

In-Vitro-In-Vivo Correlation Definitions



and

Regulatory Guidance



Nattee Sirisuth and Natalie D. Eddington^{1,2*}

¹ Pharmacokinetics Biopharmaceutics Laboratory

² Department of Pharmaceutical Sciences School of Pharmacy, University of Maryland at Baltimore 100 Penn Street, AHB Baltimore, MD 21201-6808 (410) (Fax) 706-6710 (410) 706-6580 neddingt@rx.umaryland.edu

ABSTRACT

The purpose of this report is to present definitions of the various levels of in vitro in vivo correlations (IVIVCs) and to provide a regulatory perspective on its utility in product development and optimization.

The importance of a representative dissolution testing method that accurately describes the in vivo release rate is discussed in the context of developing a predictive IVIVC.

The role of the dissolution testing method in IVIVC development and validation is to serve as a surrogate measure of the rate and extent of oral absorption.

In addition, the Biopharmaceutical Classification System provides a science-based guidance on solubility and permeability drug issues, which are indicators of predictive IVIVCs.

A valid IVIVC will allow for dissolution testing for subsequent formulation changes which take place as a function of product optimization without the need for additional bioavailability / bioequivalency studies.

INTRODUCTION

Formulation development and optimization is an ongoing process in the design, manufacturer and marketing of any therapeutic agent.

Depending on the design and delivery goals of a particular dosage form, this process of formulation development and optimization may require a significant amount of time as well as financial investment.

Formulation optimization may require altering formulation composition, manufacturing, equipment and batch sizes. In the past when these types of changes are applied to a formulation, bioavailability studies would also have to be performed in many instances to ensure that the “new” formulation displayed statistically similar in-vivo behavior as the “old” formulation.

Of course this requirement delayed the marketing of the new formulation and added time and cost to the process of formulation optimization.

Recently a regulatory guidance was developed to minimize the need for additional bioavailability studies as part of the formulation design.

This guidance referred to as the, *In Vitro/In Vivo Correlation Guidance* was developed by the Food and Drug Administration and was based on scientifically sound research.(1)

It states that the main objective of developing and evaluating an IVIVC is to enable the dissolution test to serve as a surrogate for *in vivo* bioavailability studies (Figure 1).

This may reduce the number of bioequivalence studies required for approval as well as during scale-up and post-approval changes. (2)

Definition of In Vitro-In-Vivo Correlations

An *In-vitro in-vivo* correlation (IVIVC) has been defined by the Food and Drug Administration (FDA) as “a predictive mathematical model describing the relationship between an *in-vitro* property of a dosage form and an *in-vivo* response”.¹

Generally, the *in-vitro* property is the rate or extent of drug dissolution or release while the *in-vivo* response is the plasma drug concentration or amount of drug absorbed.

The United States Pharmacopoeia (USP) also defines IVIVC as “the establishment of a relationship between a biological property, or a parameter derived from a biological property produced from a dosage form, and a physicochemical property of the same dosage form”.(3)

Typically, the parameter derived from the biological property is AUC or C_{max} , while the physicochemical property is the *in vitro* dissolution profile.

A linear relationship with slope of unity, if possible, is preferred, as the dissolution profile is a representative of the absorption profile.(1,3)

Figure 2 presents a linear correlation between C_{max} and the percent dissolved in 15 minutes for an immediate release dosage form.

Since, IVIVCs are basically mathematical relationships, non-linear

correlations may also be appropriate. IVIVC plays an important role in product development in that it:-

- first, serves as a surrogate of *in vivo* and assists in supporting biowaivers;
- second, supports and / or validates the use of dissolution methods and specifications; and
- Thirdly, assists in quality control during manufacturing and selecting appropriate formulations (1,4).

The first and main role of establishing IVIVC is to use dissolution test as a surrogate for human studies.

The benefit of this is to **minimize** the number of bioequivalence studies performed during the initial approval process and during the scaling-up and post-approval changes (1).

Additional advantages of an IVIVC is to assist in validating or setting dissolution specifications. This is because the IVIVC includes *in-vivo* relevance to *in-vitro* dissolution specification. In other words, dissolution specifications are set based on the performance of the biobatch *in-vivo*.

The general dissolution time point specification is $\pm 10\%$ deviation from the mean dissolution profile obtained from the biobatch (1).

Bioequivalency between formulations would be expected if the formulation(s) fall within the upper and lower limits of the specification.

Dissolution specification setting based on an IVIVC can also be used as a quality control for product performance. However, this quality control may sometimes be more rigorous than the usual control standard since it depends on the product bioavailability.

The use of IVIVC, however, is limited to a certain drug product. It can be used only on that particular formulation.

The IVIVC cannot be used across the products, especially drug product with different release mechanisms (1,5).

This premise has been recently investigated in our laboratory. In this work, two major types of oral extended release dosage forms were compared:

- coated pellets filled in a gelatin capsule and

- a hydrophilic matrix tablet.

The tablet formulation was manufactured under separate investigations using fluid bed granulation.

The active compound, metoprolol tartrate, was blended with the release rate-controlling polymer (hydroxypropyl methylcellulose) and with other excipients, such as a filler (lactose and dicalcium phosphate), a binder (hydroxypropylmethylcellulose) and a lubricant (magnesium stearate).

The granules were then compressed into a tablet. A correlation developed with the hydroxypropyl methylcellulose system and was applied to predicting the *in vivo* behavior of the multi-particulate gelatin capsule.

The IVIVC was predictive of the extent of absorption. Prediction errors associated with AUC were found to be less than 10 percent.

However, the IVIVC was unable to accurately estimate the rate of drug absorption, C_{max} . Prediction errors were found to be greater than 20 %.

These results support the contention that IVIVCs are product specific. IVIVC is usually developed when drug dissolution is a rate-limiting step for the *in vivo* absorption.

The absorption and consequently the bioavailability of an oral solid dosage

form depends on two main processes, drug dissolution and permeation.

Drug dissolution is the process in which the drug is released and available in solution and ready to be absorbed.

Physicochemical properties of a drug such as solubility as well as the gastrointestinal environment are the crucial parameters affecting dissolution.

Drug permeability is the second process beginning after the solid drug is converted into a solution form. Permeability is the ability of the drug to penetrate across a membrane into the systemic circulation.

The extent of permeation and ultimately absorption also depends upon the physicochemical properties of the drug and blood perfusion (6).

The complete penetration of a highly permeable drug occurs in a short time. Thus, the *only* factor governing drug absorption is drug release and/or dissolution from the dosage form.

In-vitro drug dissolution then can be used as a surrogate for the *in-vivo* absorption.

On the contrary side, the dissolution rate of immediate release drug products is relatively very rapid. The rate of absorption then is likely to be a function of the gastric emptying rate or the intestinal permeability. In this case, the IVIVC may not be obtained (5).

In Vitro - In Vivo Correlations Examples

Previous IVIVC studies have been reported for various drugs (7-18). The studies were conducted both in animal, such as rat, rabbit, and dog and human.

Most of the studies focused on the development of a level B and level C correlations. The level B is a correlation in which it compares the mean *in-vivo*

dissolution to the mean *in-vitro* dissolution as outlined in Figure 3.

Whereas the level C correlation describes a relationship between the amount of drug dissolved at one time point and one pharmacokinetic parameter.

The level C is also considered the lowest level of correlation. Figure 4 displays a typical level C correlation between C_{max} and percent dissolved at 15 minutes.

Level B and C IVIVCs have been developed for several purposes in formulation development, for example, for selecting the appropriate excipients and optimizing manufacturing processes, for quality control purposes, and for characterizing the release patterns of a newly formulated immediate release (IR) and modified release (MR) products relative to the reference (7-18).

However, current IVIVC studies have focused on the development and validation of a level A correlation.

It is a point-to-point relationship between drug release *in-vitro* and *in-vivo*. Although, a concern of non-linear correlation has been addressed, no formal guidance on the non-linear IVIVC has been established (1).

In summary, the IVIVC is established to enable the dissolution test to be used as a surrogate for bioequivalency.

A validated IVIVC is of significant benefit for pharmaceutical manufacturers due to minimizing the time and cost invested in additional bioavailability studies.

In addition, IVIVC is normally expected for highly permeable drugs or drugs under dissolution rate-limiting conditions. This statement is further

supported by the regulatory Biopharmaceutical Drug Classification (BCS), which anticipates the successful IVIVC for highly permeable drugs (4).

Biopharmaceutics Classification System (BCS)

Biopharmaceutics Classification System (BCS) is a fundamental guideline for determining the conditions under which *in-vitro in-vivo* correlations are expected (4).

It is also used as a tool for developing the *in-vitro* dissolution specification (5, 19).

The classification is associated with drug dissolution and absorption model, which identifies the key parameters controlling drug absorption as a set of dimensionless numbers: the **Absorption number**, the **Dissolution number** and the **Dose number** (4, 5, 19).

The **Absorption number** is the ratio of the mean residence time to the absorption time.

The **Dissolution number** is a ratio of mean residence time to mean dissolution time.

The **Dose number** is the mass divided by an uptake volume of 250 ml and the drug's solubility.

The **mean residence time** here is the average of the residence time in the stomach, small intestine and the colon.

The **fraction of dose absorbed** then can be predicted based on these three parameters. For example, Absorption number 10 means that the permeation across the intestinal membrane is 10 times faster than the transit through the small intestine indicating 100% drug absorbed.

In the BCS, a drug is classified in one of four classes based solely on its

solubility and intestinal permeability (19):

Class I

HIGH solubility / **High** permeability,

Class II

LOW solubility / **High** permeability,

Class III

HIGH solubility / **LOW** permeability

Class IV

LOW solubility / **LOW** permeability.

Class I drugs such as metoprolol exhibit a high Absorption number and a high Dissolution number.

The rate-limiting step to drug absorption is drug dissolution or gastric emptying rate if dissolution is very rapid.

Class II drugs such as phenytoin have a high Absorption number but a low Dissolution number. *In-vivo* drug dissolution is then a rate-limiting step for absorption (except at very high Dose number).

The absorption for Class II drugs is usually slower than Class I and occurs over a longer period of time. IVIVC is usually expected for Class I and Class II drugs.

For Class III drugs, permeability is the rate-controlling drug absorption. Furthermore, Class III drugs exhibit a high variability of rate and extent of drug absorbed. Since the dissolution is rapid, the variation is due to alteration of GI physiological properties and membrane permeation rather than dosage form factors.

Class IV drugs are low solubility and low permeability drugs. Drugs that fall in this class exhibit a lot of problems for effective oral administration. Drug example for class III and IV is cimetidine and chlorothiazide, respectively.

In general, a high soluble drug is characterized based on the largest dosage strength soluble in 250 ml or less of water over a pH range of 1-8.

In addition, if the extent of drug absorption is greater than 90% given that the drug is stable in the gastrointestinal environment, it will be considered as a high permeable drug (5).

Table 1 and 2 illustrate the BCS and the expected IVIVC for immediate and extended release formulations (4).

In vitro dissolution

The purpose of the *in-vitro* dissolution studies in the early stage of drug development is to select the optimum formulation, evaluate the active ingredient and excipient, and assess any minor changes for drug products.

However, for the IVIVC perspective, dissolution is proposed to be a surrogate of drug bioavailability. Thus, a more rigorous dissolution standard may be necessary for the *in-vivo* waiver (5).

Generally, a dissolution methodology, which is able to discriminate between the study formulations and which best reflects the *in vivo* behavior would be selected.

Four basic types of dissolution apparatus, i.e.

- [1] rotating basket,
- [2] paddle method,
- [3] reciprocating cylinder,
- [4] flow through cell,

are specified by the USP and recommended in the FDA guidance especially, for modified release dosage form (20).

Other dissolution methodologies may be used, however, the first four are preferred, especially the basket and paddle. It is also recommended to start

with the basket or paddle method prior to using the others (5).

The *in vitro* dissolution release of a formulation can be modified to facilitate the correlation development. Changing dissolution testing conditions such as the stirring speed, choice of apparatus, pH of the medium, and temperature may alter the dissolution profile.

As previously described, appropriate dissolution testing conditions should be selected so that the formulation behaves in the same manner as the *in vivo* dissolution.

The appropriate dissolution testing conditions should also discriminate between different formulations that possess different release patterns.

A common dissolution medium is water, simulated gastric fluid (pH 1.2), or intestinal fluid (pH 6.8 or 7.4) without enzyme, and buffers with a pH range of 4.5 to 7.5 (20).

For sparingly water-soluble drugs, use of surfactants in the dissolution medium is recommended (6).

A simple aqueous dissolution media is also recommended for BCS Class I drug as this type of drug exhibits lack of influence of dissolution medium properties (21).

Water and simulated gastric fluid then are the default mediums for most of the Class I drugs. A typical medium volume is 500 to 1000 ml.

The normal test duration for immediate release is 15 to 60 minutes with a single time point. For example, BCS class I recommend 15 minutes.

Additionally, two time points may be required for the BCS class II at 15 minutes and the other time at which 85% of the drug is dissolved (6). In contrast, *in vitro* dissolution tests for a modified

release dosage form require at least three time points to characterize the drug release.

The first sampling time (1-2 hours or 20-30% drug release) is chosen to check dose-dumping potential. The intermediate time point has to be around 50% drug release in order to define the *in vitro* release profile.

The last time point is to define essentially complete drug release (2, 20). The dissolution limit should be at least 80% drug release. Further justification as well as 24-hours test duration are required if the percent drug release is less than 80 (20).

Once the discriminatory system is established, dissolution testing conditions should be fixed for all formulations tested for development of the correlation (1).

A dissolution profile of percentage or fraction of drug dissolved versus time then can be determined.

The similarity of the dissolution profiles in particular dissolution testing conditions is evaluated using the similarity factor (f_2 metric) defined by equation 1 (22,23).

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n W_t (R_t - T_t)^2 \right]^{0.5} \times 100 \right\} [1]$$

Where R_t and T_t are the cumulative percentage dissolved at time point t for reference and test products, respectively, and n is the number of pool points.

The f_2 equation is a logarithmic transformation of the sum of squares of the difference between test and reference profiles (22).

The results are values between 0 and 100. The value of f_2 is 100 when the test and reference profiles are identical and approaches zero as the dissimilarity increases.

An average difference of 10% at all time points results in the f_2 value of 50. The f_2 value between 50 and 100, therefore, suggests the similarity between two dissolution profiles (23).

This equation is only applicable in comparing profiles in which the average difference between R and T is less than 100. If this average difference is greater than 100, the equation will yield a negative number (22).

Normalization of the data is required to compare values in which the difference is not between 1 and 100.

In vivo absorption

The FDA requires *in vivo* bioavailability studies to be conducted for a New Drug Application (NDA). Bioavailability studies are normally performed in young healthy male adult volunteers under some restrictive conditions such as fasting, non-smoking, and no intake of other medications.

The drug is usually given in a crossover fashion with a washout period of at least five half-lives.

The bioavailability study can be assessed via plasma or urine data using the following parameters: (I) area under the plasma time curve (AUC), or the cumulative amount of drug excreted in urine (D_{u^∞}), (II) maximum concentration (Cmax), or rate of drug excretion in urine (dD_u/dt), and (III) a time of maximum concentration (Tmax).

Despite the knowledge of these parameters, cumulative amount absorbed or the *in vivo* absorption rate is required as the *in vivo* data for the IVIVC development.

Several approaches can be employed for determining the *in vivo* absorption. Wagner-Nelson, Loo-Riegelman, and numerical deconvolution are such

methods (23, 24). Wagner Nelson and Loo-Riegelman are both model-dependent methods in which the former is used for a one-compartment model and the latter is for multi-compartment system.

The Wagner Nelson method is less complicated than the Loo-Riegelman as there is no requirement for intravenous data (24).

However, misinterpretation on the terminal phase of the plasma profile may be possible in the occurrence of a flip-flop phenomenon in which the rate of absorption is slower than the rate of elimination

Deconvolution is a numerical method used to estimate the time course of drug input using a mathematical model based on the convolution integral (1).

For example, the absorption rate time course (r_{abs}) that resulted in plasma concentration ($c(t)$) may be estimated by solving the convolution integral equation for r_{abs} .

$$c(t) = \int_0^t C_\delta(t-u) r_{abs}(u) du \quad [2]$$

The function C_δ represents the concentration time course that would result from the instantaneous absorption of a unit amount of drug and it is typically estimated from intravenous injection bolus data or reference oral solution data. $c(t)$ is the plasma concentration vs. time level of the extended release formulation.

r_{abs} is drug input rate of the oral solid dosage form and

u is variable of integration.

Deconvolution is a model independent method which can be employed for either one- or multiple-compartment models.

The key to developing an IVIVC is identifying a dissolution testing method

that is descriptive of the in vivo absorption of the test compound.

In vitro testing has several purposes. It serves an important tool for characterizing the biopharmaceutical quality of a product at different stages of formulation development.

In early drug development, in vitro dissolution properties are decisive for choosing between different alternative dosage forms for further development of the respective drug product.

Also, in vitro dissolution data can be helpful in the evaluation and interpretation of possible risks, especially in the case of extended release dosage forms, e.g. dose dumping, food effects and drug-drug interaction. In addition, in vitro dissolution data has great importance when assessing minor changes in production site or manufacturing process and respective decision on the necessity of bioavailability studies.

None of these purposes can be fulfilled by in vitro dissolution testing without sufficient knowledge of its in vivo relevance, that is by studying in vitro-in vivo correlations.

If a correlation can be established with an individual drug, an in vitro dissolution test may serve not only as a guide to formulation development or as a quality control test, which indicates uniformity of manufacture or stability, but also as a reliable predictor of drug absorption.

In summary, this report outlined the regulatory requirements for the development and validation of an IVIVC. It focuses on the role of the Biopharmaceutical Classification system as an indicator of developing a predictive IVIVC and also examined the importance of drug dissolution and permeability on IVIVC validity.

Table 1.

Biopharmaceutics Drug Classification and Expected IVIVC for Immediate Release Drug Products.⁴			
Class	S	P	IVIVC
I	High	High	Correlation (if dissolution is rate limiting step)
II	Low	High	IVIVC expected
III	High	Low	Little or no IVIVC
IV	Low	Low	Little or no IVIVC
S = Solubility			P = Permeability

Table 2.

Biopharmaceutics Drug Classification for Extended Release Drug Products.⁴			
Class	S	P	IVIVC
IA	High & Site Independent	High & Site Independent	IVIVC Level A expected
IB	High & Site Independent	Dependent on site & Narrow Absorption Window	IVIVC Level C expected
IIa	Low & Site Independent	High & Site Independent	IVIVC Level A expected
IIb	Low & Site Independent	Dependent on site & Narrow Absorption Window	Little or no IVIVC
Va: Acidic	Variable	Variable	Little or no IVIVC
Vb: basic	Variable	Variable	IVIVC Level A expected
S = Solubility			P = Permeability

Figure 1.
Representative mean fraction of drug dissolved convolved to provide plasma drug concentration vs. time profile.

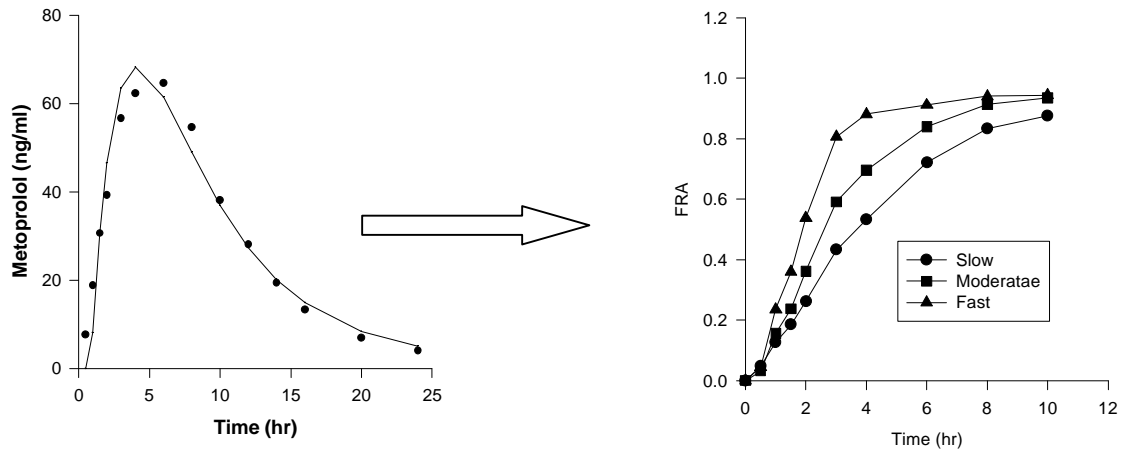


Figure 2
Level C In Vitro In Vivo Correlation between Cmax and percent dissolved at 15 minutes.

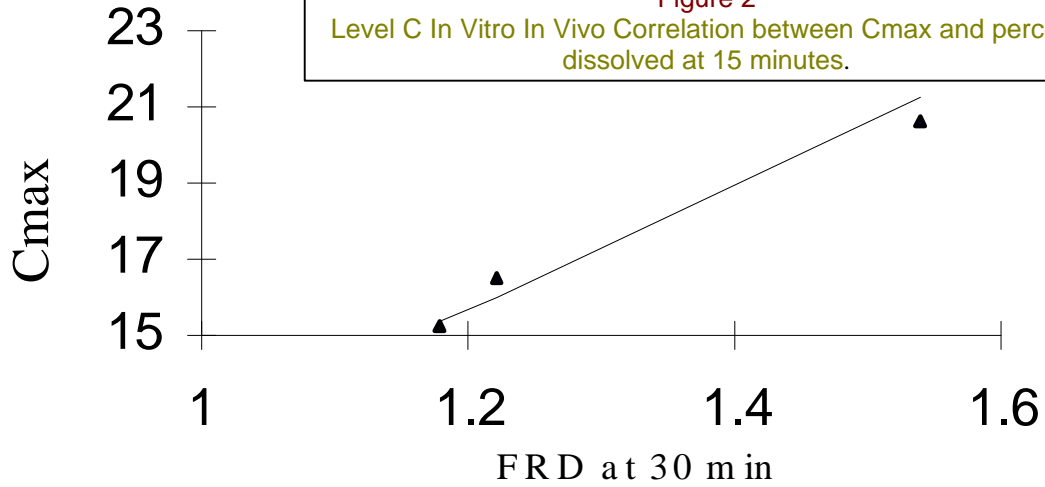
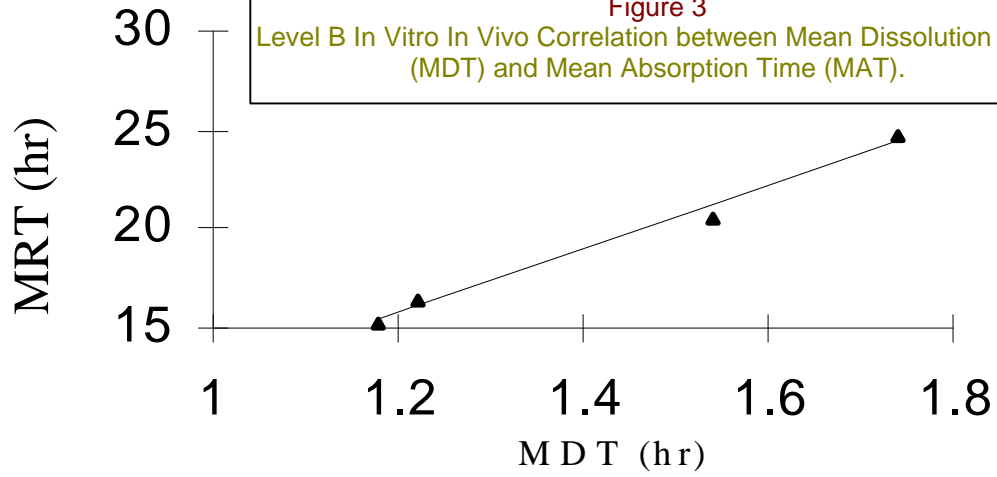


Figure 3
Level B In Vitro In Vivo Correlation between Mean Dissolution Time (MDT) and Mean Absorption Time (MAT).



Subsequent topics in this series will include:

- (1) **S**ystematic method for the development and validation of an IVIVC with relevant examples,
- (2) **D**evelopment of an IVIVC for a Class I agent metoprolol tartrate using two formulations,
- (3) **T**he role of stereoisomerisms in IVIVC development,
- (4) **T**he application of IVIVC for immediate release products, a Class I and III drug example,
- (5) **T**he role of mathematical modeling in IVIVC development, Case Report Using a Non-linear relationship between FRA and FRD, and
- (6) **T**he role of pharmacokinetic variability in individual IVIVC in product development....

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Please send editorial correspondence and reprint requests to:

Natalie D. Eddington, Ph.D. Pharmacokinetics Biopharmaceutics Laboratory Department of Pharmaceutical Sciences School of Pharmacy, University of Maryland at Baltimore 100 Penn Street, AHB Baltimore, MD 21201-6808 Tel (410) 706-6710 Fax: (410)-706-6580 neddingt@rx.umaryland.edu

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