

# PQRI Workshop Report:

## Application of IVIVC in Formulation Development

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### ABSTRACT

This article summarizes the proceeding of the September 2012 Workshop on Application of In vitro–In vivo correlation (IVIVC) in Formulation Development. The workshop brought together international experts with the goal of establishing common concepts that could be utilized to facilitate the development and validation of IVIVCs in the registration of and post-approval changes to oral solid dosage forms. The workshop was organized by the Product Quality Research Institute (PQRI) and cosponsored by AAPS, FDA, FIP, and USP. Open access of this information is available to all interested parties.

### INTRODUCTION

IVIVC is an important concept and a tool in the development and evaluation of pharmaceutical dosage forms. A properly conducted IVIVC provides assurance of the robustness of a dosage form and provides justification of manufacturing changes during drug product development. A filed IVIVC can accelerate internal decision making of proposed SUPAC changes by providing linkage back to preapproval formulations. As such, a well-conducted IVIVC may have substantial value to pharmaceutical manufac-

turers, regulatory bodies, and ultimately, consumers of the product.

Early history (1982–1992) suggests that few IVIVCs were filed. Since the advent of the FDA guidance (1) approximately fifteen years ago, the number of NDAs containing IVIVC studies has increased, and it is anticipated that exploration of IVIVCs and IVIVRs will continue to grow. FDA scientists confirmed that most IVIVCs filed are for modified-release (MR) products with fewer for immediate-release (IR) dosage forms. Many of the latter were identified as insufficient and not approvable. Early statistics immediately following the issuance of the FDA Guidance

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show a gradual uptick within European submissions. It is hoped that an increase in European submissions will follow the trend seen in the United States.

Prior to the issuance of the FDA Guidance, the United States Pharmacopeia (USP) issued General Chapter <1088> outlining In Vitro and In Vivo Evaluation of Dosage Forms; this chapter has been recently updated (2).

The PQRI Workshop set as its goals:

- 1) Review the current status of IVIVC.
- 2) Discuss applications and potential benefits of IVIVC.
- 3) Review and evaluate different methodologies and their potential use in IVIVC assessment.
- 4) Assess advantages and limitations for IVIVC in formulation development.

As such, this report on the proceedings of the workshop includes the thinking of the individual presenters at the workshop and, in addition, includes their efforts to meld the various pieces of the workshop into a transparent document that will be a resource to all development scientists interested in understanding and developing IVIVCs. Therefore, this paper's ultimate goal is to outline the potential for development and successful registration of IVIVC studies within worldwide regulatory submissions.

## FUNDAMENTALS OF IVIVC

### What is IVIVC?

The term IVIVC refers to a predictive mathematical model 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, for example, plasma drug concentration or amount of drug absorbed (1). The quantitative relationship between the in vivo and in vitro properties is an IVIVC. The most important utilization of an IVIVC is that of predictability, rendering it as a surrogate for in vivo bioequivalence studies. In a successful correlation, the actual blood drug concentration profile may be predicted or simulated from in vitro dissolution data. If prediction cannot be accomplished, it does not mean that the in vitro release method is necessarily invalid. The release method can still be used as a quality control tool. If a rank-order, qualitative relationship can be established between dissolution and bioavailability of a dosage form, an in vitro–in vivo relationship (IVIVR) or association can be of great value to a formulation group. For example, it can allow for the determination of the clinical relevance of the release method (e.g., a method that has been shown to discriminate for batches that are not bioequivalent). Thus, the term IVIVC has proliferated in pharmaceutical publications as a result of the need to validate dissolution methods by establishing their biorelevance.

Historically, IVIVC analysis has been more widely applied to MR, especially extended-release (ER) versions of MR oral products, than to IR dosage forms. Recent statistics show

that of all FDA IND/NDA submissions containing IVIVCs, only about 10% are for IR formulations. This difference in success probably reflects the application of specific data analysis techniques and interpretation that require dissolution rate-limited drug absorption, which is easier to demonstrate with ER dosage forms. For an IR dosage form, it is more difficult to arrive at different dosage forms with different dissolution rates without deviating substantially from the compositional formulation. The difference in applicability probably reflects the perceived increased benefit in ability to justify post-approval changes to MR products. Nevertheless, IVIVCs have been reported for IR dosage forms (3).

The release of drug substance from IR and MR dosage forms is significantly affected by the drug product formulation. Numerous attempts have been made to correlate various in vivo pharmacokinetic (PK) parameters with in vitro dissolution data. Single-point correlations (see Level C below) show that increasing or decreasing the in vitro dissolution rate of a MR or IR dosage form can result in a corresponding directional change in the in vivo performance of the product (e.g.,  $C_{max}$  or  $AUC$ ). However, such single-point correlations do not reveal much information regarding the overall plasma concentration–time profile. Thus, correlation methods that utilize all available plasma drug concentration and in vitro data are preferred (discussed below as Level A). Three correlation levels have been defined and categorized in descending order of the quality of predictive scope (2), but there are significant differences in the quality of the correlation obtained with each procedure. These methods are outlined in terms of the advantages of each along with the resulting potential utility as predictive tools. The concept of correlation level is based upon the ability of the correlation to reflect the entire plasma drug concentration–time curve that will result from administration of the given dosage form. It also relates the entire in vitro dissolution curve to the entire plasma concentration–time profile; the strength of this relationship defines its inherent predictability.

### IVIVC Levels

#### Level A Correlation

The Level A correlation is the strongest correlation. It represents a point-to-point relationship between the in vivo input rate (absorption rate) and in vitro dissolution of the drug. In one approach to a Level A correlation, a product's in vitro dissolution curve is compared with either its in vivo release in the lumen of the intestine (mechanistic absorption model IVIVC) or its in vivo input to the systemic circulation. A common approach applies the classical deconvolution methods using mass-balance, model-dependent techniques, such as the Wagner–Nelson or Loo–Riegelman methods, or model-independent, numerical deconvolution. Population PK methods are also finding increased attention in IVIVC modeling because of

their ability to handle inter-individual and inter-occasion variability rigorously. Ideally (though not an absolute requirement), the in vitro and in vivo curves are superimposable or may be made to be superimposed by the use of transformations (e.g., time-scaling) that are the same across all formulations. Alternatively, if the dissolution and absorption curves are different, a mathematical relationship may be developed that relates the two variables resulting in a tool that allows the prediction of a plasma concentration–time profile using in vitro dissolution data. This relationship needs to be demonstrated not only at that single input rate, but also over the entire release rate range used during construction and validation of the correlation. In cases where it is known that the release rate is dependent on the dissolution method conditions, the two curves may be made to superimpose by altering the dissolution method conditions (e.g., mixing speed, pH, medium).

The advantages of a Level A correlation are as follows:

- A point-to-point correlation utilizes the entire plasma concentration–time and in vitro release profiles collected. When validated, a Level A correlation serves as a surrogate for in vivo performance. Therefore, changes in manufacturing site, manufacturing process, and raw materials and some formulation modifications, including product strength using the same formulation, can be justified without the need for additional bioavailability/bioequivalence studies.
- Allows for the establishment of a release-rate method for quality control purposes that is meaningful and predictive of dosage form in vivo performance.
- The ranges of the proposed drug product specifications (e.g., TPP) can be justified by predicting the plasma level profile from the dissolution profile by a convolution procedure.
- Facilitates the verification of the design space in QbD submission by predicting the clinical impact of “movements” within the design space without the need for additional in vivo studies.
- May allow the setting of wider than standard ( $\pm 10\%$ ) in vitro release acceptance criteria resulting in regulatory flexibility.

#### Level B Correlation

This correlation utilizes the principles of statistical moment analysis. The mean in vitro dissolution time is compared with either the mean residence time or the mean in vivo dissolution time. As with a Level A correlation, Level B utilizes all of the in vitro and in vivo data but is not a point-to-point correlation. It does not correlate the actual in vivo plasma profiles, but rather a parameter that results from statistical moment analysis of the plasma profile such as mean residence time (MRT). Because there are a number of different plasma profiles (shapes) that

will produce similar mean residence time values, it is not possible to rely upon a Level B correlation alone to predict a plasma profile from in vitro dissolution data. In addition, in vitro data from a Level B correlation should not be used to justify the extremes of a product’s quality control standards. One example is where the dissolution data are based on a multipoint parameter, such as in vitro mean dissolution time, which is used in the correlation to MRT (or in vivo mean dissolution time).

#### Level C Correlation

This category relates one dissolution time point (e.g.,  $t_{50\%}$ ,  $t_{90\%}$ ) to a single pharmacokinetic parameter such as  $AUC$ ,  $C_{max}$ , or  $T_{max}$ . Similar to a Level B correlation, a Level C correlation represents a single-point correlation and does not reflect the complete shape of the plasma profile that best defines the performance of a drug product. It is generally only useful as a guide in formulation development and may be used to support the design-space ranges for some product parameters in QbD submissions. Because of its obvious limitations, a Level C correlation has limited usefulness in predicting in vivo drug performance and is subject to the same caveats as a Level B correlation in its ability to support product and site changes. The FDA guidance *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (1)* states that it is possible to obtain Biowaivers based on a multiple Level C correlation. The manner in which one should achieve this correlation is defined in the guidance. However, the guidance indicates that if such a correlation is achievable, it is likely that the development of a Level A correlation is also feasible for that particular product.

### GENERAL CONSIDERATIONS FOR DEVELOPING IVIVC

The following concepts were adopted from the FDA IVIVC Guidance (1). General considerations for developing and evaluating a Level A in vitro–in vivo correlation include:

- Human data should be used in the construction of an IVIVC.
- An IVIVC should utilize sufficient subjects (i.e., a sample size with appropriate statistical power) to adequately characterize drug product performance. Crossover studies are preferred, but appropriately powered parallel studies may be acceptable. For a deconvolution-based IVIVC approach, a crossover study design is recommended. This will enable the use of individual values in the deconvolution step.
- The in vitro release rate should be optimized as much as possible to achieve a successful IVIVC. The use of a physiologically relevant medium may be needed to achieve this goal; however, less complex methods (e.g., USP method) have been utilized successfully.
- The in vivo study should be conducted under fasting conditions. The use of data from a fed study should be

justified and used only for safety reasons and for drug products whose bioavailability is not affected by the presence of food.

- It is expected that several formulations with different release rates may need to be evaluated.
- The IVIVC should be demonstrated consistently with two or more formulations with different release rates that result in corresponding differences in absorption profiles. Although an IVIVC can be defined with a minimum of two formulations with different release rates, three or more formulations with different release rates are recommended to establish a more robust relationship.
- In vitro release rate differences may be verified by conducting a similarity test. A failed similarity test is an indication of a significant difference in the in vitro release rates.
- Internal and external predictability of the IVIVC should be assessed. An average absolute percent prediction error of 10% or less for  $C_{max}$  and AUC is preferred.
- IVIVC development should be planned a priori instead of being a post hoc event.
  - Ensures the use of a robust, appropriate analysis of the data.
  - Increases the outcome of a successful correlation.

### Correlation for IR Dosage Forms

To date, most of the correlation efforts with IR dosage forms have been based on the Level C approach, although there also have been efforts employing statistical moment theory (Level B). Although it is conceivable that the same Level A correlation approach may be utilized with IR dosage forms, until data have been gathered to support this concept, Level B and Level C appear to be the usual approaches with these dosage forms. Feasibility may ultimately depend on whether absorption is rate-limited by dissolution. Consideration of BCS characteristics may assist feasibility considerations.

### Correlation for MR Dosage Forms

Level A correlations have been demonstrated primarily for MR oral dosage forms, especially for ER formulations for which in vivo release is the rate-limiting step to absorption. Most likely, this has been the result of sufficient modifications to ER formulations to demonstrate different dissolution rates without altering the mechanism of drug release. Typically, this has been accomplished by slight quantitative variations in the excipients used to control drug release without qualitative changes (i.e., the same excipients have been utilized in all the different formulations). Deconvolution of plasma profiles from formulations with different dissolution profiles can be accomplished by different methods as discussed above. The results of this deconvolution step essentially are absorption profiles that can then be correlated to the dissolution profiles. Plots of percent dissolved at each

certain time point versus percent absorbed, percent released, or percent bioavailability at the same time point can then lead to a mathematical description of the resultant correlation. This mathematical description or IVIVC model can then be used to simulate or predict plasma profiles based on hypothetical dissolution profiles. A linear relationship with a slope = 1 is ideal but not necessary. As illustrated in *USP* General Chapter <1088> (2), nonlinear relationships can also be used to describe a Level A IVIVC. As per the FDA guidance, to establish a Level A correlation, the prediction of plasma profiles is a strict requirement. If such a correlation cannot be established, it is still likely that an IVIVR can be demonstrated if a change in dissolution profile results in a change in the absorption profile.

### Use of Biorelevant Dissolution Methods Linked to GI Physiology: Advantages & Difficulties

A biorelevant dissolution method links the in vitro performance to the in vivo performance of a drug product. Depending on the drug substance and drug product, the biorelevant dissolution method can utilize a simple aqueous buffer in a standard dissolution apparatus or may necessitate physiologically defined media, testing conditions, or both. The currently accepted hypothesis is that the more closely the dissolution test conditions mimic the physiology at the site in the GI tract where the dissolution occurs, the better the chances are of using the dissolution results to predict in vivo performance. However, other factors that affect drug absorption or factors such as first-pass metabolism may diminish the biorelevance of the dissolution methodology. For the development of the best dissolution test, there are three important considerations: (1) the sections of the GI tract where the drug is released from the dosage form, (2) the time that is available for the dosage form to release the drug, and lastly (3) the composition of the fluids into which the drug is released. Pharmaceutical scientists should begin designing an appropriate dissolution test by considering the solubility of the drug contained in the dosage form. For highly soluble drugs (both IR and MR), simple buffers may be sufficient, whereas for MR dosage forms of less soluble drugs, the choice of medium will depend on the release mechanism. For less soluble drugs with high permeability, media that simulate the fluid in the gastrointestinal tract and meet sink conditions should be considered. In a worst-case scenario where the drug is poorly soluble and has low permeability, using sink conditions may lead to over-prediction of absorption. In summary, the best dissolution test to generate an IVIVC will consider the drug substance properties, mechanism of release, dosage form size and dimensions, excipient properties, and dosing conditions in the in vivo study. While numerous physiologically relevant dissolution test conditions have been developed, one should also

take into consideration that whatever test conditions are developed to establish an IVIVC, these same test conditions must be suitable for routine quality control use. The FDA has indicated that it expects the IVIVC and QC dissolution test methods to be identical.

### Use of IVIVC in Product Development

A key application of IVIVC is that of assisting in understanding critical formulation variables that in turn allows for justification of product specifications (e.g., dissolution acceptance criteria). When done properly, a potential application may be that of facilitating approval of biowaivers for the manufacturing changes in the product during its lifecycle.

Usually the requirements of the in vivo side of an IVIVC are to test a minimum of two, preferably three, formulations with different release rates and then compare the PK parameters of those formulations with those of a solution, IR, or IV reference product. Typically, the PK studies are performed in a crossover study design using fasted subjects. The in vitro portion requires development of formulations exhibiting at least a 10% dissolution rate difference. These formulations should be evaluated using the typical dissolution method for the intended finished product. This may require some adjustment of the dissolution method to fit the in vivo data, the use of time scaling to find the best fit, or both. External and internal validation of the IVIVC model should be evaluated recognizing that proof of external validation provides greater confidence in IVIVC than does internal validation alone.

While there are traditional approaches to Level A IVIVC, there is also the possibility of gaining regulatory approval of nontraditional approaches that are justified with appropriate validation data. The benefits to these efforts are that an IVIVC can provide a framework for formulation development while it promotes prioritizing of formulation efforts. In addition, an IVIVC places the development of a biorelevant dissolution method formally into the development process thereby defining manufacturing parameters at an early stage and reducing the risk of requiring BE studies for bridging Phase 3 to the to-be-marketed formulation.

These benefits are commensurate with the current Quality by Design (QbD) approach being adopted by the pharmaceutical industry as a result of regulatory encouragement. The potential dilemma is how to determine if batches that fall within and outside of the design space have any clinical relevance. The easiest answer to this can be found in using these principles from the earliest development stages (i.e., beginning with preclinical and Phase 1). Because of the limitations in amounts of API that often limit early development batch sizes, it is often necessary to develop in vitro methods that utilize micro dissolution apparatus. Other innovative techniques are being evaluated and show promise. The

application of QbD early in the candidate selection and drug development process along with more reliance on IVIVC or IVIVR may provide important advances in the selection and use of clinically relevant methods in later stage development.

### Modeling Programs

A variety of modeling programs are useful in developing robust IVIVCs. Their value lies in their ability to integrate complex mathematical inputs from a large array of existing data to create models applicable to API and dosage forms. These models can then be used to predict outputs based on incomplete or hypothetical data inputs where the inputs may be taken from absorption or dissolution data. When absorption data are available and used, these models have been shown to be predictive of clinical differences resulting from age, ethnicity, and other population differences as well as from BCS classification or formulation differences.

### Approaches Used for Level A IVIVC

An IVIVC (Level A) is usually developed by a two-stage procedure: deconvolution followed by comparison of the fraction of drug absorbed to the fraction of drug dissolved. Alternative approaches to developing a Level A IVIVC are possible. One alternative is based on a convolution procedure that models the relationship between in vitro dissolution and blood concentration in a single step. This one-stage method may overcome the following limitations of the deconvolution-based two-stage method: deconvolution may be not stable and study objectives are often related to the drug concentrations, not the fraction of drug dissolved. The one-stage method may use a population approach by implementing the convolution-based procedure and compartment modeling based on differential equations.

## CURRENT REGULATORY GUIDANCE ON IVIVC

### Europe

In Europe, the Medicines and Healthcare Products Regulatory Agency (MHRA) utilizes the *EMA Guidance on MR Dosage Forms (4)* and the *Note for Guidance on Quality of Modified Release Products (5)* to control the content of all submission dossiers. Separate sections of the guidance cover oral dosage forms, transdermal dosage forms, quality aspects, pharmacokinetics, and clinical evaluation. EMA is considering a revision to include aspects of IVIVC. An outline of the anticipated IVIVC topics to be covered in the Quality section currently includes the following:

- Definitions of levels of IVIVC.
- Advantages and disadvantages of the different levels of IVIVC.
- Role of IVIVC and program rationale for formulation development.

- Choice of reference formulations.
- Life cycle extensions based on IVIVC.

Additional topics in the Quality section include study design (dissolution media sampling times) and applications of specification setting and biowaivers for product variations.

The IVIVC topics found in the Clinical section are in vivo study design, IVIVC analysis, validation, and reporting.

EMA foresees the major reason for adoption of an IVIVC is that it provides in vitro release testing as a surrogate for the BE study, therefore saving money and time. One of the reasons the regulators encourage IVIVC is that during post-approval, there is the reassurance that a positive benefit/risk balance will be maintained throughout life of the product. There are valuable insights available from an IVIVC provided the dissolution test is discriminatory and provides a link to the clinical batches.

### U.S. FDA Experience on IVIVC

In the United States, IVIVC can be used by both branded and generic companies. The primary objective for an IVIVC by innovator companies is to obtain a biowaiver by using the dissolution test as a surrogate for bioequivalence data. A properly validated IVIVC enhances drug product understanding and provides justification of manufacturing changes during drug product development. With the implementation of QbD into the pharmaceutical industry, the role and integration of IVIVC in product development is eminent. IVIVC allows for the prediction of the clinical impact of movements within the design space without the need for additional in vivo studies. These “validated movements” within the design space may lead to regulatory flexibility resulting in wider drug product specifications. In addition, IVIVC enhances the significance of the in vitro testing leading to drug product specification setting based on targeted clinically relevant plasma concentrations. As such, a properly validated IVIVC reduces the regulatory burden leading to time and cost savings during product development.

There are optional approaches undertaken to establish an IVIVC. These may include a retrospective analysis of existing PK–dissolution data along with the more typical prospective planning and developing of clinical study designs for IVIVC. The challenges of retrospective studies versus proactive studies are clear, and it is obvious that FDA wants to encourage more proactive studies. One of the most common challenges to developing an IVIVC is that of how to obtain multiple release rates while maintaining the same release mechanism within the dosage form. Another recognized challenge is how to develop an IVIVC on BCS Class 2 IR drug products (1). In addition, there is the question of whether there should be a standardized approach to evaluate dose dumping from any MR dosage forms and how that would impact on the development of an IVIVC.

Recent FDA statistics on IVIVC submissions show that about 90% of the IVIVCs are submitted for the first time at the NDA stage and only about 10% at the IND stage. FDA encourages the submission of IVIVCs as early as possible during the IND stage to obtain agency feedback, especially in those cases where the IVIVC is critical for the approval of the NDA (e.g., when supporting a major manufacturing change to the clinical trial formulation). Statistics also show that of the IVIVCs submitted to New Drugs, about 75% have followed a Level A correlation, about 15% a Level C, and about 3% contained a Level B correlation. In addition, 75% of all IVIVCs submitted have followed a two-stage independent approach, 9% a one-stage direct convolution, and 9% a one-stage compartmental approach. The rest contained a modified Level A IVIVC for non-oral dosage forms that correlated the in vitro dissolution directly to in vivo release rate not derived directly from plasma concentrations.

One of the most important aspects of the regulatory approval of an IVIVC is the demonstration of the robustness of the correlation as proven by meeting the criteria for internal and external predictability. The FDA guidance mentions that these criteria are met when mean percent prediction error (%PE) for internal predictability is 10% or less and the %PE for each formulation does not exceed 15%. If these criteria are not met, that is, if the internal predictability of the IVIVC is inconclusive, evaluation of external predictability of the IVIVC should be performed as a final determination of the ability of the IVIVC to be used as a surrogate for bioequivalence. The external predictability should be less than 10% (1). If these criteria are not met, then the model is not acceptable. The challenging part for those instances is when the criterion is borderline (e.g., average %PE is 16% for internal predictability). In those cases, it is recommended to challenge the IVIVC by shifting the formulations used for internal and external validation and reconstructing and revalidating the model. A robust model should be able to accurately predict the in vivo plasma concentrations in the range of release rates tested. Note that meeting the internal and external validation criteria is not the only requirement for a successful IVIVC. Even if these criteria are met, the IVIVC will not be found acceptable if other requirements (see list below) are not met. The following is a list of the most common reasons (besides not meeting the validation requirements) for IVIVC rejection:

- 1) Failing to meet the criteria for in vitro and in vivo experimentation in terms of the number of in vitro release characteristics of the formulations used in the construction of the IVIVC. In vitro release rate differences may be verified by conducting a similarity test. A failed similarity test is an indication of a significant difference in the in vitro release rate.
- 2) Lack of a rank-order correlation.

- 3) The IVIVC should be developed in the fasted state and in fed conditions only when the drug is not tolerated. FDA experience shows that the agency has approved only one IVIVC constructed under fed conditions for a drug that exhibited no food effect.
- 4) The use of mean-based deconvolution instead of individual-based deconvolution in the case of a two-stage approach correlation.
- 5) The IVIVC was over-parameterized and not fully mechanistic.
- 6) The use of different scaling factors for the formulations.
- 7) When it comes to the applicability of the IVIVC (e.g., post-approval changes, support of wider dissolution acceptance criteria), a similarity test (e.g.,  $f_2$  test) is often used instead of IVIVC predictions. It should be noted that IVIVC supersedes similarity testing.

These same technical issues exist for generic products making it difficult to justify the benefit versus the cost. FDA limited experience with generic drugs shows that the three common uses of IVIVC are: (1) support of Level 3 changes in scale-up; (2) post-approval changes to manufacturing site, process, non-release-controlling excipients, and release-controlling excipients (especially for MR products); and (3) justification for setting dissolution specifications.

FDA agrees that while an IVIVR is not as robust as an IVIVC, it can be an important tool in the QbD approach to formulation development and justification, and it is possible that some permutation of an IVIVR could be used to target a specific profile. Potential benefits include use as a predictor of commercial batch performance and in the assessment of post-approval changes. However, to date, there has been limited documented success with IVIVRs, and the applicability of IVIVRs to development efforts likewise does not appear to be well established. While verification of the design space and the clinical relevancy of the specifications for material attributes and process parameters can still be determined in the absence of an IVIVC, clinical relevancy can only be assured for those changes whose dissolution profiles fall within the extremes of dissolution profiles for batches that were bioequivalent.

## TERMINOLOGY

- AAPS: American Association of Pharmaceutical Scientists
- API: active pharmaceutical ingredient
- AUC: area under the curve for a plasma, serum, or blood concentration-versus-time profile after a drug dose
- BE: bioequivalence
- cGMP: current Good Manufacturing Practices (as defined in 21CFR Part 11)
- $C_{max}$ : maximum plasma or serum concentration after dosing with a drug
- Deconvolution: mathematical method whereby a drug plasma-concentration profile can be converted into an

- in vivo luminal release or a systemic absorption profile
- EMA: European Medicines Agency
- ER: extended release
- FDA: Food & Drug Administration
- FIP: International Pharmaceutical Federation
- ICH: International Conference on Harmonization
- IR: immediate release
- IV: intravenous
- IVIVC: in vitro–in vivo correlation
- IVIVR: in vitro–in vivo relationship
- Loo–Riegelman Method: method for two-compartment drugs to convert a plasma concentration profile into an absorption profile (6)
- MAM: mechanistic absorption model
- MHRA: Medicines & Healthcare Products Regulatory Agency
- MR: modified release
- MRT: mean residence time
- NIR: near infrared
- PQRI: Product Quality Research Institute
- QbD: Quality by Design
- $T_{max}$ : time at which  $C_{max}$  was achieved
- TPP: target product profile
- $T_{50\%}$ : In dissolution, the time at which 50% of the theoretical amount of available drug is dissolved
- $T_{90\%}$ : In dissolution, the time at which 90% of the theoretical amount of available drug is dissolved
- USP: United States Pharmacopeia
- Wagner–Nelson Method: method for one-compartment drugs to convert a plasma concentration profile into an absorption profile (7)

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