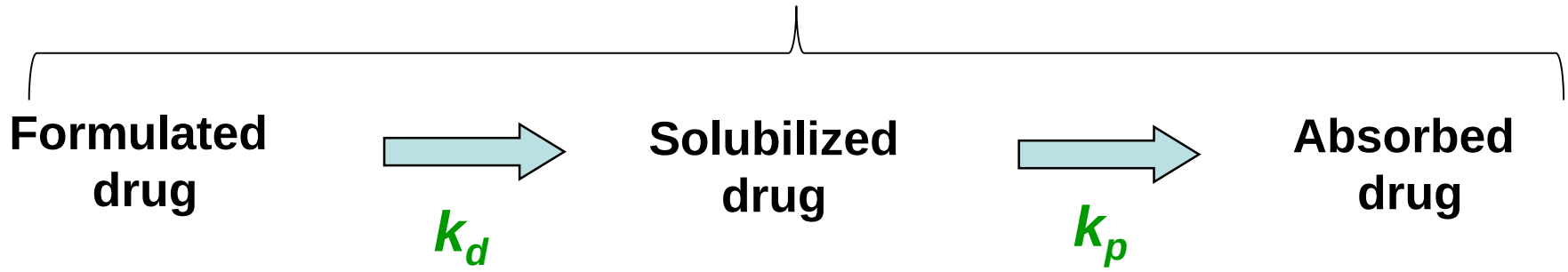
- Investigate commont problem of IVIVC
  - Limiting factor
  - Improvment of BA
  - Averaging
  - Lag time
  - Flip Flop
  - Dissolution limits
  - Dissolution test for QC

Limiting step, Pharmacokinetics?

- Even in Pharmacokinetic a part is link with biopharmacy
- Take the simple 1 compartment equation after extra vascular admministration



What is k_a



k_d = dissolution rate (solubility, including food and formulation)

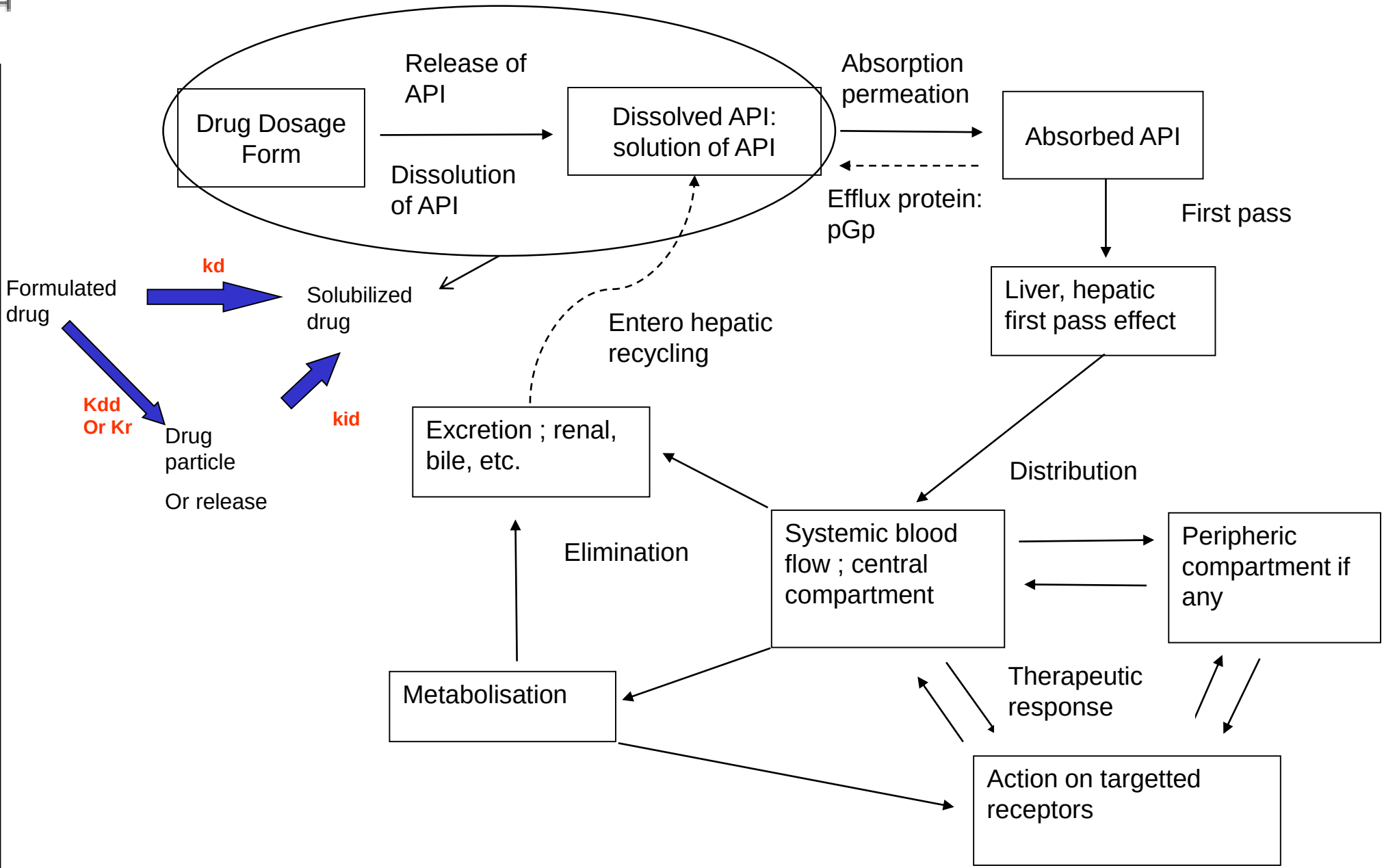
k_p = permeability rate (API molecular structure)

kd & kp fast Well absorbed

kd>> kp **Permeation** control

kd<< kp « **Solubilisation »** controlled

General scheme in vivo

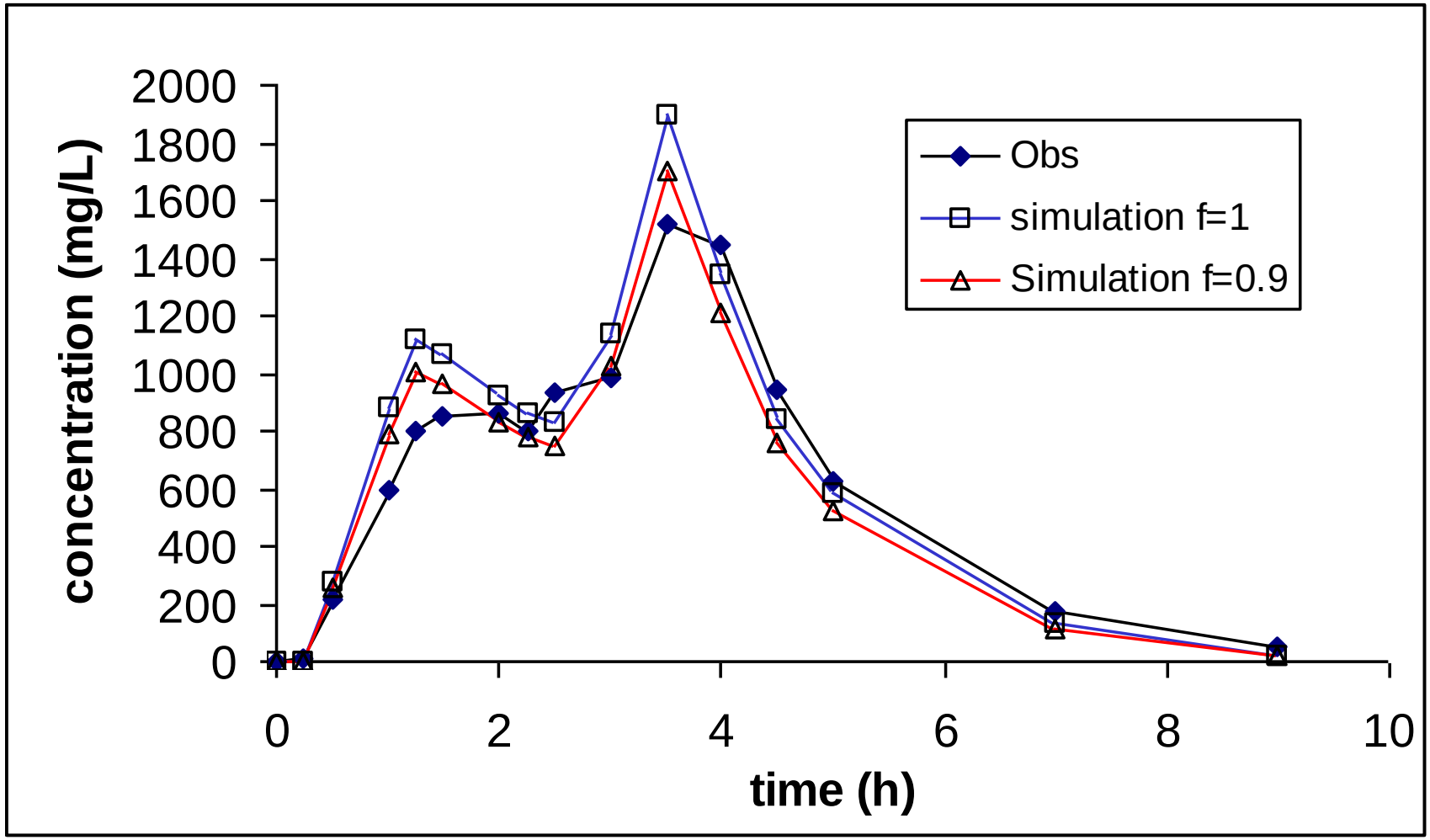


Limiting

- IVIVC not for IR formulation as the in vivo limiting factor will be
  - « Nothing » class I
  - API Class II IV
  - Permeability III IV
  - DR is an IR with lag time!
- IVIVC for PR (some exceptions existed)
  - PO
  - Injectable
  - Vaginal/uterine device
  - Etc…

Problem of F in IVIVC

- When a correlation is established we used %FD vs % dissolved
- During simulation we have to reinclude a factor F in the calculation to estimate the magnitude of the answer
- Usually we use the F obtained with the formulation used to establish IVIVC
- That assume that the new formulation exhibits an identical F


concentration (mg/L)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
2
4
6
8
10
time (h)
Obs
simulation f=1
Simulation f=0.9

Is that allowed

- When can I do it
- I could not recalculate it afterwards to adjust curve
- If I have not the correct F => I could not predict extent and rate, shape is correct (rate constant not Cmax, but not extent)
- I have to use the F of the reference formulation

Problem of averaging

- Often the IVIVC are established on mean curves
  - Mean in vitro dissolution
  - Mean in vivo plasma curve leading to an absorption curve
- On the same way simulations are performed to establish mean profile based on the mean dissolution

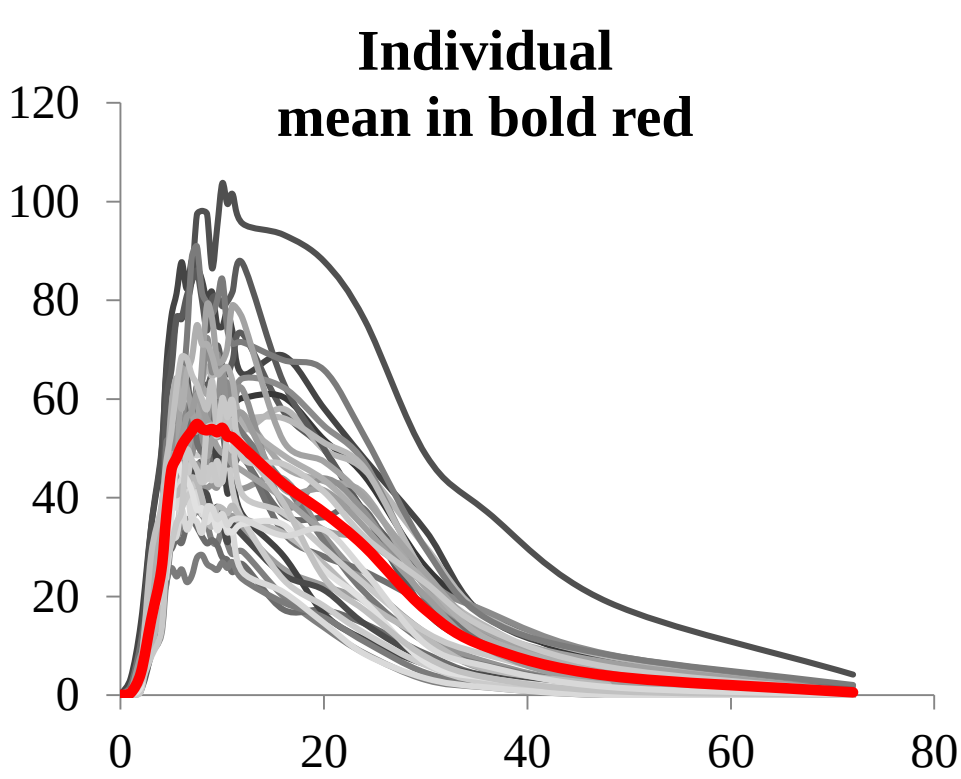
Mean dissolution

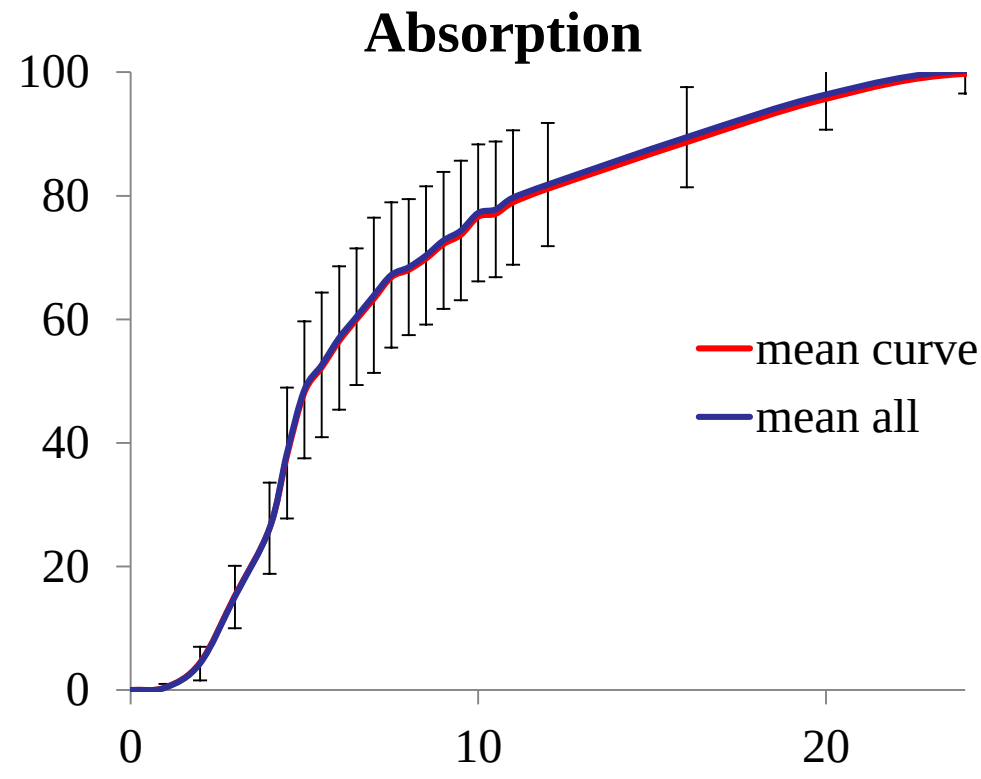
- How can one tablet be linked with one subject
- Averaging the dissolution data is something common and recognized even for statistical tests (i.e. F1/F2 test)
- It is supposed that dissolution data are less variable than in vivo data
- In case of large dispersion of in vitro => IVIVC are a nonsense, cannot predict the results in vivo

Mean in vivo curve

- The calculations performed on mean curve are not identical to the mean of the calculations performed on individual curves when great differences existed
- In addition do I have to use arithmetic or geometric means or median.

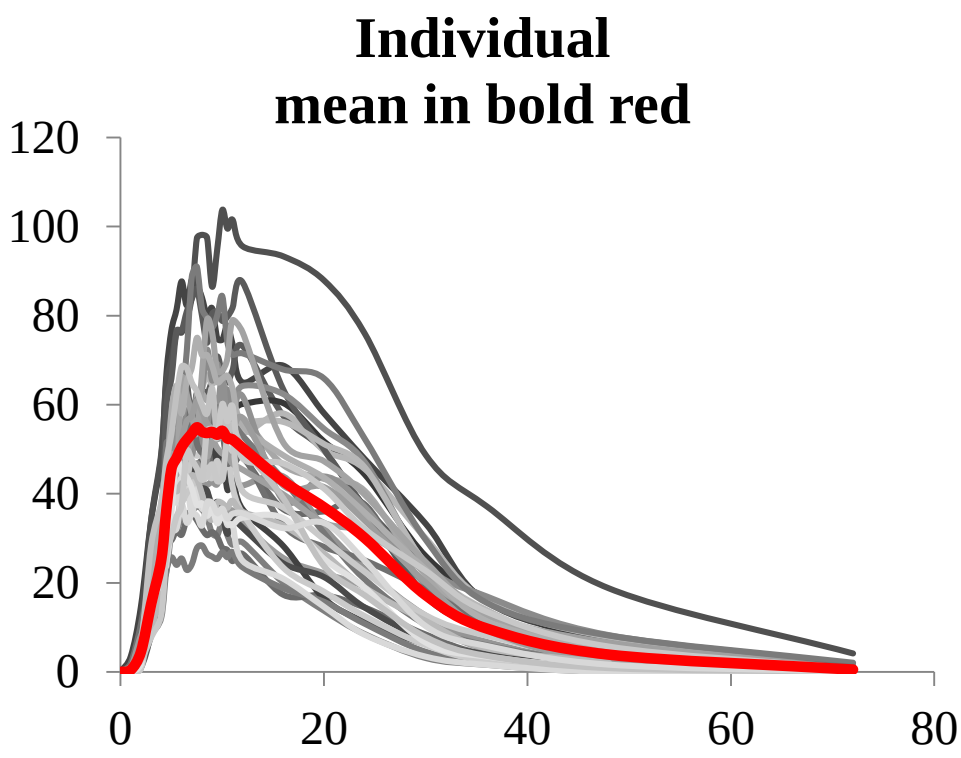
Mean curve or mean of indididuals

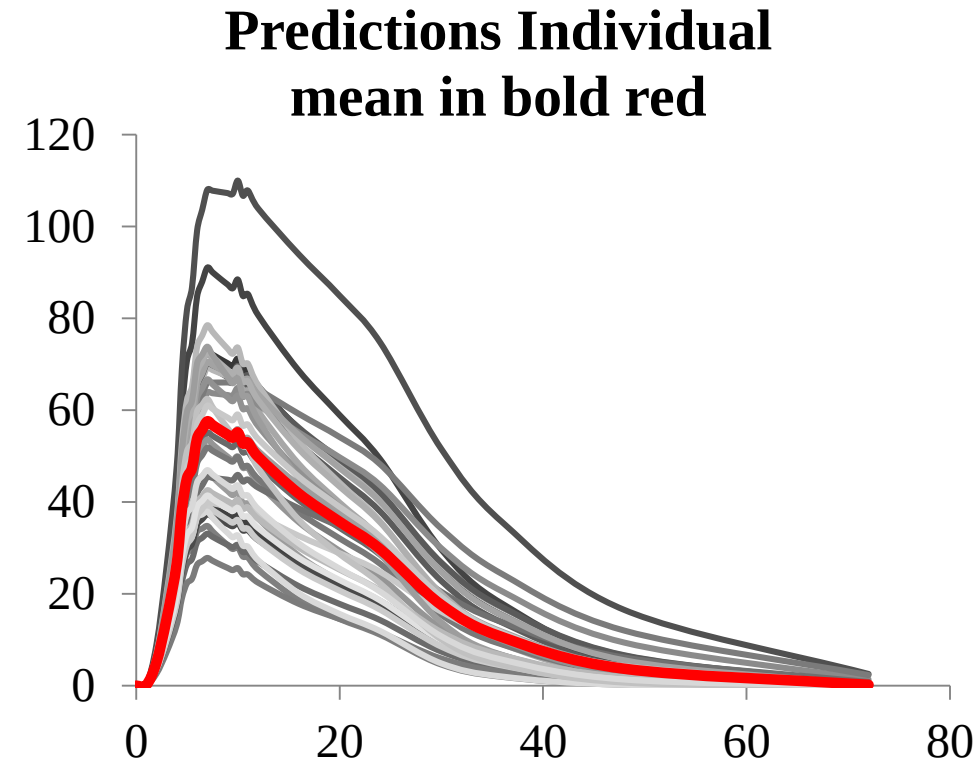




- Only one IVIVC for all subjects … or for the mean
- Variability linked with initial set of subjects
- Some agencies asked to mean only the absoption curve

and now for prediction…





- In case of prediction identical shape as input similar for all subject
- Using means restricted the pool of data to a single set, cannot estimate adequately the variability of response, underestimate the subject effect but IVIVC is usually done when intra subject variability is lower than inter subject … that being not reflected by a a set of data.
- is that a real question?

Averaging

- Meadian and geo mean less sensitive to outliers
- Mean(s) or median => recalculate the paramerts on the mean and median curve for predictability otherwise problems… (see later)
- When can I average => see Tmax (?)

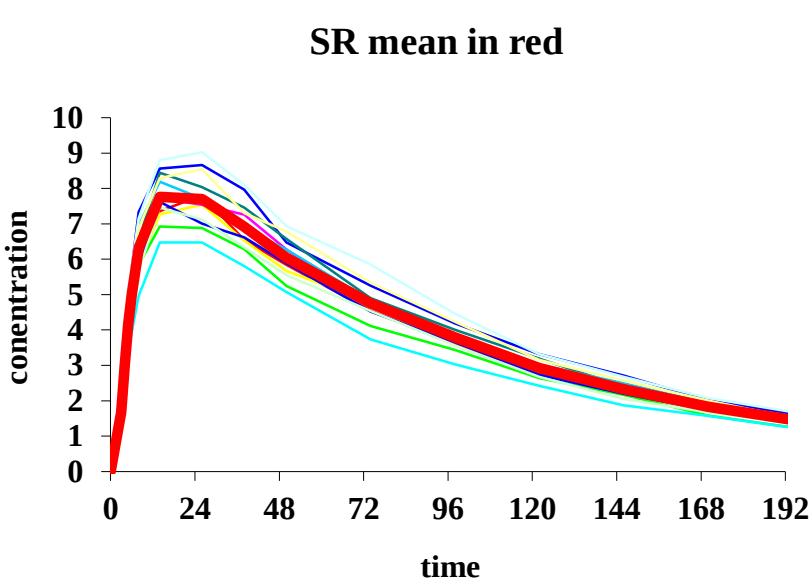
Remarks

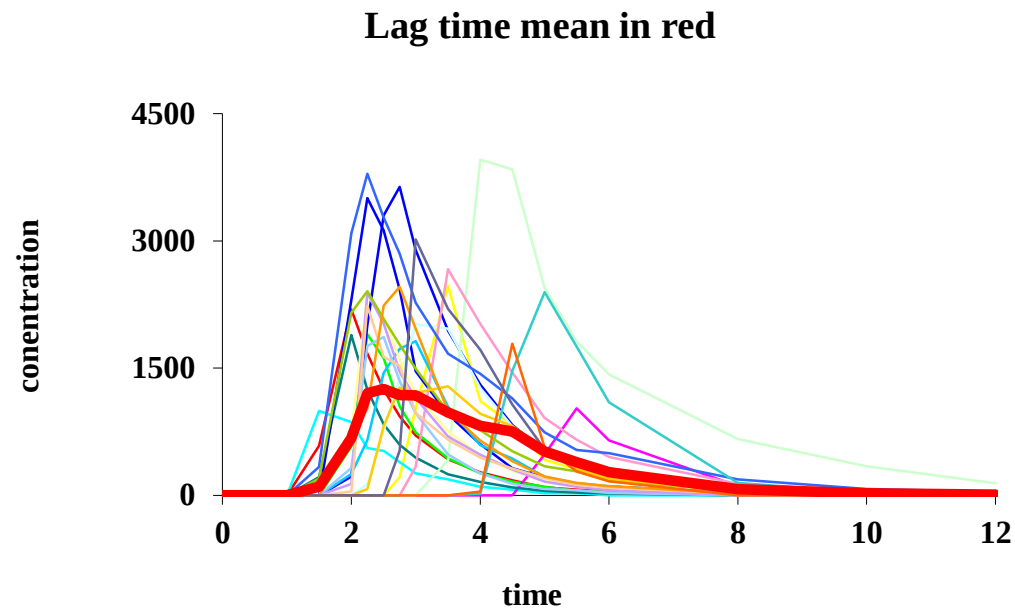
- In case of EC, the lag time is linked with gastric emptying => cannot be predicted
- Using means restricted the pool of data to a single set, cannot estimate adequately the variability of response, underestimate the subject effect but IVIVC is usually done when intra subject variability is lower than inter subject … that being not reflected by a set of data.

Problem of lag time correction

- Identical as princeps as included in the formula conception
- Cannot shift a posteriori the simulated curves to have them closed to expected/observed
- Could I substract it ?
- Could I make IVIVC for DR formulation (they are IR after a lag time … => in theory no IVIVC)

mean value (step 2) and lag time correction

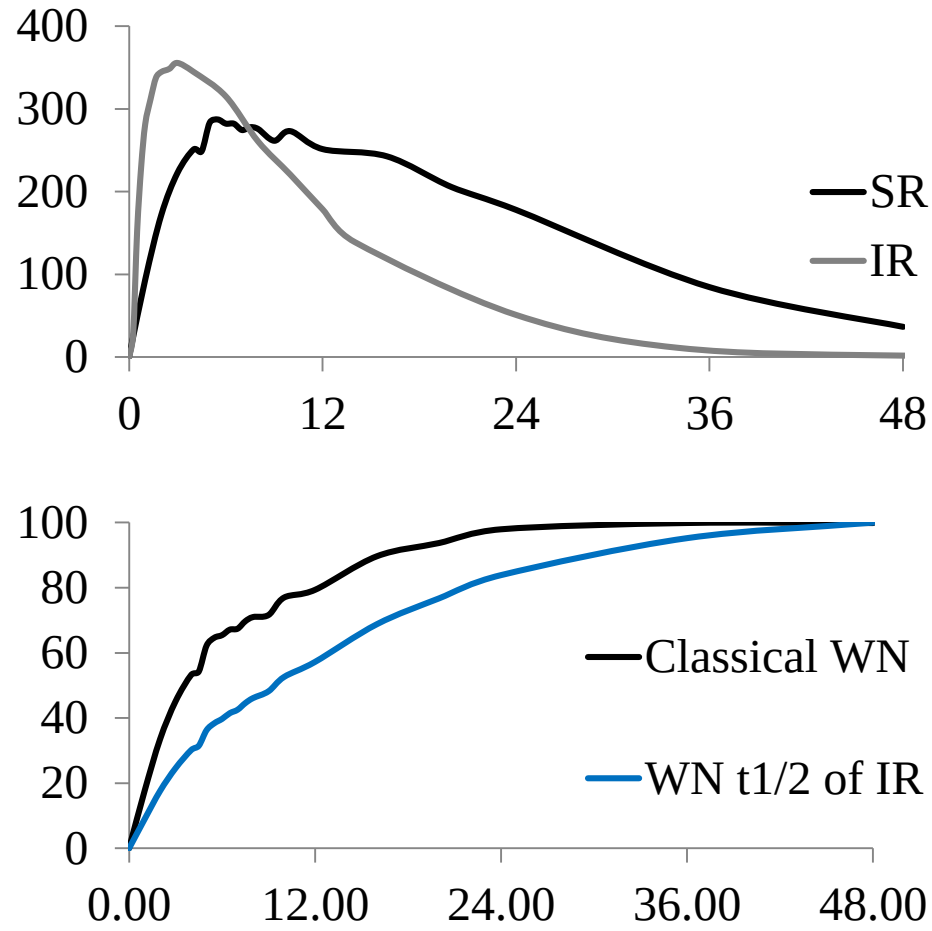




- In case of lag time fonction of subjects mean is quite a nonsence
- Correction of lag time could be done if linked with formulation, similar for all of them and not physiology (not for EC)
- In case of EC, the lag time is linked with gastric emptying => cannot be predicted

Flip flop model especially in case of Wagner Nelson

- Always verify the terminal half-life of SR vs IR
- In case of WN could overestimate absorption
- Lead to bad IVIVC with wrong time scaling
- Decrease predictability



Problem of content

- The content uniformity of the reference and new formulation is important.
- It is assumed that
  - The U of content is within the legal limits
  - That the final formulation will have the same uniformity
  - The extreme will not bring pharmacological Pb

Predictability

- On the mean value
  - Geometric
  - Arithmetic
- On individual predictions
  - Variability linked with the initial data
- Limitations
  - In all cases based on intra subject variability
  - No improvement of F allowed or expected

Predictability

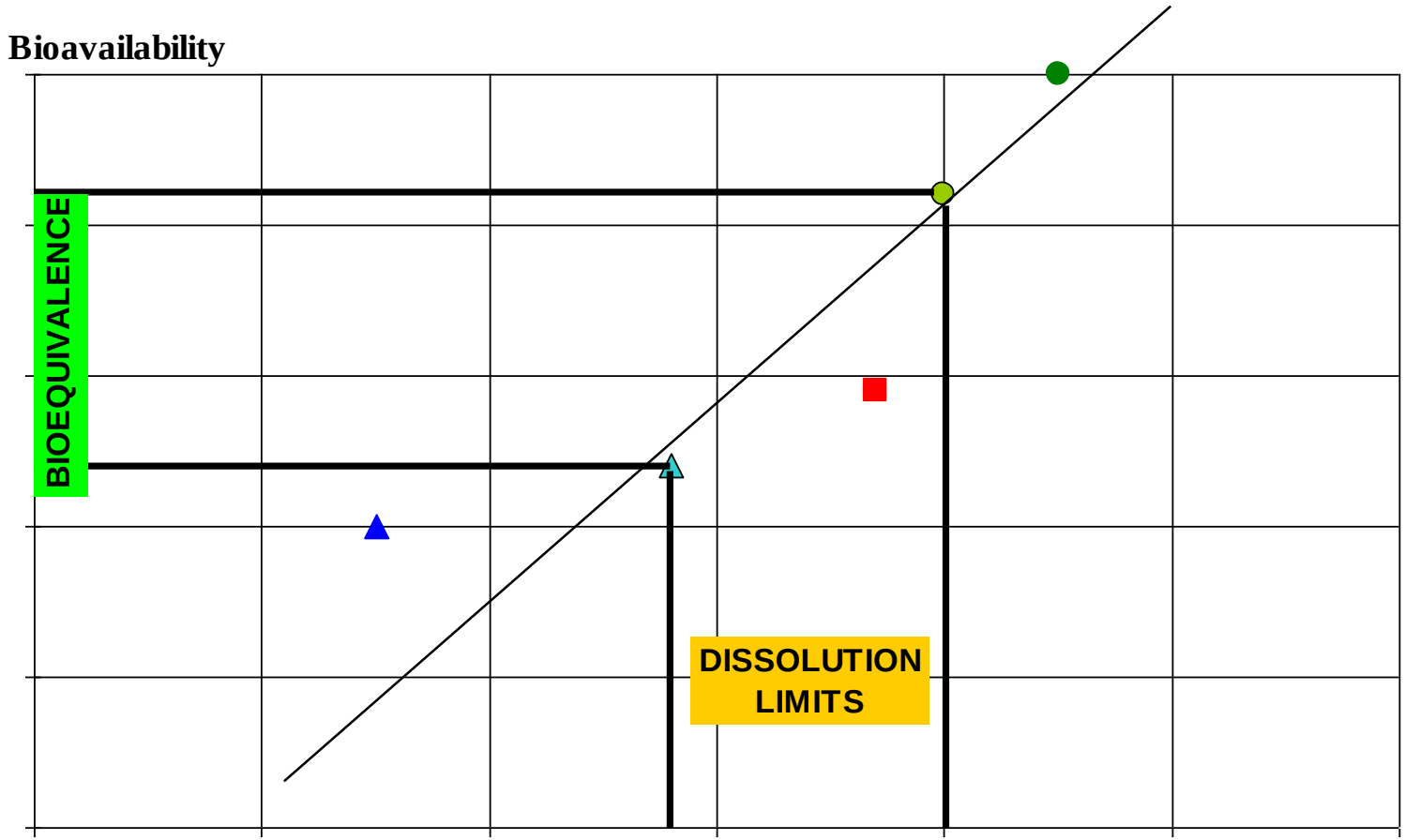
- On the mean value
  - Geometric
  - Arithmetic
- On mean curves
- Guideline "lots with the fastest and slowest release rates that are allowed by the dissolution specifications result in a maximal difference of 20% in the predicted Cmax and AUC"
- On individual predictions or using residual error
  - intra subject variability of initial set
  - initial n
- No improvement of F allowed or expected

Parameter	Cmax
Arithmetic mean	63898 (+0.9%)
Geometric mean	62434 (-1.4%)
Cmax of mean curve	60392 (-4.7%)
LS means (used in 90% CI)	*63323*

Parameter based on LS means	limits
+/-10% of Cmax	56991-69655
+/-20% of Cmax	50658-75988
Based on 90% CI n=20	52983-75680
Based on 90% CI n=40	52291-76681

Dissolution limit setting

Based on +/- 10% of PK parameters
Based on 90% CI



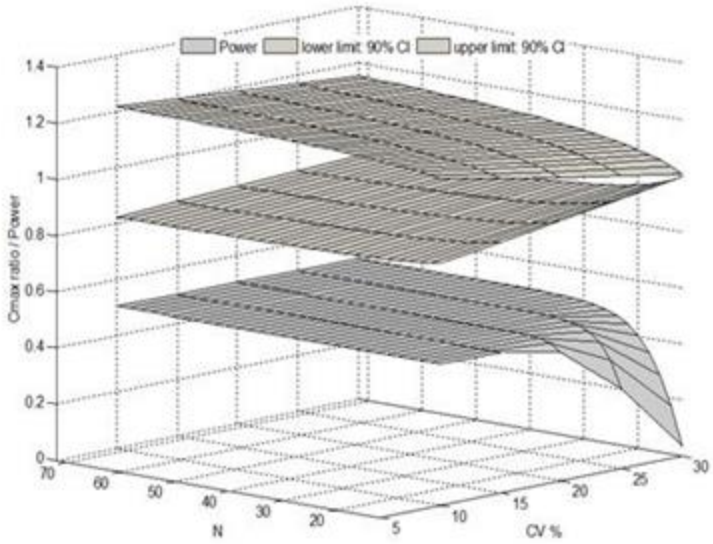
Equation if 90% CI is used

$$e^{\left[Ln(0.80)+\frac{t\times s_r}{\sqrt{n/2}}+Ln(\overline{m}_{ref})\right]}=\overline{m}_{lower}$$

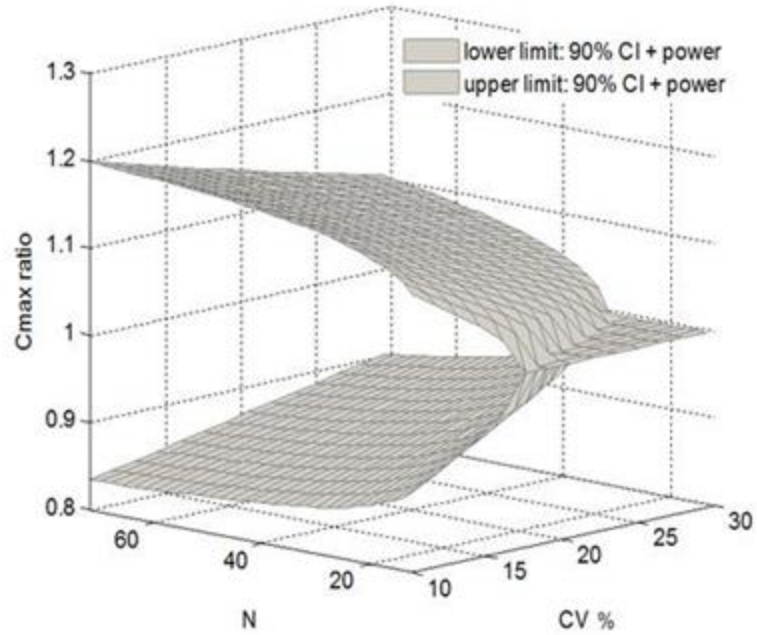
$$e^{\left[Ln(1.25)-\frac{t\times s_r}{\sqrt{n/2}}+Ln(\overline{m}_{ref})\right]}=\overline{m}_{higher}$$

Associated or not to power calculation

Comparison with CV and N



Without power



With power

90% CI method

- 90% CI method allows also to calculated and define a priori the number of subject that would help to succeed in case of BE study and therefore could set dissolution limits with all the condition to be fulfilled in case of in vivo BE study. For example with 48 subjects the method based on a 90% CI associated with the power calculation presented an advantage up to around 25% of intra subject CV.
- However the IVIVC must never be seen to fix more drastic limits that the limits that would have been establish with this tool i.e. ± 10% of the dissolution of the target formulation. IVIVC trial must never be punishable and the broader limits either based on the classical approach or IVIVC must be selected by the authorities.

Dissolution method of QC

- In theory in case of IVIVC it must be the method developped for the IVIVC
- Be carefull in developping this method
- Be carefull that the method will have to be validated
- This method will be used for release and stability …. (and validated before stability studies)
- Dissolution limits based on IVIVC

Population PK

- In my opinion never at the begining
- Could be used when the key factors and possible covariates are known
- For example a good approach for dissolution limit setting

Conclusion

- IVIVC is not a simple tool to handle
- Numerous problem must be evaluated before start
- A number of other topics existed such as
  - Time scaling
  - Adjustment to covariate factor
  - Etc….

That is for next year in Prague!