Bioequivalence and in vitro-in vivo correlations

Martin Čulen

Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences, Palackeho 1-3, 612 42 Brno, Czech Republic

Lecture

Outline

Generic vs. Innovator drugs

Bioequivalence

IVIVC

(In vitro-in vivo correlations)

Lecture

Outline

Generic vs. Innovator drugs

Bioequivalence

IVIVC

Innovator drugs

Basic facts

1/1000 new drug candidates is approved for the market

Cost = 300-1000 million USD

Time spent = 12-15 years

20-year patent (approx. 10 y during development + 10 y during marketing)

Generic drugs

By 2016, generics constituted 89% of total prescriptions, while only accounting for 27% of total drug costs*

**https://www.optum.com/resources/library/7-fast-facts-generic-drugs.html?o=optum:soc:RX_8.1_2017:tw:rx:lib:17imtkv04cm24*

Generic drugs

vs. originator drugs

Identical:

- Active ingredient
- Dosage form type (e.g. immediate release tablet)
- Route of administration
- Strength
- Indication
- Quality
- Performance

Generic drugs

vs. originator drugs

Differences:

- Formulation shape, color…
- Packaging
- Release mechanisms
- Clinical tests – only bioequivalence study required!
  – safety and efficacy data provided by innovator

Generics production – copy & paste??

Not exactly…

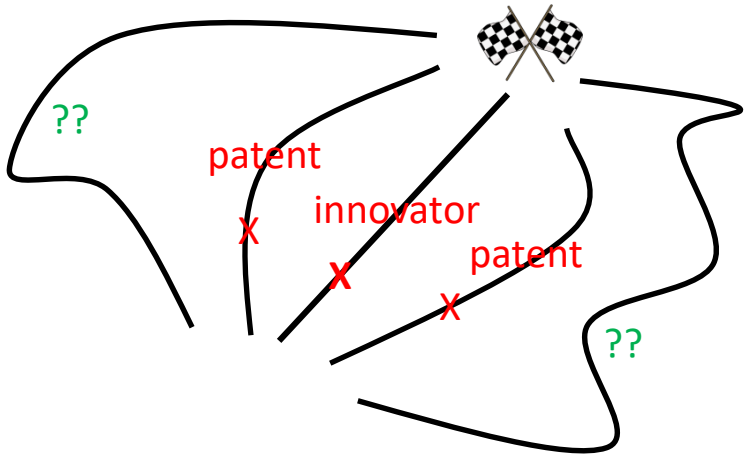
Generic drugs

vs. originator drugs

Obstacles implied by intellectual property patents:

- Active ingredient
  - e.g. patented polymorphs (different crystal structures)
- Dosage form type (e.g. immediate release tablet)
  - e.g. patented excipients, formulation content

Making the same product, but different way…



Lecture

Outline

Generic vs. Innovator drugs

Bioequivalence

IVIVC

Bioequivalence

Equal performance of generic vs. innovator drug

= bioequivalence

= equal bioavailability

Two products or formulations containing the same active ingredient are bioequivalent if their rates and extents of absorption **(bioavalabilities)** are the same (within predefined limits).

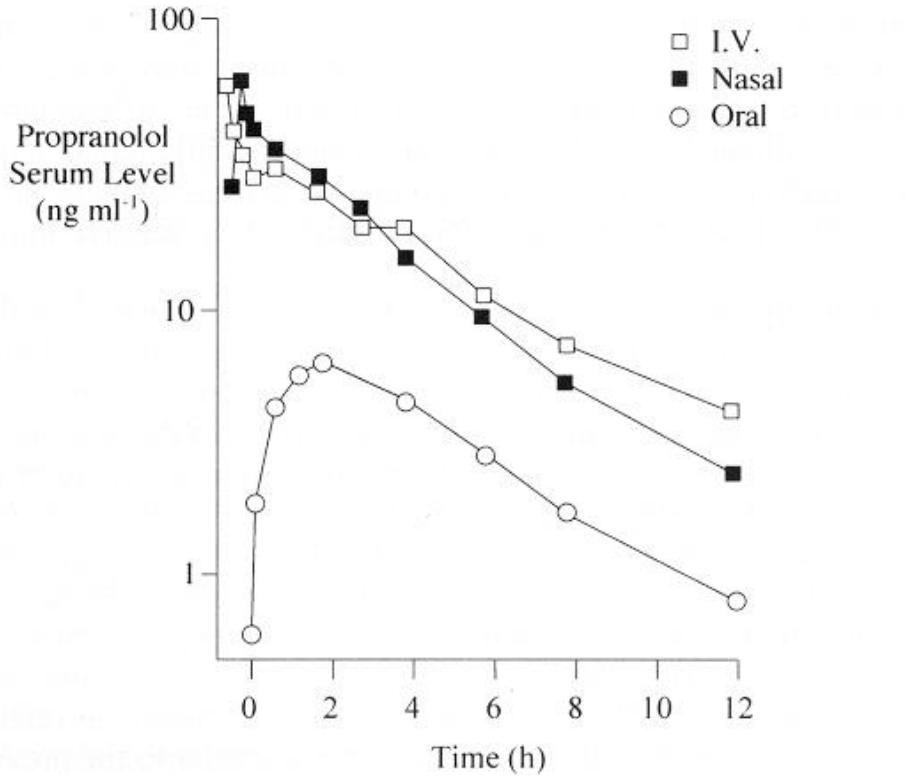
Bioequivalence may be demonstrated through in vivo or in vitro test methods, comparative clinical trials, or pharmacodynamic studies.

Bioequivalence

Bioavailability

Absolute bioavailability

$$F = \frac{AUC_{oral}}{AUC_{iv}} \times \frac{DOSE_{iv}}{DOSE_{oral}}$$

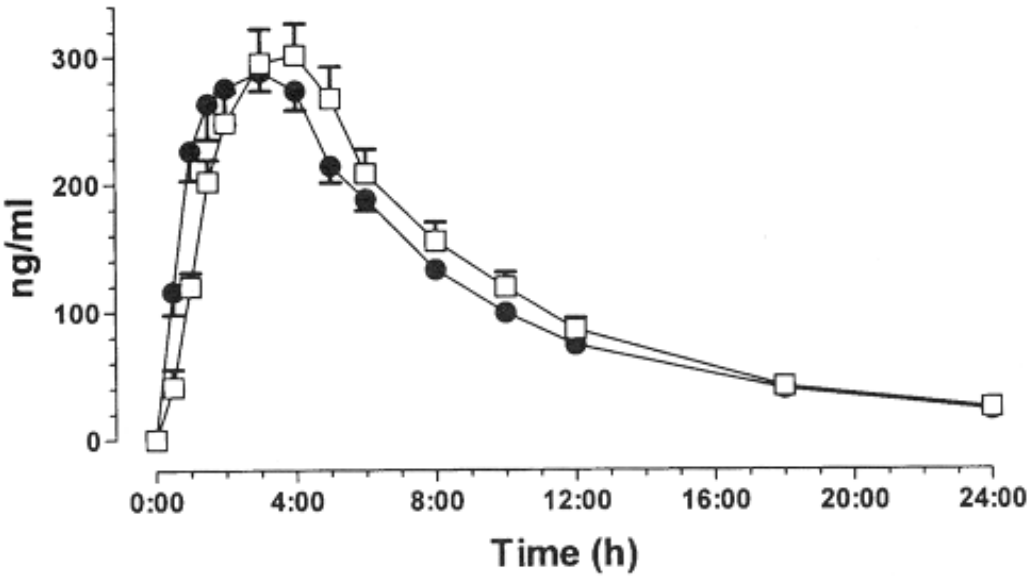


Bioequivalence

Bioavailability

Relative bioavailability

$$F_{rel} = \frac{AUC_{formA}}{AUC_{formB}}$$



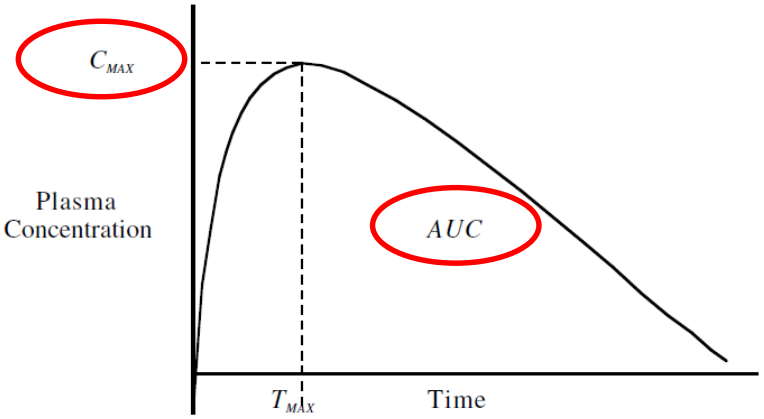
Identical bioavailability = bioequivalence

Bioequivalence

In vivo studies

Investigated parameters:

- $AUC_{0\text{-}t}$
- C_{MAX}



Acceptance criteria:

- 80-125%* range for 90% confidence interval of test/reference product

DOES NOT MEAN THAT:

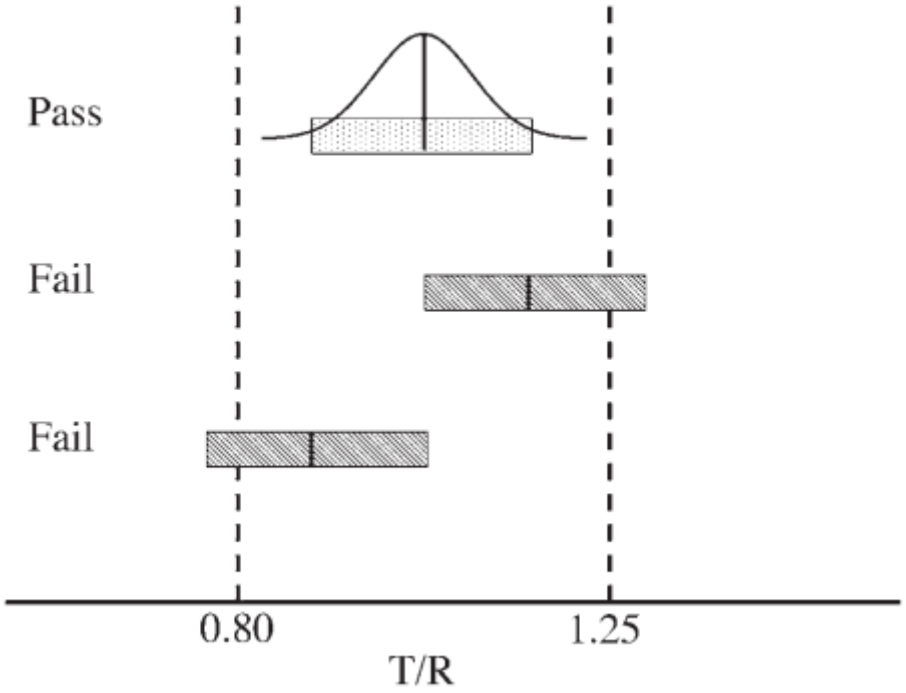
"GENERIC CAN BE ±20% DIFFERENT FROM THE ORIGINAL"

*in specific cases, more narrow (90-111%) or wider (75-133%) intervals are acceptable

Bioequivalence

In vivo studies

90% confidence interval has to fit the 80-125% interval

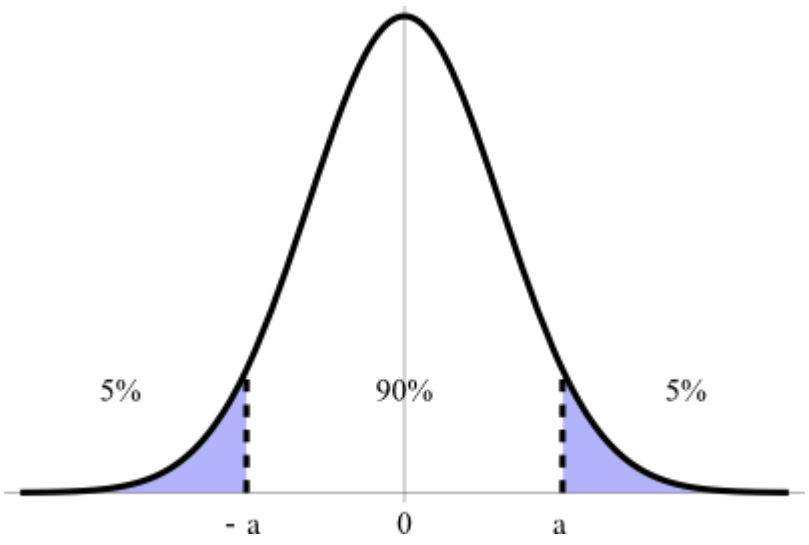


Bioequivalence

In vivo studies

What is the 90% confidence interval???

If the BE study was repeated 100 times - 90 times the population value (mean C_{max} or AUC) would fall inside this interval, and 10 times outside (biological variability).



Bioequivalence

In vivo studies

In practice (data from 2070 BE studies):

- the generic/innovator ratios were **1.00 ± 0.06 for C_{max}** and **1.00 ± 0.04 for AUC** (mean ± SD)
- the average difference in C_{max} and AUC between generic and innovator products was **4.35%** and **3.56%**, respectively
- in nearly 98% of the BE studies, the generic product AUC differed from that of the innovator product by less than 10%

Davit et al., Ann. Pharmacother. 2009, *Comparing Generic and Innovator Drugs: A Review of 12 Years of Bioequivalence Data from the United States Food and Drug Administration.*

Bioequivalence

In vivo studies

EMA Guideline on the Investigation of Bioequivalence, 2010

STUDY DESIGN :

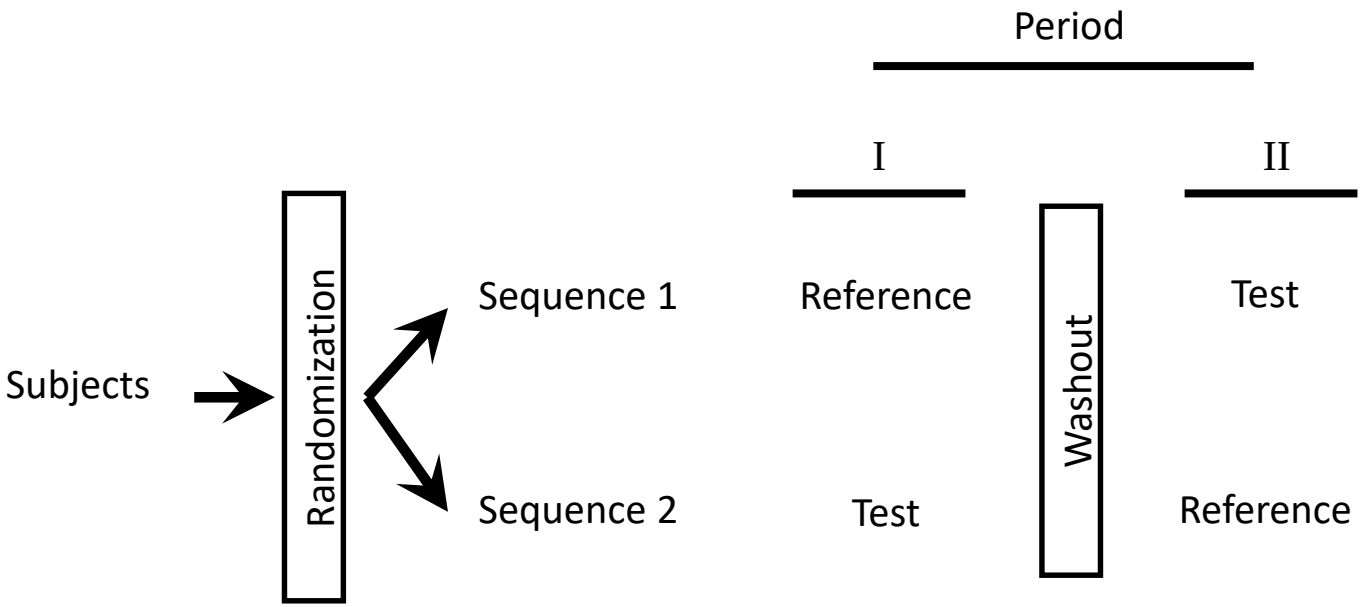
- standard design: randomized, two-period, two-sequence, single dose cross-over design
- alternative designs: parallel design (substances with very long half-lives) and replicate designs (in case of highly variable drugs or drug products)

Bioequivalence

In vivo studies

Standard 2×2 Crossover design

- standard design: randomized, two-period, two-sequence, single dose, cross-over design

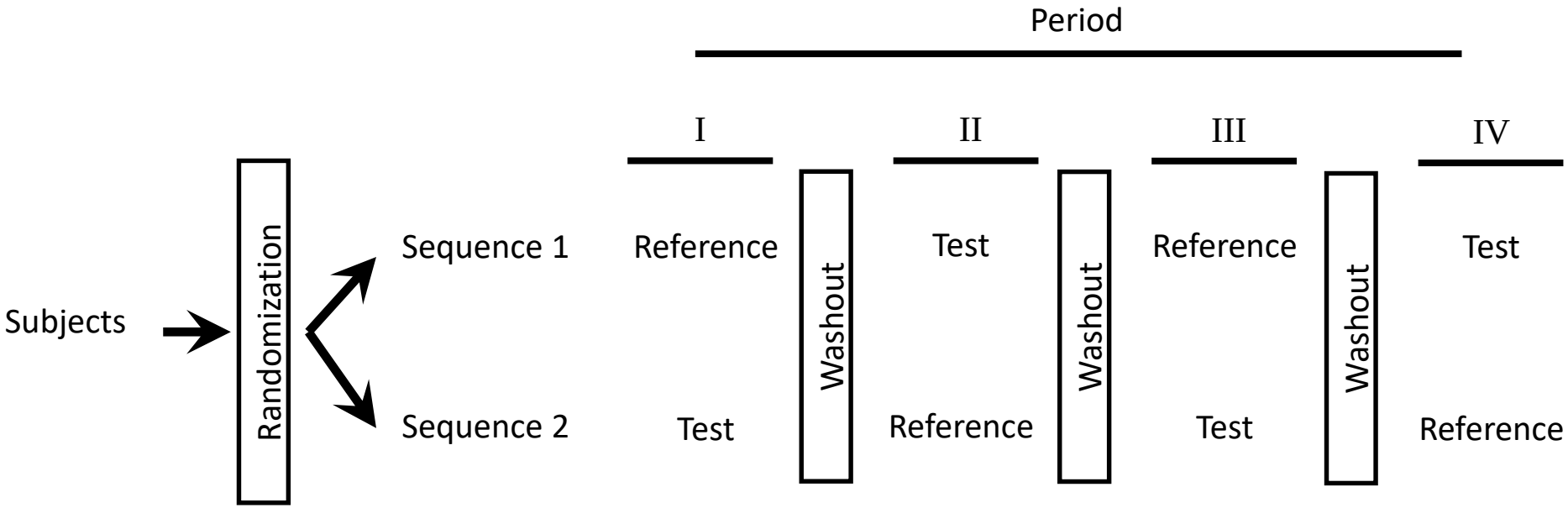


Bioequivalence

In vivo studies

Replicate design

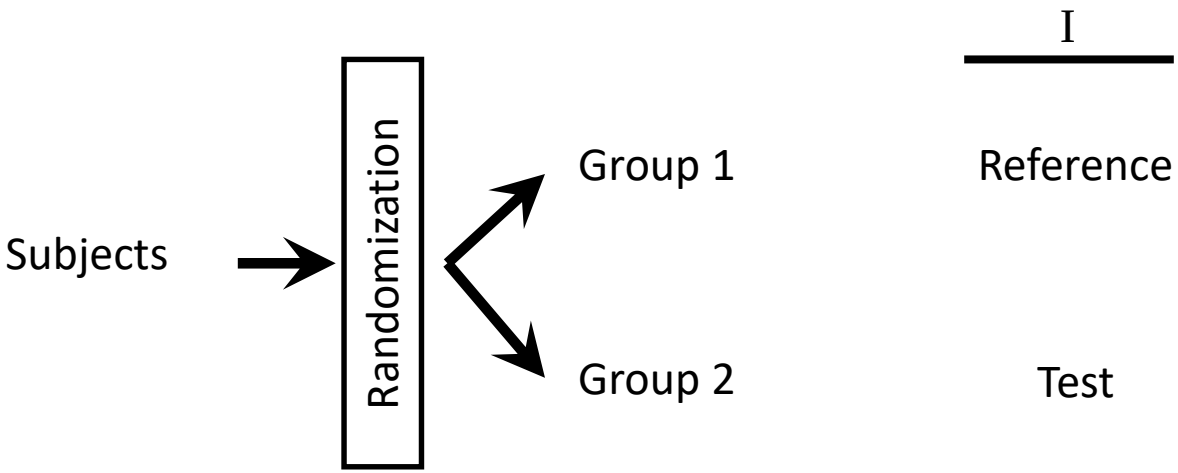
- randomized, **four**-period, two-sequence, single dose, cross-over design (highly variable drugs or drug products)



Bioequivalence

In vivo studies

Parallel design
(substances with very long half-lives)



Bioequivalence

In vivo studies

EMA Guideline on the Investigation of Bioequivalence, 2010

STUDY SUBJECTS:

- **≥ 12 subjects**
  - more subjects = better homogeneity, “more accurate result”
- healthy volunteers to reduce variability (patients, e.g. for chemotherapy)
- strict inclusion/exclusion criteria,
- subjects could belong to either sex,
- preferably non-smokers and without a history of alcohol or drug abuse

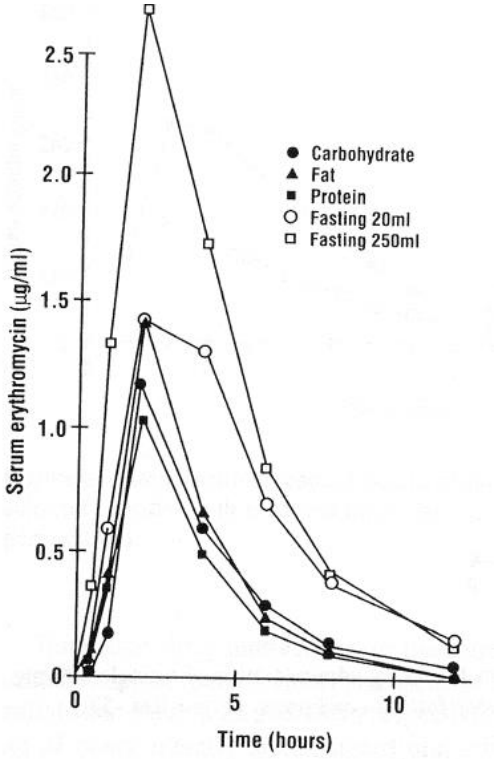
Bioequivalence

In vivo studies

EMA Guideline on the Investigation of Bioequivalence, 2010

SAMPLING TIMES

- frequent sampling around the predicted t_{max}
- C_{max} should not be the first point of the concentration-time curve

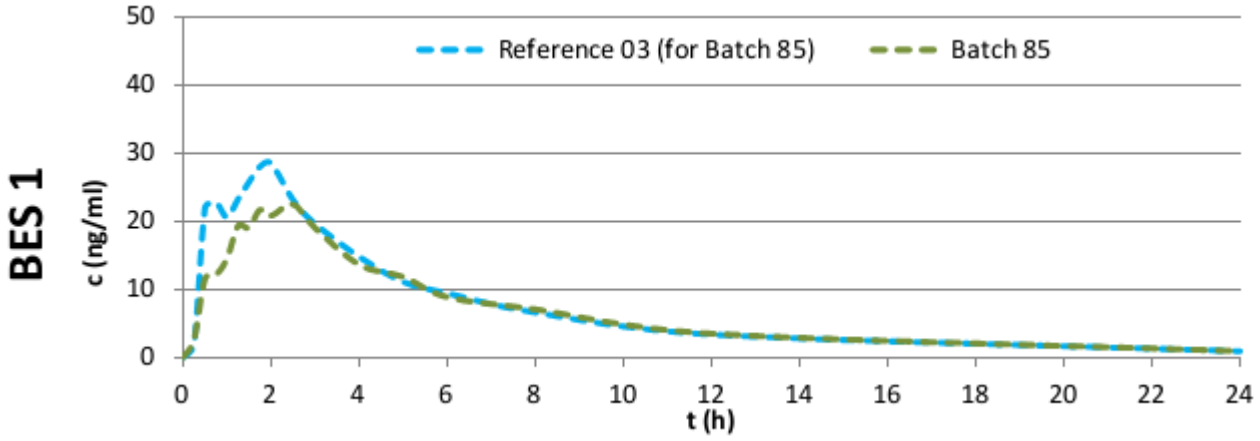


INAPPROPRIATE STUDY DESIGN IS ONE OF THE MOST COMMON CAUSES OF FAILURE

personal communication, Helmut Schutz

Bioequivalence

In vivo studies



BES 1, pilot

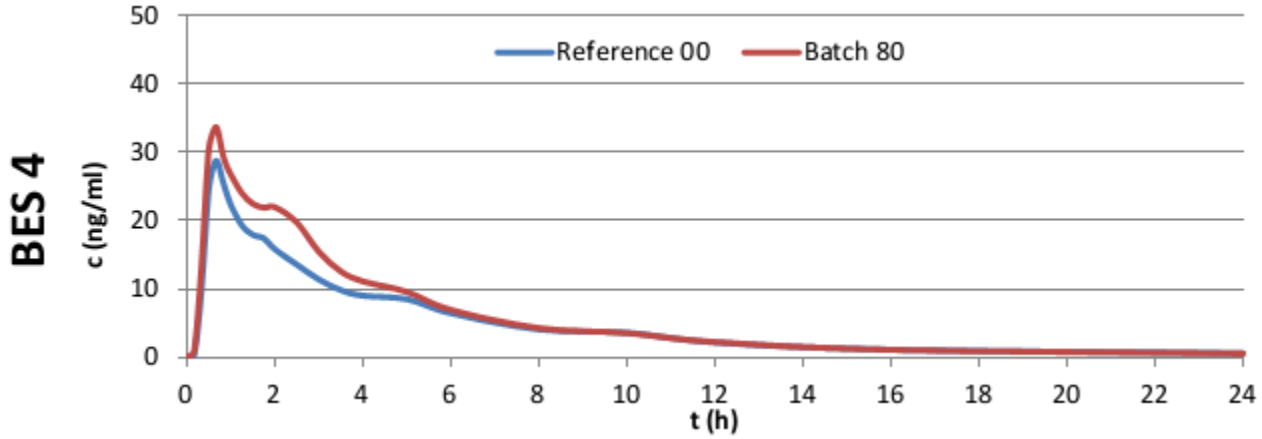
Batch 85 and Reference 03; n = 24;

acceptance criteria: 80-125 % range for 90 % CI

	Mean (CV%) - Test	Mean (CV%) - Reference	Test/Reference 90 % CI	Lower 90 % CI	Upper 90 % CI
C_{max} (ng/ml)	33.6 (71.5)	41.6 (48.1)	75.2	63.8	88.6
AUC_{0-t} (ng/ml*h)	160.8 (59.5)	175.2 (51.8)	91.4	82.3	101.5
AUC_{0-inf} (ng/ml*h)	165.7 (58.1)	179.4 (50.3)	91.8	82.9	101.6
T_{max} (h)	2.0 (56.1)	1.5 (67.6)			
$T^{1/2}$ (h)	6.8 (34.8)	7.2 (47.8)			

Bioequivalence

In vivo studies



BES 4

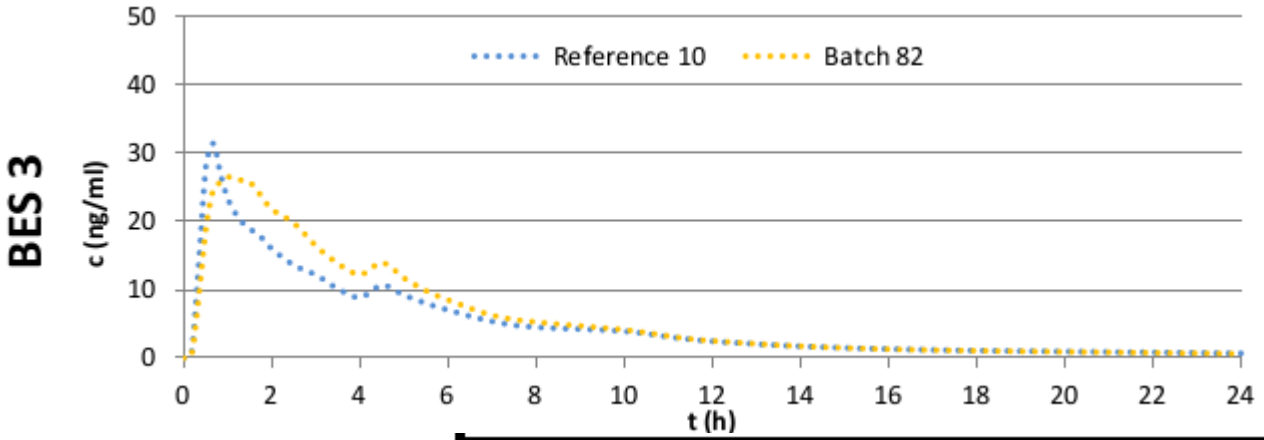
Batch 80 and Reference 00, n = 81;

acceptance criteria: 80-125 % range for 90 % CI

	Mean (CV%) - Test	Mean (CV%) - Reference	Test/Reference 90 % CI	Lower 90 % CI	Upper 90 % CI
C_{max} (ng/ml)	46.0 (62.4)	37.6 (49.8)	115.6	105.1	127.2
AUC_{0-t} (ng/ml*h)	137.2 (62.4)	117.7 (57.0)	114.0	109.5	118.8
AUC_{0-inf} (ng/ml*h)	142.3 (64.3)	123.1 (57.2)	112.9	108.5	117.5
T_{max} (h)	0.7	0.7			
$T^{1/2}$ (h)	9.45 (28.5)	9.8 (22.7)			
K_{el} (h^{-1})	$7.9*10^{-2}$ (31.7)	$7.5*10^{-2}$ (26.5)			

Bioequivalence

In vivo studies



BES 3

Batch 82 and Reference 10, n = 102;

acceptance criteria: 80-125 % range for 90 % CI

	Mean (CV%) - Test	Mean (CV%) - Reference	Test/Reference 90 % CI	Lower 90 % CI	Upper 90 % CI
C_{max} (ng/ml)	42.4 (57.7)	39.0 (62.1)	110.1	100.2	121.0
AUC_{0-t} (ng/ml*h)	153.1 (51.2)	134.8 (54.5)	114.6	110.1	119.3
AUC_{0-inf} (ng/ml*h)	155.5 (52.2)	138.0 (54.2)	113.5	109.1	118.0
T_{max} (h)	1.4 (74.4)	0.9 (83.6)			
$T^{1/2}$ (h)	13.0 (24.5)	14.3 (41.6)			
K_{el} (h^{-1})	$5.3*10^{-2}$ (21.2)	$5.3*10^{-2}$ (26.6)			

Lecture

Outline

Generic vs. Innovator drugs

Bioequivalence

IVIVC

IVIVC

In vitro-in vivo correlations

FDA definition: “a predictive mathematical model describing the relationship between an in-vitro property *(dissolution)* of a dosage form and an in-vivo response *(PK curve)*”

Purpose: to utilize *in vitro* dissolution profiles as a surrogate for *in vivo* bioequivalence

Application:

- supporting biowaivers (approval without *in vivo* BE)
- Scale-Up and Post-Approval Changes (SUPAC) and line extensions (e.g., different dosage strengths)
- support of dissolution methods

Bioequivalence

During development

Scale-Up and Post-Approval Changes (SUPAC)

1) Components or composition
2) Manufacturing site
3) Scale-up (increasing production)
4) Manufacturing (process or equipment)

Effect on quality and performance:
LEVEL1 – UNLIKELY any detectable effect
LEVEL2 – COULD HAVE significant effect
LEVEL3 – LIKELY to have significant effect

Bioequivalence

SUPAC

Example 1:

Changing a coloring agent in IR tablet

Type of change: **Components or composition**

LEVEL: **1**

BE required: **NO**

Example 2:

Changing direct compression to wet granulation:

Type of change: **Manufacturing process**

LEVEL: **3**

BE required: **YES**

IVIVC

submission examples

14 examples from FDA database:

- Change in dissolution method and specifications
- Level 3 site manufacturing change
- Waiver for lower strengths
- Waiver for higher strengths
- To support dissolution method
- Batch-to-batch variation in the particle size, coating weight, process changes, test product composition do not impact the BE
- Change in dissolution specifications
- Change in dissolution specifications
- Challenge the results of a failed BE study
- Batch-to-batch variation in pellet coating does not impact the BE
- Change in dissolution specifications
- Exploratory to guide the development of pivotal formulation

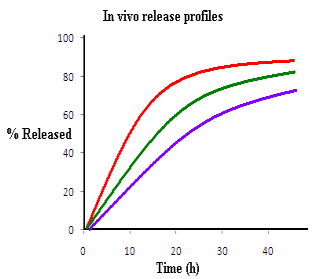
Kaur et al., The AAPS Journal. 2015, Applications of *In Vitro–In Vivo* Correlations in Generic Drug Development: Case Studies.

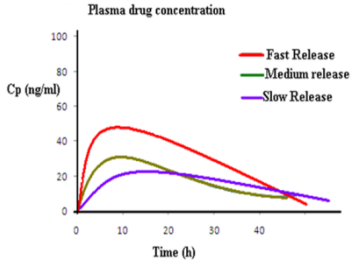
IVIVC

Procedure

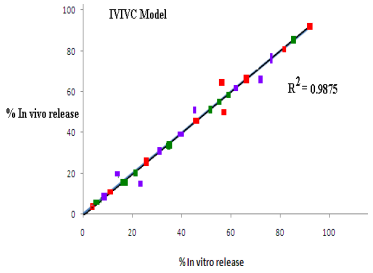
Description/procedure:

1) **Obtaining dissolution (in vitro) and PK (in vivo) data for "input" formulations**





2) **Building a mathematical IVIVC model using the "input" formulations**



3) **Testing the predicition power of the established model**

IVIVC

Division

LEVEL A

- highest level of correlation.
- point to point relationship between *in vitro* dissolution rate and *in vivo* input rate

LEVEL B

- mean absorption time is plotted against mean dissolution time for ≥ 3 formulations

LEVEL C

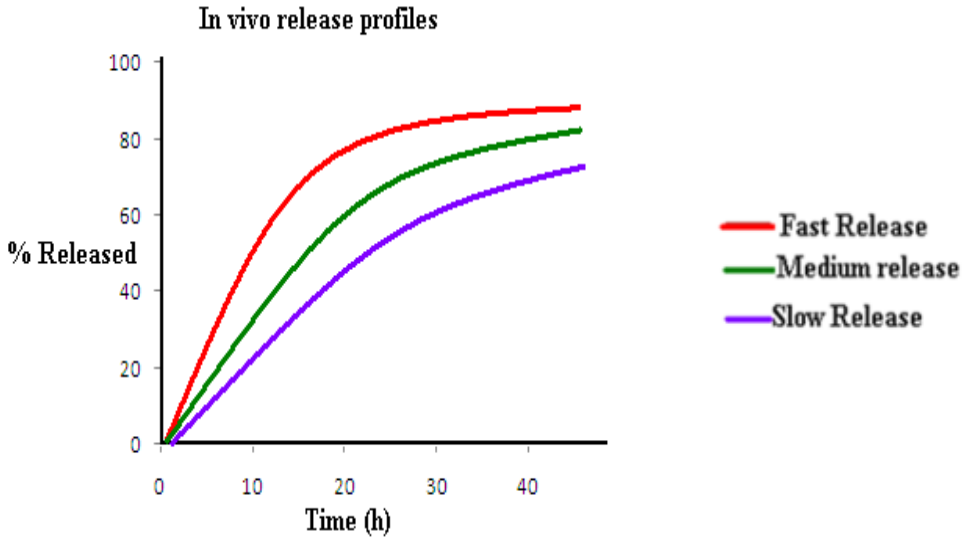
- single point correlation for ≥ 3 formulations
- % drug dissolved in X min vs. AUC or Cmax or Tmax

IVIVC

1) Obtaining dissolution (in vitro) and PK (in vivo) data for “input” formulations

Dissolution data

- Idealy 3 formulations with different release rates
- any in vitro dissolution method can be utilized
  (the preferred dissolution apparatus is USP apparatus I or II)
- the same for all formulations tested
- an aqueous medium either water or buffered solutions not exceeding pH 6.8 is recommended



IVIVC

1) Obtaining dissolution (in vitro) and PK (in vivo) data for “input” formulations

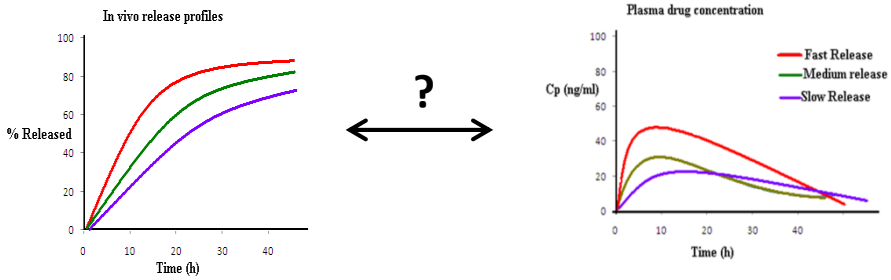
PK data

- > 6 subjects
- Crossover design preferred
- 3 formulations + inclusion of a reference treatment is advised:
  - **IV solution**
  - Oral solution
  - Immediate release product

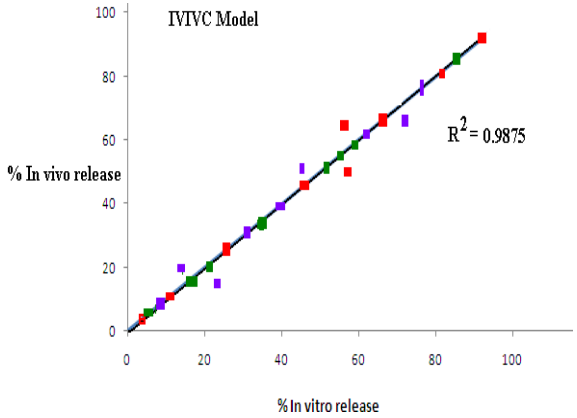
IVIVC

2) Building a mathematical IVIVC model using the “input” formulations

a) Making the PK and dissolution data “comparable”



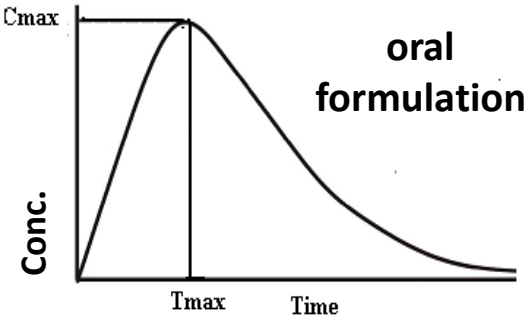
b) Correlating the mathematically processed PK and dissolution curves



IVIVC

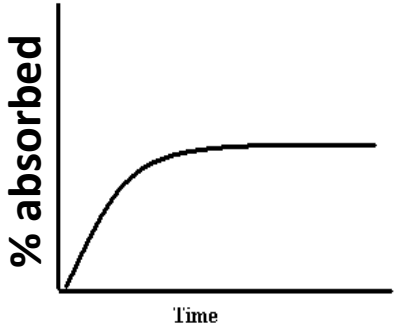
2) Building a mathematical IVIVC model using the “input” formulations

a) Making the PK and dissolution data “comparable”



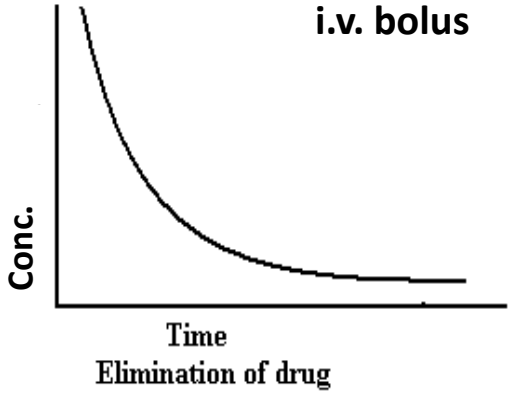
deconvolution

convolution

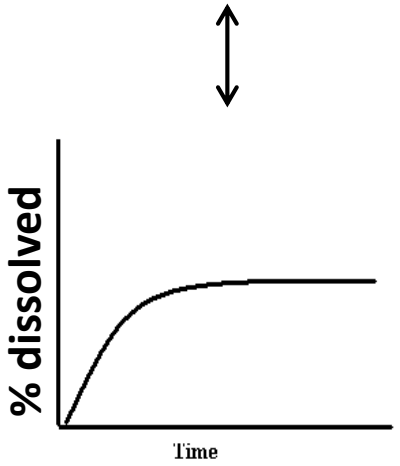


Absorption + elimination

Absorption



Elimination



IVIVC

2) Building a mathematical IVIVC model using the “input” formulations

a) Making the PK and dissolution data “comparable”

Deconvolution - calculating the fraction absorbed from PK curve

Wagner-Nelson method

One compartmental method

Loo-Riegelman method

Multi-compartmental method

Numerical deconvolution

Model independent method

Commercial software (e.g. Gastroplus)

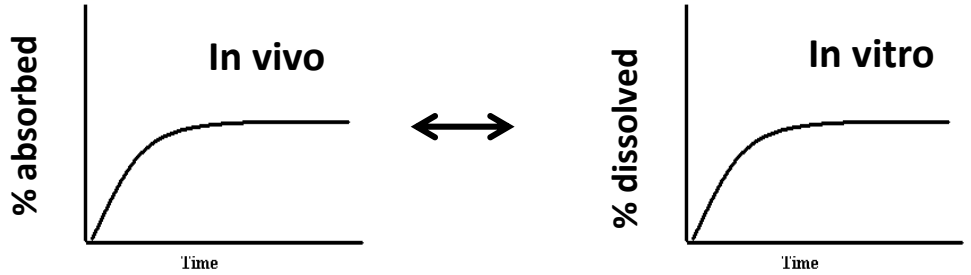
Convolution - calculating the PK curve from fraction absorbed/dissolved

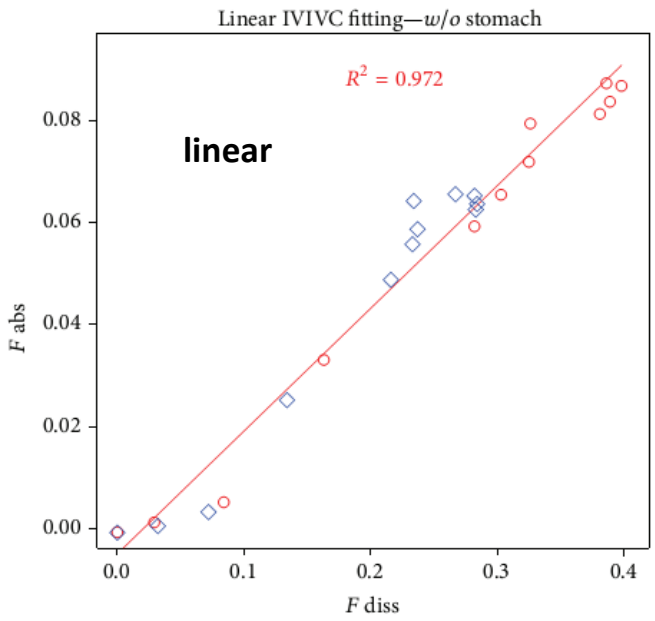
Weibull function

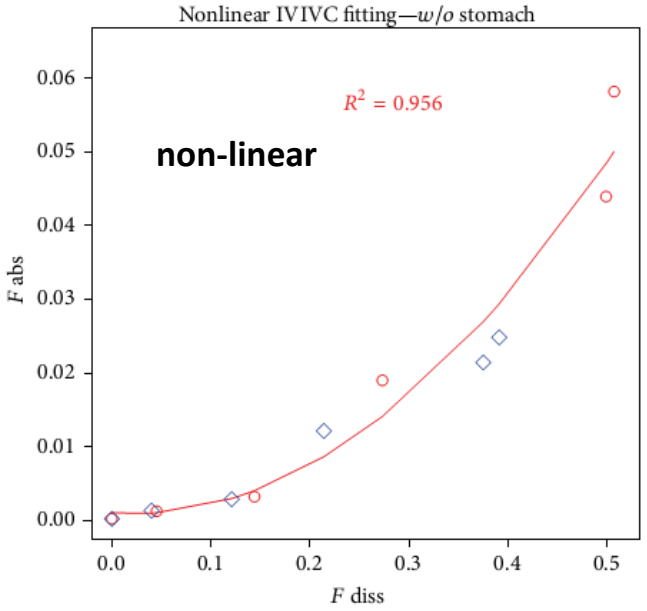
IVIVC

2) Building a mathematical IVIVC model using the “input” formulations

b) Correlation of PK and dissolution data



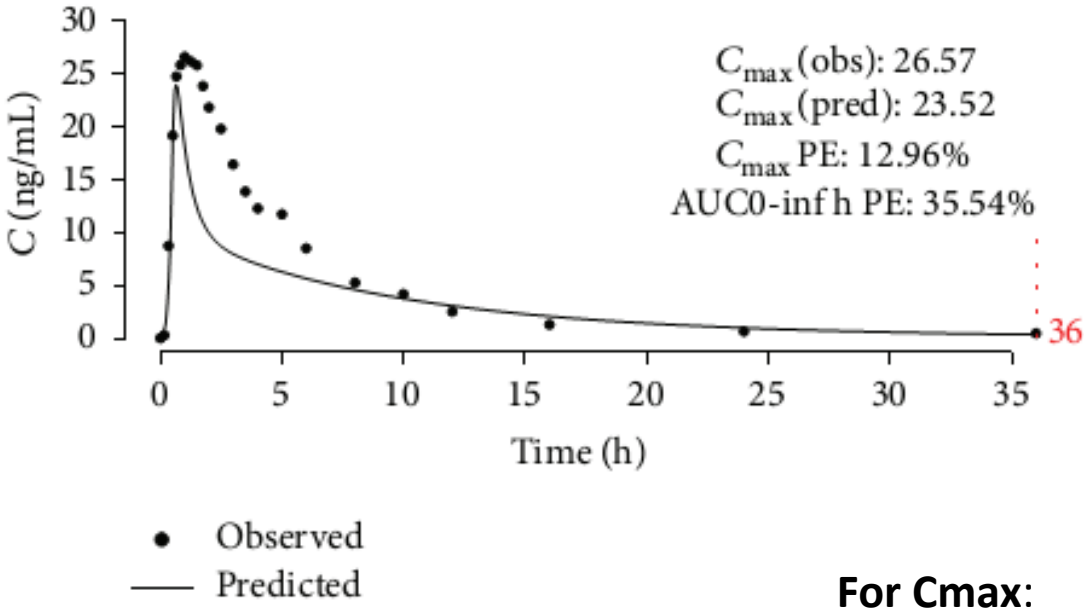




IVIVC

3) Testing the prediction power of the established model

Prediction of C_{max} and AUC from dissolution data using the established model. Comparing the predicted vs. real PK data



For Cmax:

$$\%\ \text{Prediction error (P.E.)} = \frac{(\text{C max observed-Cmax predicted})}{\text{Cmax observed}} \times 100$$

For AUC:

$$\%\ \text{Prediction error (P.E.)} = \frac{(\text{AUC observed} - \text{AUC predicted})}{\text{AUC observed}} \times 100$$

IVIVC

3) Testing the prediction power of the established model

Prediction of C_{max} and AUC from dissolution data using the established model. Comparing the predicted vs. real PK data

Acceptance criteria: According to FDA guidance

- ≤ 15% for absolute prediction error (%P.E.) of each formulation.
- ≤ 10% for mean absolute prediction error (%P.E.)

IVIVC

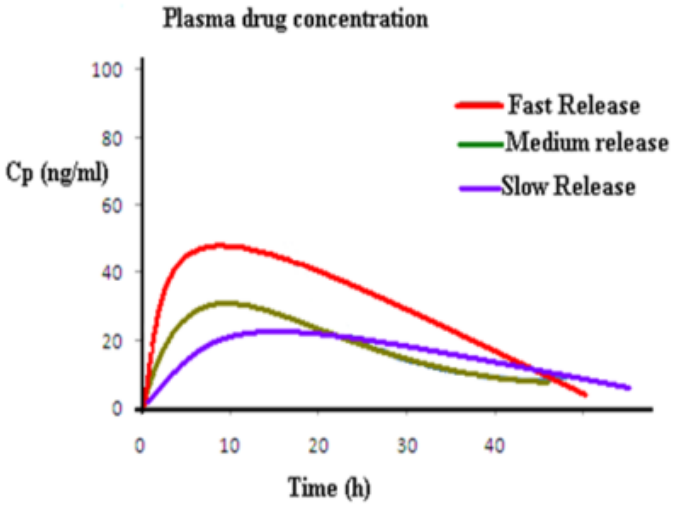
3) Testing the prediction power of the established model

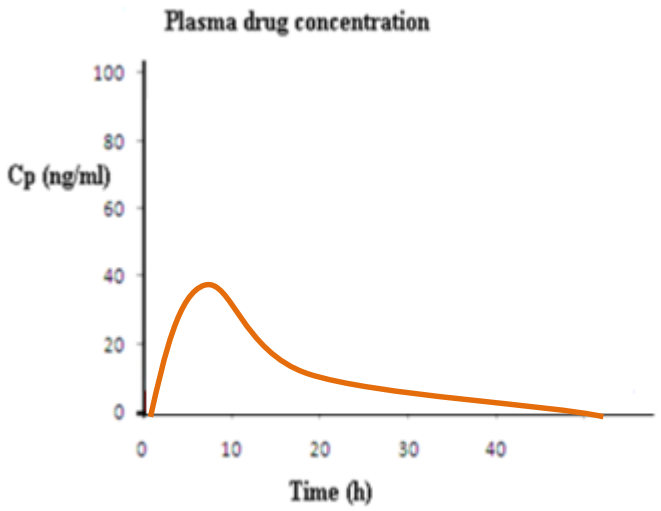
Internal predictability

- 2-3 different formulations used for model building
- identical mathematical processing

External predictability

- 1 formulation not used for model building
- identical mathematical processing





IVIVC

Additional considerations – BCS classification

Class	Solubility	Permeability	Absorption rate control step	IVIVC
I	High	High	Gastric emptying time	Correlation (if dissolution is slower than GET)
II	Low	High	Dissolution	Correlation
III	High	Low	Permeability	Little or no correlation
IV	Low	Low	Case by case	Little or no correlation

IVIVC

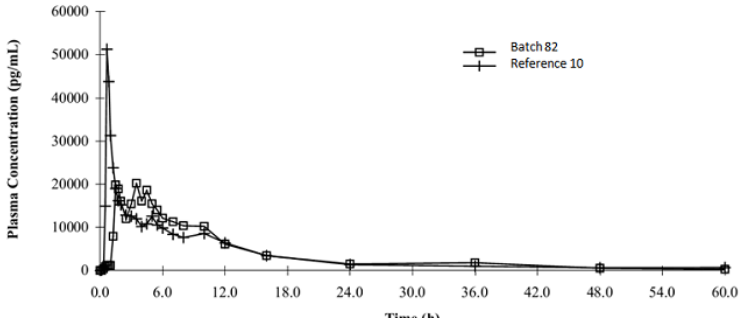
Additional considerations – possible issues

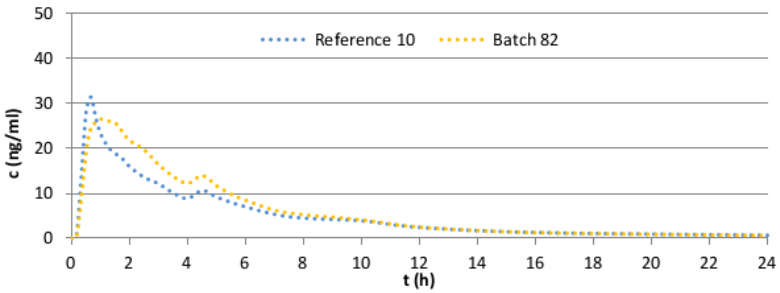
Dissolution

- inaccurate *in vitro* dissolution data
- complex *in vivo* dissolution processes (precipitation, API binding, poorly identified release mechanisms/kinetics)

Pharmacokinetics

- absorption rate limitations
- non-linear elimination or elimination kinetics
- enterohepatic recycling or second peak
- inter-individual variability





Thank you for attention!