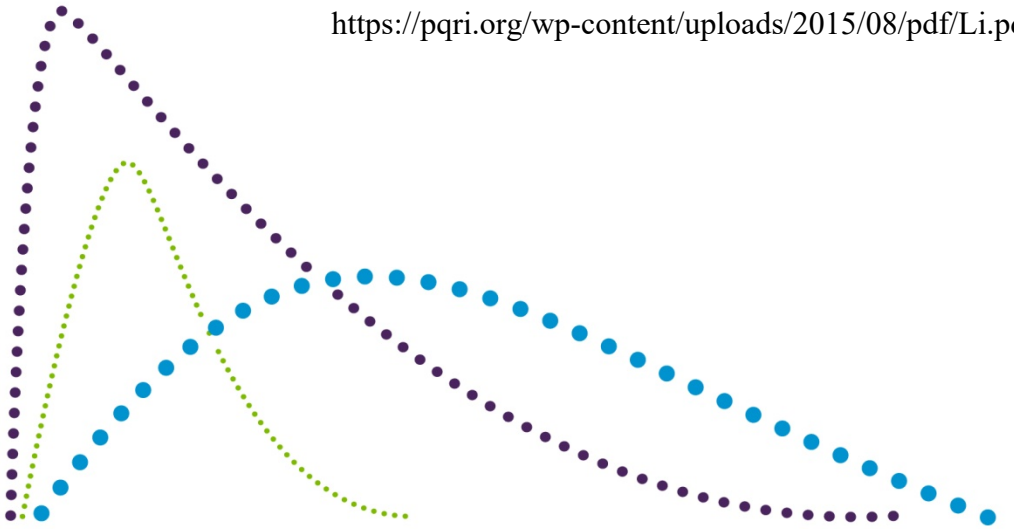
IVIVC Industry Perspective with Illustrative Examples



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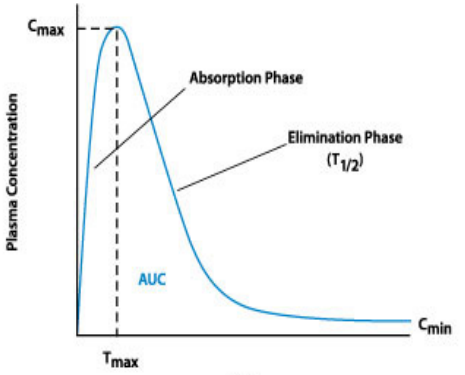
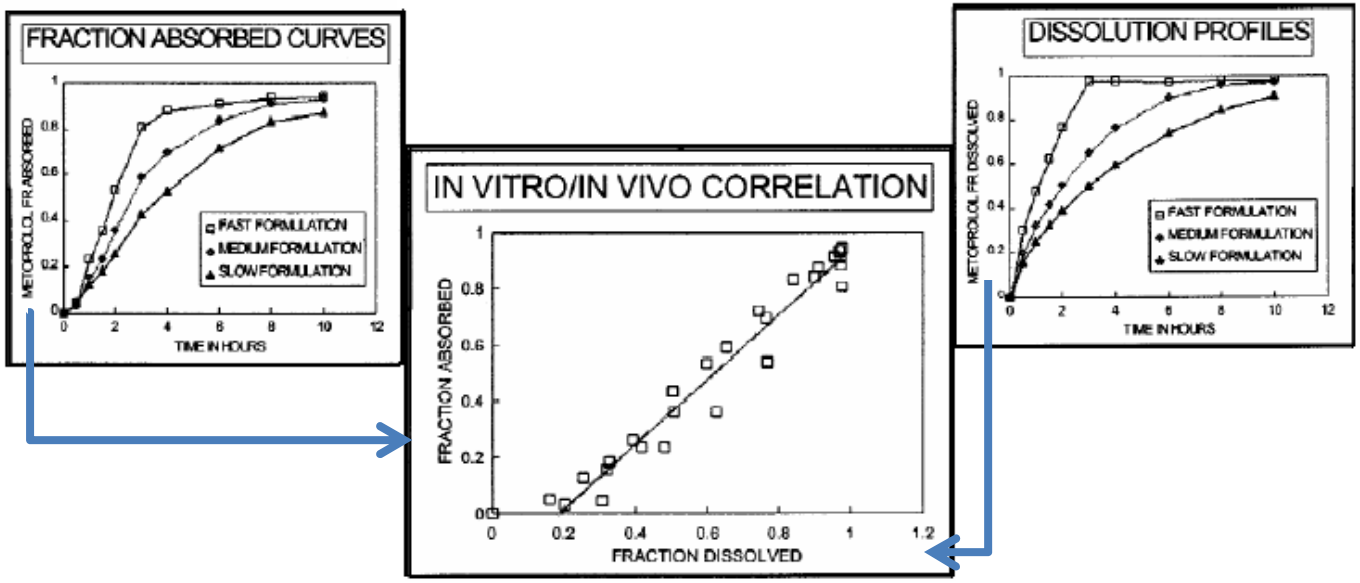
IVIVC definition[1]

- 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. drug concentration in plasma or amount of drug absorbed)





Convolution

Deconvolution

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[1] *Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/ In Vivo Correlations, September 1997*

Typical industrial applications of IVIVC

Primary Objective : Obtain Biowaiver
- i.e. use dissolution test as a surrogate for pharmacokinetic data

- Used as surrogate to bioequivalency studies which might typically be required with scaling up or minor post-approval changes (SUPAC), which may include
  - Site of manufacture
  - Formulation composition
  - Dose strength
- To waive bioequivalence requirements for lower strengths of a dosage form
- To reduce development time and optimize the formulation
- Setting dissolution specifications
- Recommended by regulatory authorities for most modified release dosage forms

Basic steps towards establishing IVIVC

- In vitro
  - Dissolution: drug release as a function of time
  - Ensure same mechanism of release of drug from dosage form
  - Calculation of percent of drug release as function of time: Weibull
- In vivo
  - Linear pharmacokinetics & knowledge of BCS category
  - Pharmacologic properties of the drug (Therapeutic Index)
- Unit impulse function
  - Oral solution
  - Immediate release tablet/capsule
  - Population PK analysis
  - IV

Basic steps towards establishing IVIVC

- Convolution

  The convolution method is a simulation method used to predict the blood/plasma concentration using percent absorbed data

  solving *c(t)* given *f(t)* and $c_\delta(t)$

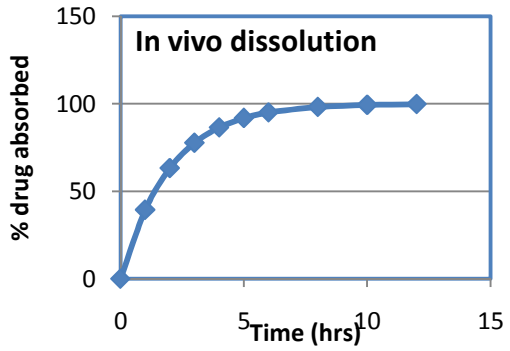
- Deconvolution

  Deconvolution is the process to obtain input function (percent absorbed) using known plasma concentrations

  solving *f(t)* given *c(t)*and $c_\delta(t)$

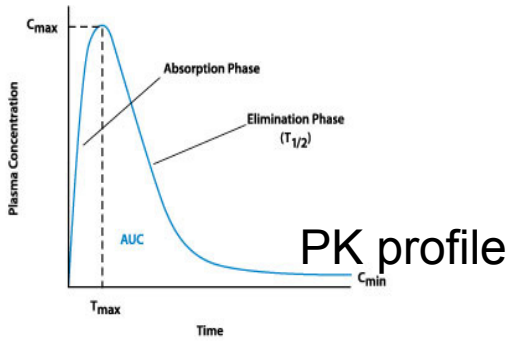
Deconvolution is the reverse process of convolution

$$c(t) = \int_0^t f(\tau) \cdot c_\delta(t-\tau) \cdot d\tau$$



Convolution

Deconvolution



PK profile

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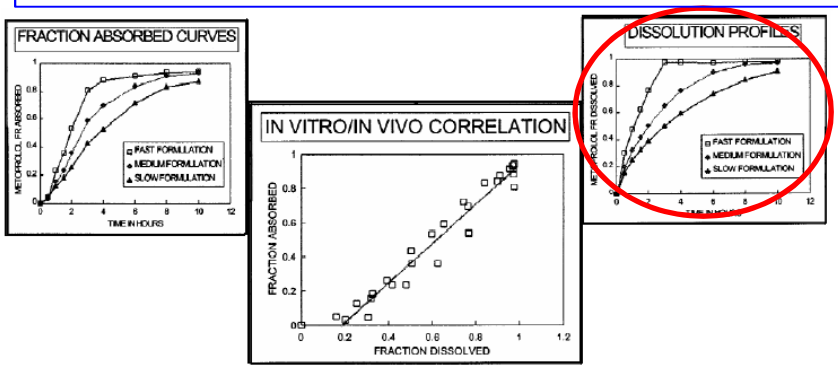
Approaches undertaken to establish IVIVC

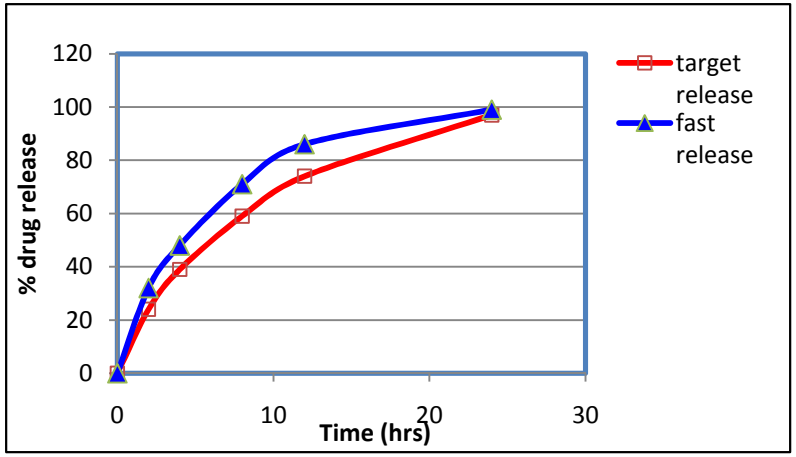
- Retrospective analysis of existing PK/dissolution data
  - Historical dosage development and PK data
  - Often full cross-over comparison of formulations is not available
- Prospective planning & developing clinical study designs for establishing IVIVC
  - Formulation scientists develop and provide:
    - Formulations with different release rates, such as slow, medium and fast
    - IV or oral solution or IR dosage form for unit impulse
  - Analytical scientists: obtain in vitro dissolution profiles
  - Clinical: in vivo plasma concentration profiles for these formulations
  - Money and Time

Illustrative example: Compound A

Problem statement: a single Level A IVIVC was accepted by regulatory agency for Compound A at dose *X*, **can we request biowaiver for lower strengths?**

Retrospective Analysis
Matrix SR tablets
BCS 1 compound





Weibull Equation

$$W_{\max} = W_t \cdot \left(1 - e^{-[(t-\gamma)/\tau_d]^{\beta}}\right)$$

W_t : the fraction of drug dissolved/absorbed at time t
W_{max} : the maximum cumulative fraction dissolved/absorbed
γ the location parameter (the lag time before the onset of dissolution)
τ_d: the time parameter (provides information about the overall rate of the process)
β: the shape parameter

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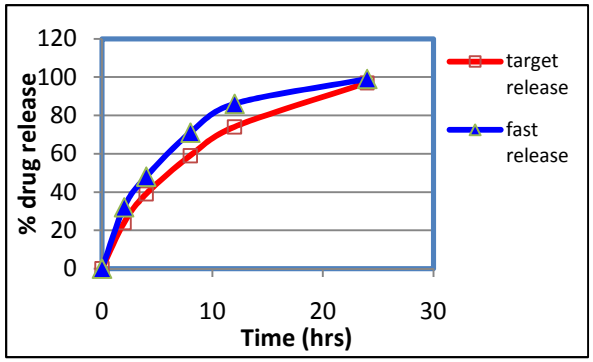
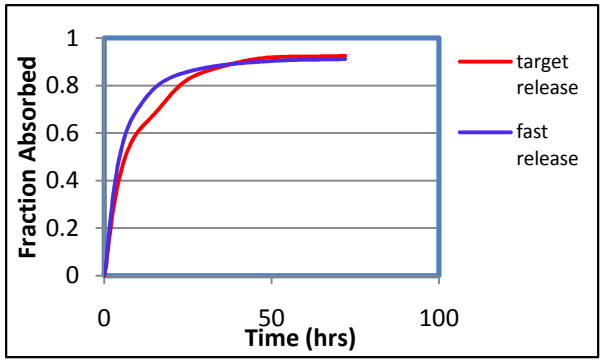
Illustrative example: Compound A





Retrospective Analysis

Matrix SR tablets

BCS 1 compound

$$\%PE_{C_{max}} = \left| \frac{C_{max}(obs) - C_{max}(pred)}{C_{max}(obs)} \right| \times 100\%$$

IVIVC - Mathematical Relationship

fraction of drug absorbed
= A *(fraction drug dissolved ^{B})

Prediction Error $\%PE_{AUC_{max}} = \left| \frac{AUC_{max}(obs) - AUC_{max}(pred)}{AUC_{max}(obs)} \right| \times 100\%$

Conclusion: the Level A IVIVC confirmed that the dissolution method developed for Compound A is sufficient to predict in vivo results for all dose strengths from *0.25*X* to *1*X* mg. The correlation was used to justify dissolution specifications.

	Formulation	Parameter	Absolute %PE	Ratio
Internal Validation	1*X (target release)	AUCINF	6.7	0.93
		Cmax (ng/ml)	2.3	1.02
	1*X (fast release)	AUCINF	1.6	0.98
		Cmax (ng/ml)	1.1	1.01
	Avg Internal	AUCINF	4.1	0.96
		Cmax (ng/ml)	1.7	1.02
External Validation	0.5*X dose (study 1)	AUCINF	6.6	0.93
		Cmax (ng/ml)	5.7	0.94
	0.25*X dose (study 1)	AUCINF	7.6	1.08
		Cmax (ng/ml)	4.5	1.04
	0.5*X dose (study 2)	AUCINF	5.7	0.94
		Cmax (ng/ml)	5.6	0.94
	0.25*X dose (study 2)	AUCINF	9.5	0.91
		Cmax (ng/ml)	2.9	0.97
	1*X dose	AUCINF	1.5	0.99
		Cmax (ng/ml)	5.3	1.05

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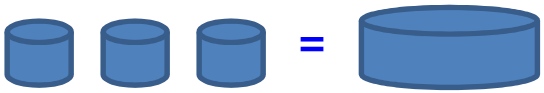
Illustrative example: Compound B

Problem statement: a single Level A IVIVC was accepted by regulatory agency for Compound B at dose X, **can we extend the current IVIVC to higher strengths? Can we use the IVIVC to request biowaiver for the site changes?**

Retrospective Analysis
Matrix SR tablets
BCS 1 compound

- Compound B
  - Compound marketed at unit dose strengths of *0.5X* mg and *1X* mg
  - The *3X* dose strength is currently registered and used as multiple units of X dose strength
  - New *3X* single dose is currently in development
  - Similar dissolution profiles and characteristics in vitro over the dose range of *X* dose to *3X* dose
  - Same formulation composition for Compound B over the dose range of *X* dose to *3X* dose
  - Both C_{max} and AUC increased in a linearly dose-proportional manner over the dose range studied over the dose range of *X* dose to *3X* dose



3 * X = 3X

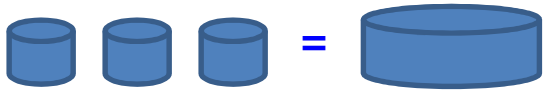
Illustrative example: Compound B

Problem statement: a single Level A IVIVC was accepted by regulatory agency for Compound B at dose X, **can we extend the current IVIVC to higher strengths? Can we use the IVIVC to request biowaiver for the site changes?**

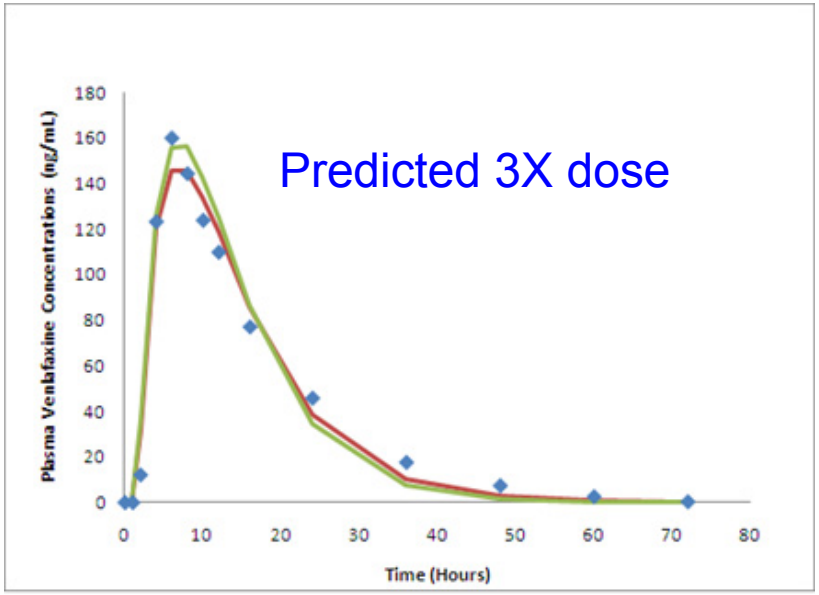
Retrospective Analysis
Matrix SR tablets
BCS 1 compound

- Compound B extended release
  - Level A IVIVC was developed using a single release rate
  - Dissolution method is independent of disso conditions (pH, agitation and media)

fraction of absorbed
= A *(fraction dissolved)+ B



3 * X = 3X



Conclusion: In vitro-in vivo correlation (IVIVC) model predicted AUC and C_{max} of Compound B at strengths up to and including *3X* dose strengths, therefore biowaiver for higher dose strength is justifiable.

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Illustrative example: Compound C

Problem statement: design clinical study to establish IVIVC based on existing development data for extended release tablets.
Which is the preferred method to be used for deconvolution?
Do we need to include IR arm in the IVIVC clinical study?

Prospective Planning
Matrix tablets
BCS 1 compound

Compound C

- Typical (ideal?)
  - Three or four formulations developed with differing dissolution profiles
  - Study in healthy volunteers
  - Three or four way crossover in 12 to 24 subjects
  - 2 or 3 formulations used to develop IVIVC, one arm of study for conducting external validation
- Can we use Wagner-Nelson equation to perform deconvolution analysis?
- Can we use population based mean IR PK data to generate unit impulse response and perform numerical deconvolution?

Determining the fraction of dose absorbed

- Model dependent methods
  - Wagner Nelson Equation (one compartment model)

$$F_t = \frac{C_t + k_{el} \cdot AUC_0^t}{k_{el} \cdot AUC_0^\infty}$$

  - Loo-Riegelman Method (multiple compartment models)

$$F_t = \frac{c_t + K_{10} AUC_0^t + (X_p)_t / V_c}{K_{10} AUC_0^\infty}$$

X_p; the amount of drug in the peripheral compartment
K_{10}: the apparent first order elimination rate

- Model independent methods
  - Deconvolution

$$c(t) = \int_0^t f(\tau) \cdot c_\delta(t-\tau) \cdot d\tau$$

Response — Impulse — Unit impulse response

- IV bolus
- Oral solution
- IR dosage form

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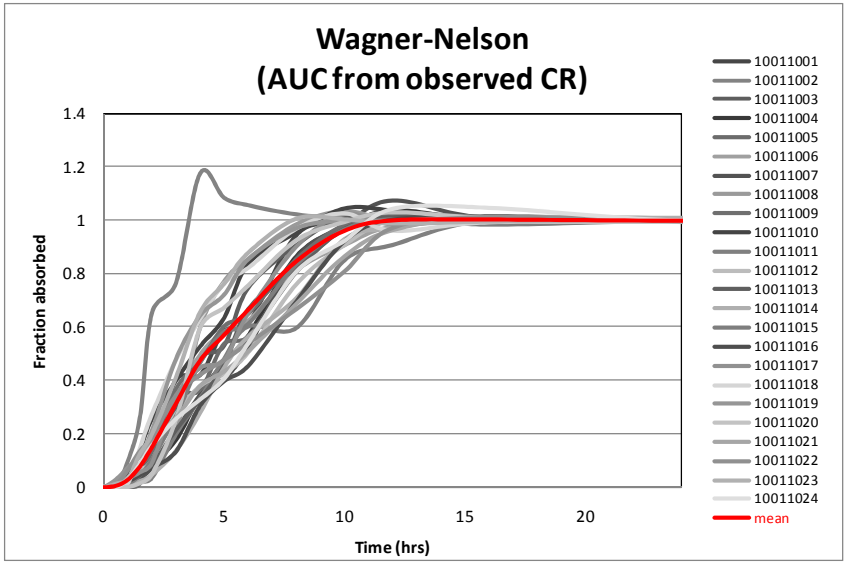
Compound C: deconvolution method

Wagner Nelson Method

Percent drug absorbed at any time

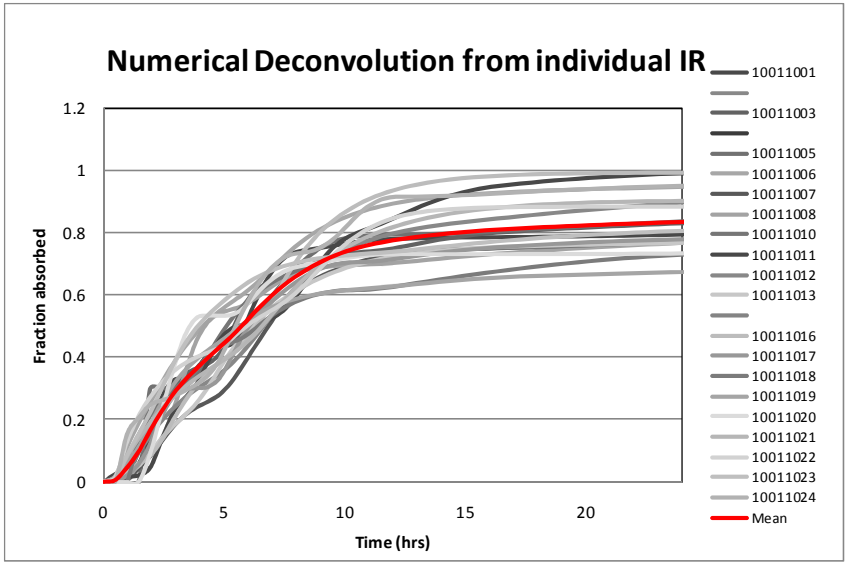
$$\%absorbed = \frac{C + k_e[AUC]_0^t}{k_e[AUC]_0^\infty} \bullet 100$$



- Some subjects demonstrated flip-flop mechanism
- Some subjects do not fit with one compartment model
- % PE not acceptable

Numerical deconvolution from individual IR data

$$c(t) = \int_0^t f(\tau) \cdot c_\delta(t-\tau) \cdot d\tau$$



- No model related restrictions on analyses
- Excellent % PE

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Compound C (two release rates)

Treatment	Description	
A	Fast dissolution	Develop IVIVC
B	Reference	Develop IVIVC
C	Immediate Release	Develop IVIVC

Prospective Analysis
Matrix tablets
BCS 1 compound

Deconvolution from individual IR data

$$F_{abs} = A * Diss(B * T_{vivo})$$

- IVIVR developed using previous clinical Data
- Two release rates
- Small PE errors (<15%) between predicted and observed values for AUC and C_{max}
- Caveats:
  - Different release mechanism

Formulation	Parameter	% PE	Ratio
A	AUClast	4.6	0.95
	Cmax	2.3	1.02
B	AUClast	1.1	1.01
	Cmax	14.9	1.15
Avg. Internal	AUClast	2.8	0.98
	Cmax	8.6	1.07

Compound C (two release rates)

Treatment	Description	
A	Fast dissolution	Develop IVIVC
B	Reference	Develop IVIVC
C	Immediate Release	Develop IVIVC

Prospective Analysis
Matrix tablets
BCS 1 compound

Deconvolution from mean IR data from previous studies

$F_{abs} = A * Diss(B * T_{vivo})$

- Small PE errors (<15%) between predicted and observed values for AUC and C_{max}

Conclusion: analysis showed that sufficient predictability could be achieved using historical reference IR data available from a number of clinical studies. The data reviewed demonstrated the consistent PK performance of the IR dosage forms. A numerical deconvolution using mean IR data is the preferred method. Therefore IR arm is not required for IVIVC study – reduce cost of study without compromising on quality.

Formulation	Parameter	Abs % PE	Ratio
A	AUClast	1.2	0.95
	Cmax	8.4	1.02
B	AUClast	3.1	1.01
	Cmax	0.6	1.15
Avg. Internal	AUClast	2.2	0.98
	Cmax	4.5	1.07

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Outcomes of IVIVC for illustrative examples

- Compound A
  - Successfully obtained biowaiver
- Compound B
  - Biowaiver justification under review with regulatory agency
- Compound C
  - No IR arm will be needed in the IVIVC clinical study use population based PK model for unit impulse
  - IVIVC design and protocol being prepared for pre-submission discussion with regulatory agency

Challenges for establishing/developing IVIVC-Industrial perspective

- Majority of focus is for modified release dosage forms
  - Obtaining multiple release rates while maintaining same release mechanism is not trivial for some compounds
  - GMP manufacturing, analytical testing, meeting dissolution criteria, etc. requires significant resources
  - Clinical studies with different release profiles preferably in cross-over design
  - Time and cost
- What about IVIVC for immediate release dosage form especially for BCS 2
  - Potential approach/how to develop?
  - Different particle size to achieve different dissolution rates
  - Develop oral solution formulation (unit impulse) that does not precipitate/crystallize during GI transit?
- Typically regulatory guidance require IVIVC to be conducted in fasted state, is it necessary for a compound with a label requirement to take it with food?
- Should there be standardized approaches to evaluating dose dumping based on MR technology used (matrix, osmotic, multi-particulates, etc.)?

Questions?

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