

IVIVC – Methods and Applications in MR Product Development

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Purpose of IVIVC and BCS

- Reduction of regulatory burden: IVIVC in lieu of additional *in vivo* experiments, leading to
- Time/Cost savings during product development
 - Scale-up, post approval changes
 - Biowaiver
- Enhanced significance of *in vitro* testing
- Justification for “therapeutic” product quality
 - therapeutically meaningful release specifications
- (Less testing in humans)

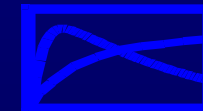
Outline

- Definitions (IVIVC, BCS)
- Mathematical Procedure
- Applications

In Vitro-In Vivo Correlation (IVIVC)

Working Definition:

A predictive mathematical treatment describing the relationship between an *in vitro* property of a dosage form (usually the rate or extent of drug release) and a relevant *in vivo* response (e.g. plasma drug concentrations or amount of drug absorbed).



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Categories of *In Vitro-In Vivo* Correlations

- Level A functional relationship between *in vitro* dissolution and the *in vivo* input rate, correlation of profiles, linear or non-linear relationship
- Level B correlation based on statistical moment analysis (*in vitro* dissolution time is correlated with mean residence time)
- Level C single point relationship between one dissolution parameter, (e.g. T50%, % dissolved in 4h) and one pharmacokinetic parameter (e.g. AUC, C_{\max})
(Level D: multiple point relationship)

Biopharmaceutics Classification System

Class	Solubility	Permeability	IVIVC Expectations
1	High	High	IVIVC possible if dissolution rate (DR) is slower than gastric emptying rate. Otherwise limited or no IVIVC.
2	Low	High	IVIVC expected if <i>in vitro</i> DR is similar to <i>in vivo</i> DR.
3	High	Low	Absorption (permeability) is rate determining, therefore limited IVIVC with DR to be expected.
4	Low	Low	Limited or no IVIVC expected.

BCS Criteria

- highly soluble drugs:
therapeutic dose is soluble in 250 mL (pH 1 – 7.5)
- highly permeable drugs:
extent of absorption: > 90%
 $P_{\text{eff, pH6.5}}$: > 2×10^{-4} cm/sec in human jejunum
 P_{app} : > 1×10^{-5} cm/sec in Caco-2 cells
- (rapidly dissolving: no less than 85% within 30 min,
USP II / 50 rpm /pH 1 - 6.8 ; always considered
similar if 85% released in less than 15 min)

The IVIVC methodology is described in
Guidances (as opposed to Guidelines)
and addresses

- *which product change* can be filed with an IVIVC
- *the quality of the raw data* which are needed for the generation of an IVIVC
- *how* the IVIVC model can/should be developed
- *the acceptable prediction error* when applying the IVIVC (validation criteria)

Drug or Product Requirements for an IVIVC

Does a correlation make medical or scientific sense?

- Caution, if narrow therapeutic range
- Linear pharmacokinetics
- Preferably BCS I or II

Data Requirements

In vitro data

- data from batches tested in vivo
- compendial method (justify other method)
- aqueous medium, $n \geq 12$ (!), $CV < 10\%$
- profiles of test products of the same type curve
- (difference factor f1, similarity factor f2)

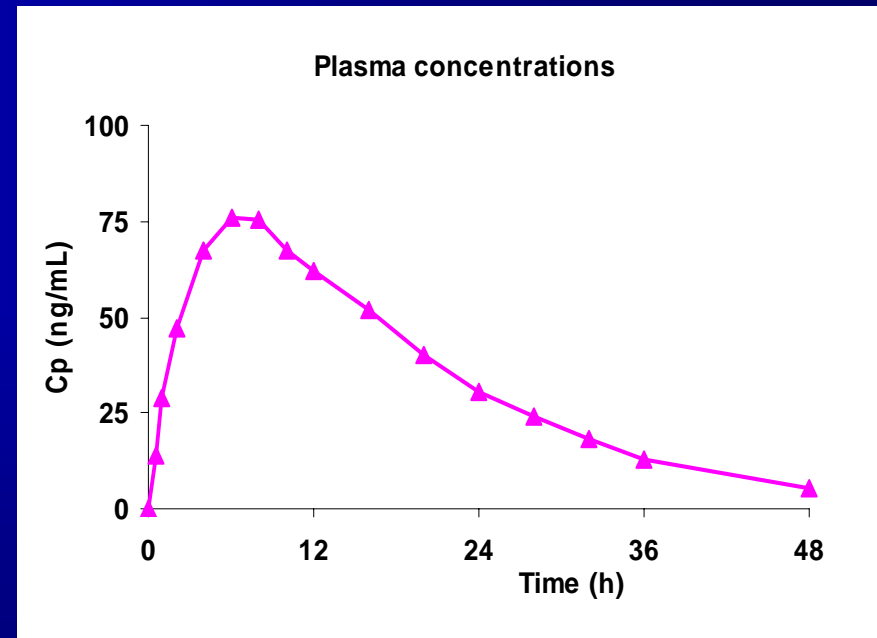
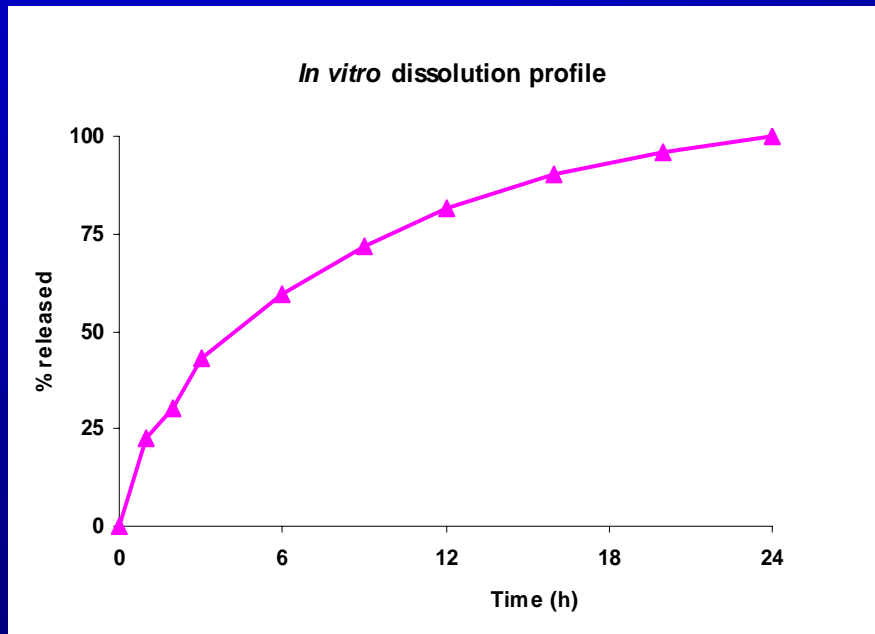
Data Requirements

In vivo data

- data from study in humans, $n \geq 6$, fasted
- cross-over design
- formulations with different release rates
- reference formulation (solution, i.v. bolus)
- same moiety as measured in vitro
- (biobatch)

Starting point:

In Vitro and *In Vivo* Data



Level A Correlation

It is not possible to directly correlate an *in vitro* dissolution curve with an *in vivo* plasma concentration profile.

Therefore,

- **Two-step procedure:**
 1. Retrospective calculation of *in vivo* dissolution from *in vivo* response (plasma concentrations)
 2. Quantitative correlation between *in vitro* and *in vivo* release profiles

Mathematical Techniques

Assessment of *in vivo* drug release or absorption from plasma profiles:

- Model-dependant

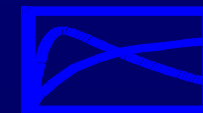
based on the mass balance among the pharmacokinetic compartments

(e.g. Wagner-Nelson, Loo-Riegelman)

- Model-independant

based on *Theory of Linear System Analysis*

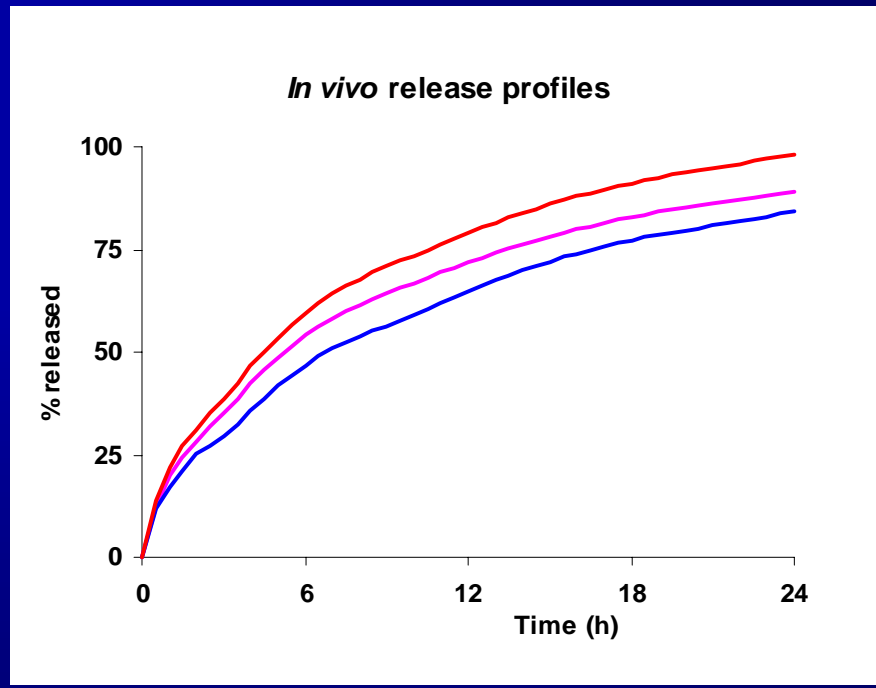
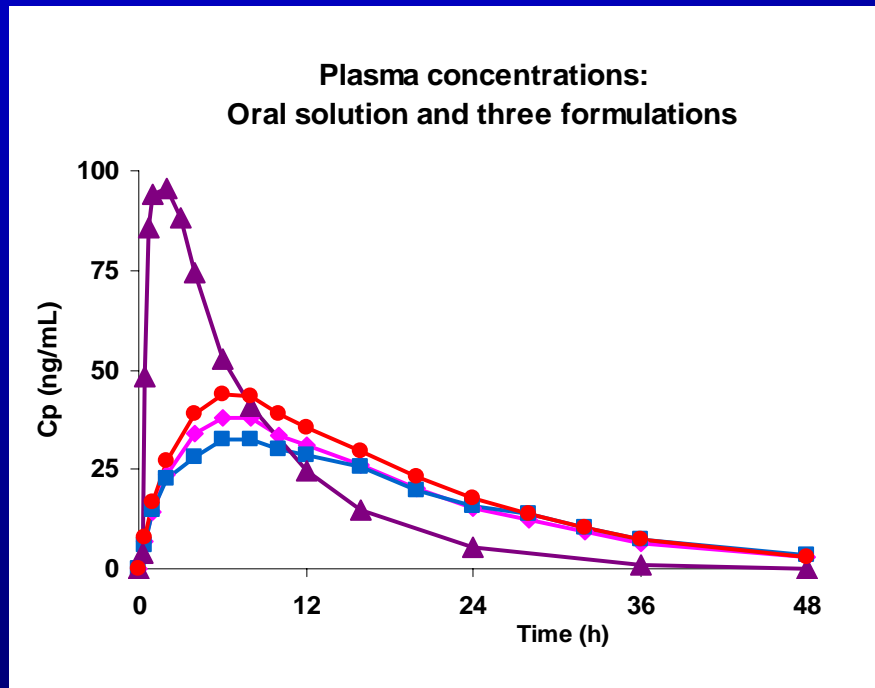
(Convolution / Deconvolution)



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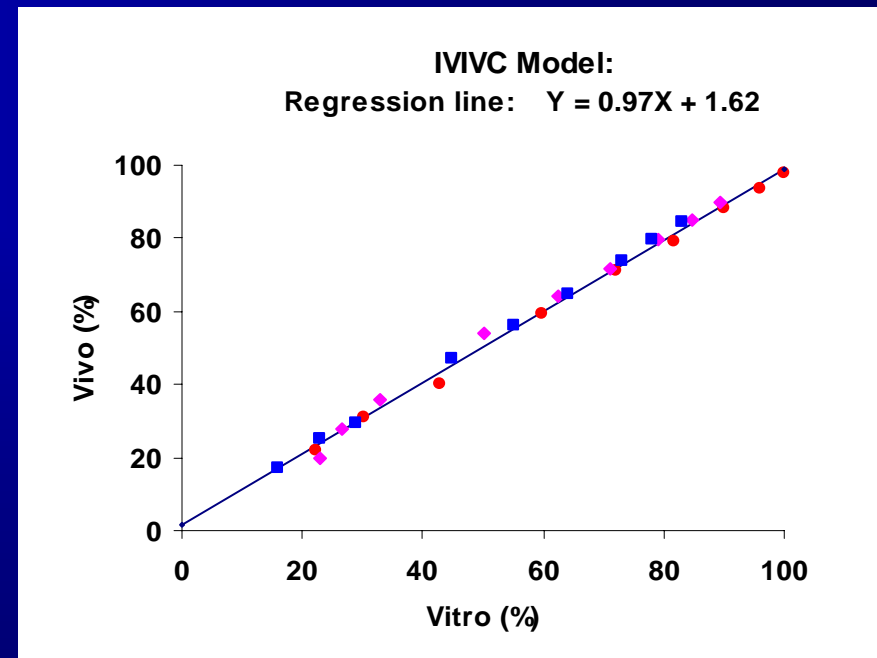
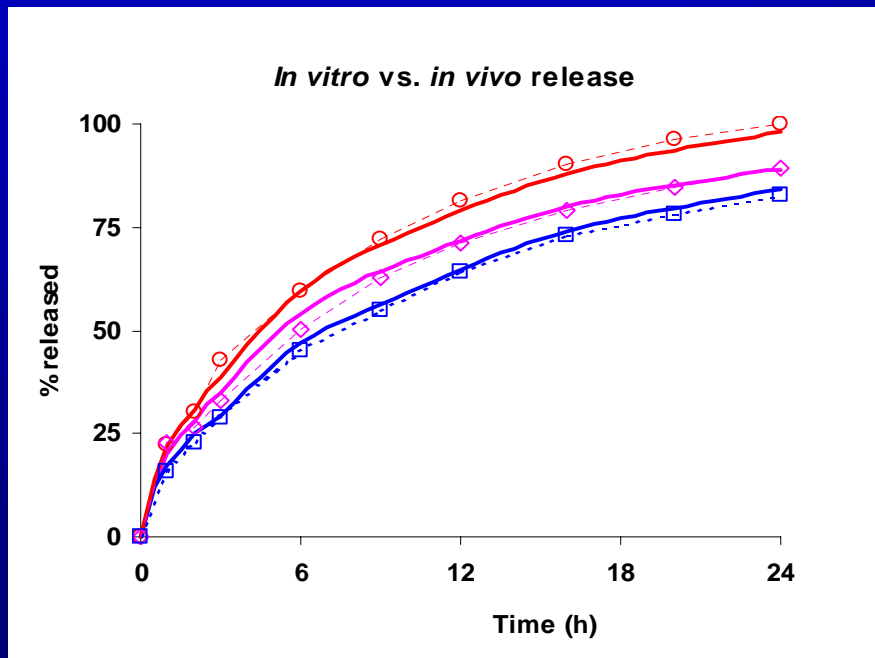
First step:

Calculation of *in vivo* release profiles from plasma concentrations of an oral solution and different formulations



Second step:

Comparison of calculated *in vivo* release with *in vitro* release data for the same formulations and establishment of a quantitative correlation model using a linear or non-linear regression



Evaluation of Predictability of IVIVC

Estimation of the magnitude of the error in predicting the bioavailability from *in vitro* dissolution data

Different approaches are acceptable:

- Internal predictability (with the formulations used for the development of IVIVC)
- External predictability (with the formulations not used for the development of IVIVC)

Metrics to Evaluate Predictability of IVIVC

Percent prediction error (%PE):

$$\text{For } C_{\max}: \quad \{ [C_{\max(\text{obs})} - C_{\max(\text{pred})}] / C_{\max(\text{obs})} \} * 100$$

$$\text{For AUC:} \quad \{ [AUC_{(\text{obs})} - AUC_{(\text{pred})}] / AUC_{(\text{obs})} \} * 100$$

Acceptance Criteria:

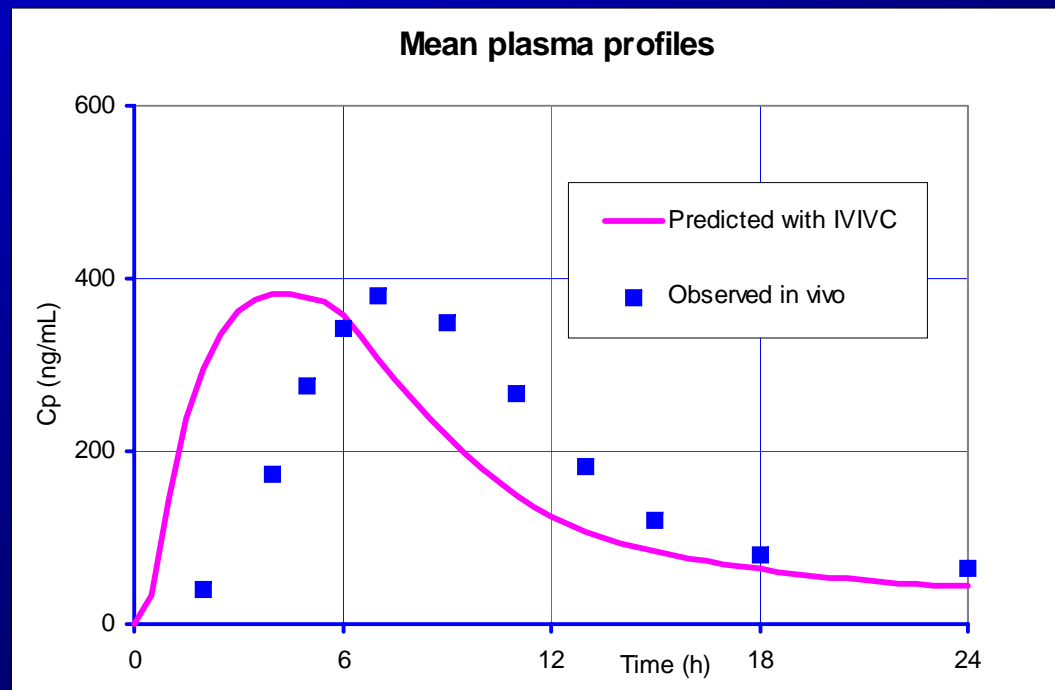
- $\leq 15\%$ for absolute prediction error (%PE) of each formulation
- $\leq 10\%$ for mean absolute prediction error (%PE)

Limitation of the Predictability Metrics

- Metrics used to evaluate the predictability is described simply as the prediction error (%PE) for C_{\max} and AUC, i.e. predicted plasma profiles are reduced to only two PK parameters
- C_{\max} predicted with the IVIVC model represents the maximum of the mean plasma profile - but is compared with the mean C_{\max} observed calculated as the average of individual profiles (at different T_{\max} !)
- T_{\max} is not included in predictability metrics

Weakness of the Predictability Metrics

C_{\max} predicted \sim C_{\max} observed, but T_{\max} different



Main Applications of the IVIVC in Product Development

- Evidence for biorelevant and/or discriminating dissolution method
- Basis for biorelevant *in vitro* release specifications
- Justification for a biowaiver
 - Wider than standard ($\pm 10\%$) *in vitro* release specifications
 - Level 3 or Type II modification of the registered product
 - Line extensions (intermediate or lower strength)

Benefit from an IVIVC for the Registration of *New* Products

- Modified release products: justification of release specifications
- Justification for discriminating in vitro test method
- Modifications made during Scale-up (basis for biowaiver)
- Line extensions (e.g. intermediate strength)
- (Anticipation of later product changes)

Registration of *Changes for Existing Products* where a Robust IVIVC can Substitute a Bioequivalence Study

- Level 3 Changes (U.S.) [SUPAC]
- Type II Variations (European Union)
- (Line extensions (bracketing principle))
- Exceptions exist, e.g. narrow therapeutic range drugs, nonlinear pharmacokinetics, etc.

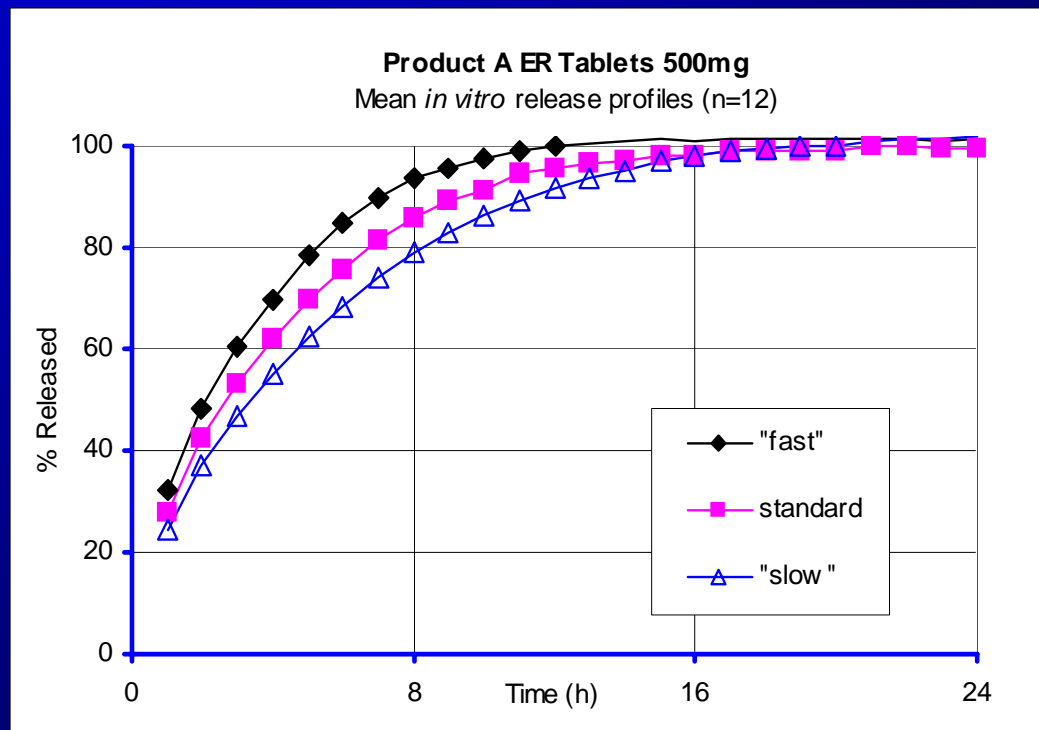
Specification Setting for Modified Release Products (EMEA)

- Three points (20-30%, around 50%, more than 80%)
- Specifications must be met during shelf-life of product
- No IVIVC: Justify that side-batches are bioequivalent
difference upper / lower limit: up to 20%
- IVIVC established: Predicted profiles from upper and lower release limits are in 20% range of AUC

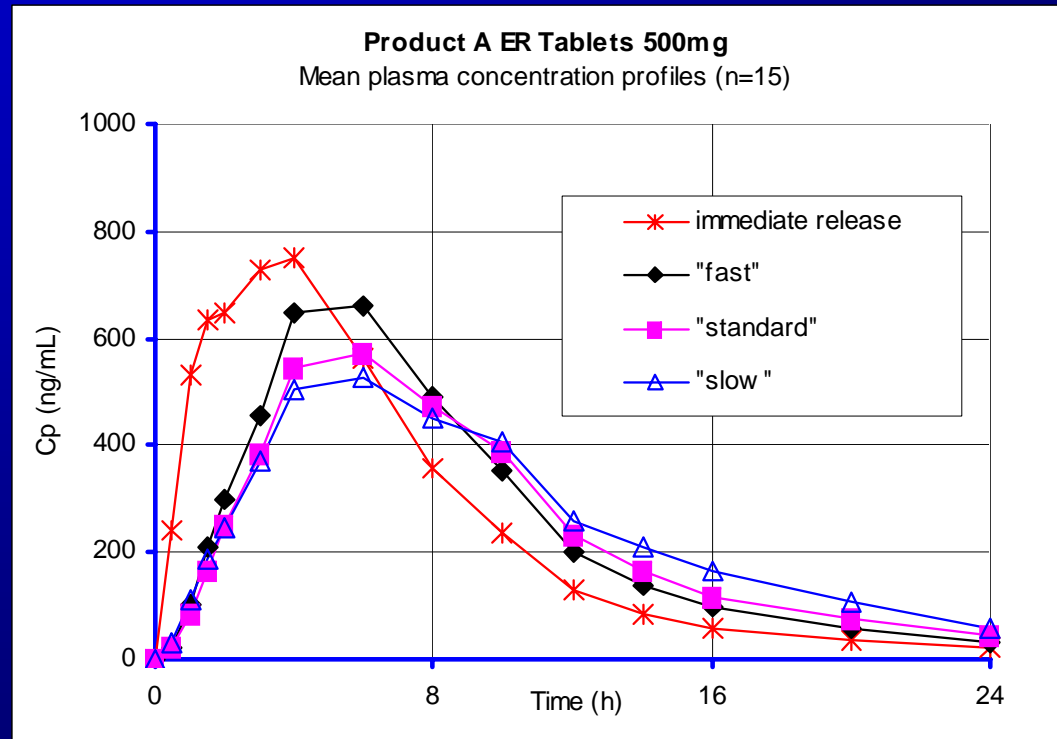
Application / Request for a Biowaiver

Phase	New Active Compound	Already Registered Compound
Preclin.	Classification according to BCS: <ul style="list-style-type: none"> • Solubility in the pH range 1.2 – 6.8 • Assessment of permeability 	If additional extended release form from registered normal product (or IVIVC exists already for normal formulation) <ul style="list-style-type: none"> • Dissolution profiles in pH range 1.2 – 6.8
I	<i>If dissolution rate determining for absorption:</i> <ul style="list-style-type: none"> • Initial development of IVIVC from first in vivo data (Inclusion of rapid formulation in study for use as weighting function) 	<ul style="list-style-type: none"> • Development of IVIVC from in vivo data from at least two ER formulations (as well as IR formulation or solution) • If imitator product (generic): IVIVC study with 2 formulations as well as reference product and solution (weighting function)
II	<ul style="list-style-type: none"> • IVIVC study with „final“ formulation • Justification for discriminating dissolution method 	<ul style="list-style-type: none"> • Justification for discriminating dissolution method
III	<ul style="list-style-type: none"> • IVIVC as base for biorelevant release specification setting • IVIVC as justification for biowaiver if formulation has to undergo Type II modification 	<ul style="list-style-type: none"> • IVIVC as base for biorelevant release specification setting • IVIVC as justification for biowaiver if formulation has to undergo Type II modification
IV (marketed)	<ul style="list-style-type: none"> • IVIVC as justification for a biowaiver <ol style="list-style-type: none"> 1. of additional strengths or line extensions 2. of Type II modifications 	<ul style="list-style-type: none"> • IVIVC as justification for a biowaiver <ol style="list-style-type: none"> 1. of additional strengths or line extensions 2. of Type II modifications

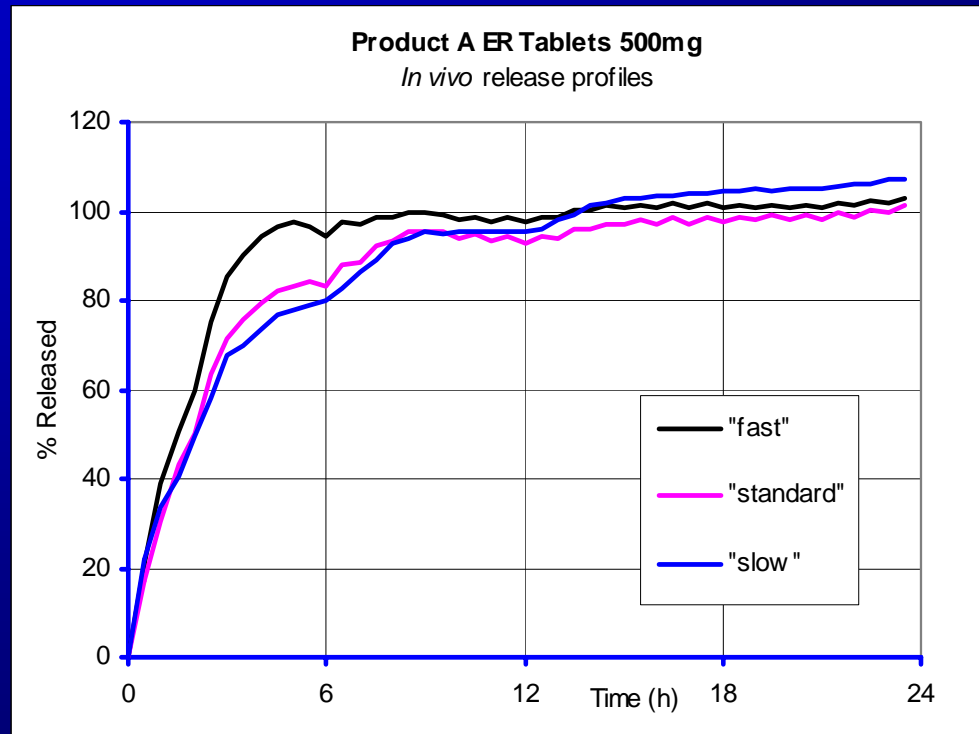
Example: *In vitro* Release of ER Tablets



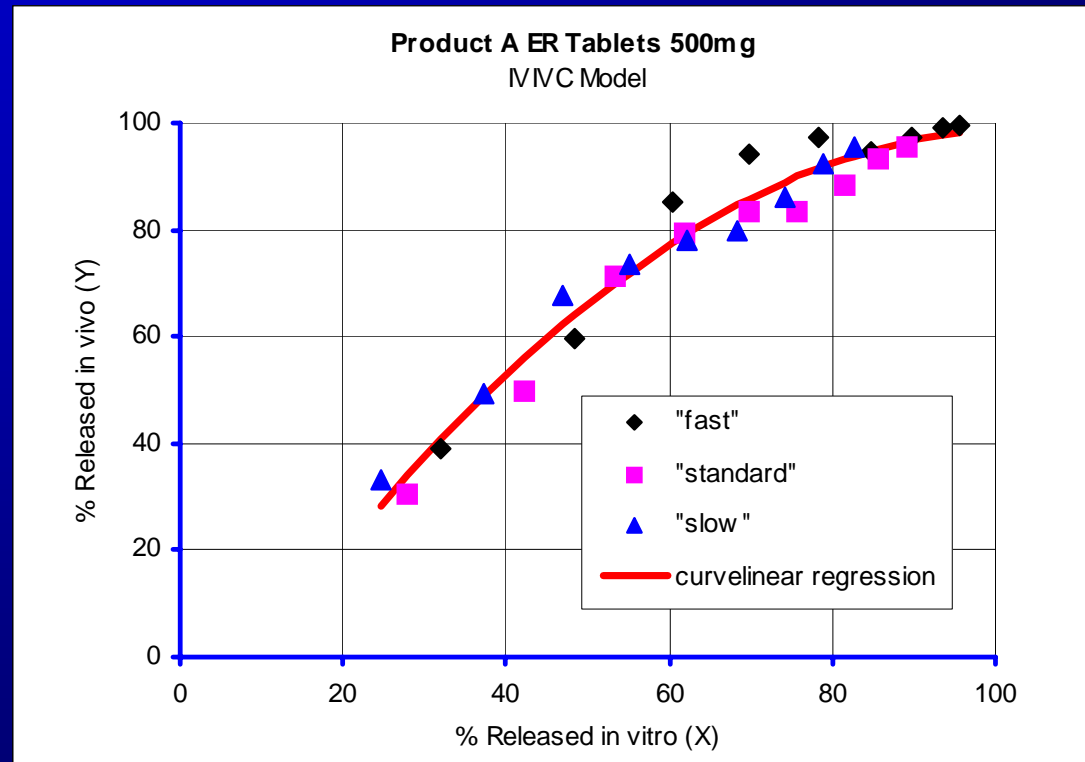
Example: *In Vivo* Data ER and IR



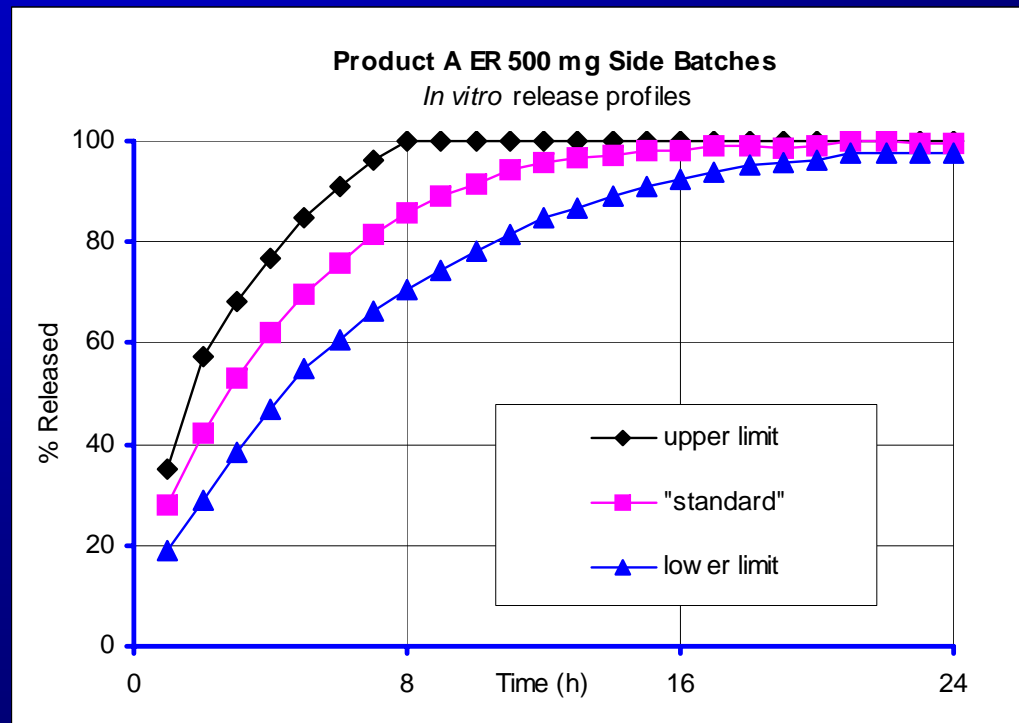
Calculated *in vivo* Release



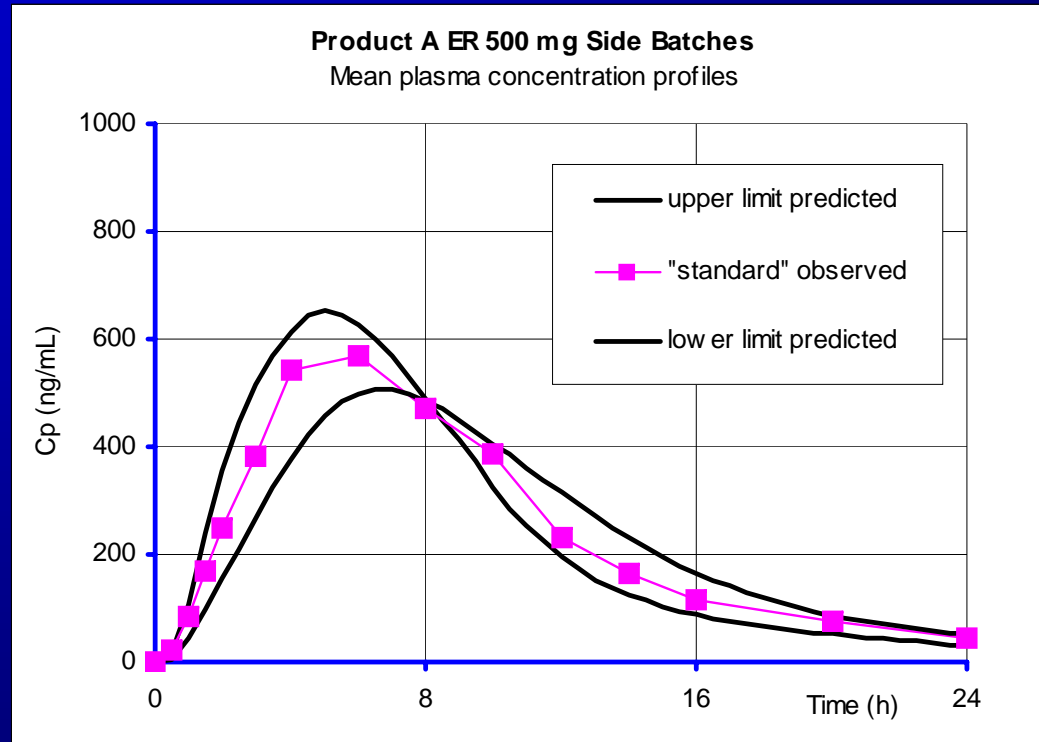
IVIVC / Nonlinear Regression



Calculated Bioequivalent Side Batches



Predicted *in vivo* Profiles

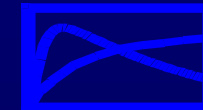


Validation Ratios for Side Batches

	Relative Bioavailability					
PK-parameters	Predicted UL	Predicted LL	Observed Standard	UL/LL	UL/Standard	LL/Standard
C _{max}	652.68	505.83	570.80	129.0	114.3	88.6
AUC(0-24h)	5976.25	5849.11	5906.58	102.2	101.2	99.0

The Regulatory Framework for the IVIVC (FDA)

- Scale up and Post Approval Changes-Immediate Release (SUPAC-IR), November, 1995
- Scale up and Post Approval Changes-Modified Release (SUPAC-MR), June, 1996
- FDA Guidance for Industry: Dissolution Testing of Immediate Release Solid Dosage Forms, August, 1997
- FDA Guidance for Industry: Development, Evaluation and Application of *In vitro-In vivo* Correlations for Extended Release Solid Oral Dosage Forms, September, 1997
- FDA Guidance for Industry: Biowaiver for IR Oral Forms Based on BCS, August, 2000
- FDA Guidance for Industry: BA and BE Studies for Orally Administered Drug Products, October 2000



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Regulatory Framework for the IVIVC

(EMEA)

- Note for Guidance on Modified Release Dosage Forms: A. Oral Dosage Forms, B: Transdermal Dosage Forms, Section I (Quality) (CPMP/QWP/604/96), July 1999
- Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/ QWP/ 1401/98), July, 2001
- Variations to Marketing Authorizations... (EC 1084/2003 - June 3 2003)

Summary

- IVIVCs cannot be generated for all drugs or formulations. But if the criteria are met, they are accepted by the authorities in USA and EU, Japan will probably also accept them as part of the ICH
- IVIVC is a credible tool to select the discriminating *in vitro* test conditions and to set therapeutically meaningful *in vitro* release specifications
- Applied correctly, the IVIVC can save substantial costs and time when registering product changes (biowaiver!)

Summary (cont'd)

- Essential data (needed for a later IVIVC) ought to be generated in the regular development path of a compound.
Following the BCS is helpful in this regard
- Deconvolution/Convolution mathematics are more widely applicable for an IVIVC than methods based on PK models
- It is advantageous to discuss the plan for filing an IVIVC - supported product change with the health authorities