dx.doi.org/10.14227/DT040497P23

FDA Guidance for Industry[1]

Extended Release Solid Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations

Working Group Members:
Henry Malinowski, Patrick Marroum, Venkata Ramana Uppoor, William Gillespie,* Hae-Young Ahn, Peter Lockwood,* James Henderson,* Raman Baweja, Mohammad Hossain,* Nicholas Fleischer,* Lloyd Tillman,* Ajaz Hussain, Vinod Shah, Angelica Dorantes, Ray Zhu,* He Sun, Kofi Kumi, Stella Machado, Vijaya Tammara, Ting Eng Ong-Chen, Houda Mahayni, Lawrence Lesko, Roger Williams**

**These individuals not currently with FDA.*
***To whom correspondence should be addressed.*

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
September 1997
BP2

This guidance provides recommendations to pharmaceutical sponsors who intend to develop documentation in support of an in vitro/in vivo correlation (IVIVC) for an oral extended release (ER) drug product for submission in a new drug application (NDA), abbreviated new drug application (ANDA), or antibiotic drug application (AADA). The guidance presents a comprehensive perspective on (1) methods of developing an IVIVC and evaluating its predictability; (2) using an IVIVC to set dissolution specifications; and (3) applying an IVIVC as a surrogate for in vivo bioequivalence when it is necessary to document bioequivalence during the initial approval process or because of certain pre- or postapproval changes (e.g., formulation, equipment, process, and manufacturing site changes).

BACKGROUND

The concept of IVIVC, particularly for ER drug products, has been extensively discussed by pharmaceutical scientists. The ability to predict, accurately and precisely, expected bioavailability characteristics for an ER product from dissolution profile characteristics is a long sought after goal. Several workshops and publications have provided information in support of this goal. These are discussed briefly as follows:

- A report from a 1987 ASCPT/DIA/APS/FDA-sponsored workshop entitled *Report of the Workshop on CR Dosage Forms: Issues and Controversies* (1987) indicated that the state of science and technology at that time did not permit consistently meaningful IVIVC for ER dosage forms and encouraged IVIVC as a future objective. Dissolution testing was considered useful only for process control, stability, minor formulation changes, and manufacturing site changes.

- A USP PF Stimuli Article in July 1988 established the classification of IVIVC into Levels A, B and C, which are currently in use.

- A report from a 1990 ASCPT/DIA/APS/FDA-sponsored workshop entitled *In vitro/In vivo Testing and Correlation for Oral Controlled/Modified Release Dosage Forms* (1990) concluded that, while the science and technology may not always permit meaningful IVIVC, the development of an IVIVC was an important objective on a product-by-product basis. Procedures for development, evaluation, and application of an IVIVC were described. Validation of dissolution specifications by a bioequivalence study involving two batches of product with dissolution profiles at the upper and lower dissolution specifications was suggested.

- USP Chapter 1088 similarly describes techniques appropriate for Level A, B, and C correlations and methods for establishing dissolution specifications.

- Further information related to IVIVCs was developed in a USP/AAPS/FDA-sponsored workshop, which resulted in a report entitled *Workshop II Report: Scale-up of Oral Extended Release Dosage Forms* (1993). This report identified the objectives of an IVIVC to be the use of dissolution as a surrogate for bioequivalency testing, as well as an aid in setting dissolution specifications. The report concluded that dissolution may be used as a sensitive, reliable, and reproducible surrogate for bioequivalence testing. The report gave support to the concepts of USP Chapter 1088 and further found that an IVIVC may be useful for changes other than minor changes in formulation, equipment, process, manufacturing site, and batch size.

These reports document increasing confidence in IVIVC to estimate the in vivo bioavailability characteristics for an ER drug product. In this regard, increased IVIVC activity in NDA submissions has been apparent. Still, the complete process of developing an IVIVC with high quality and predictability and identifying specific applications for such correlations has not been well defined.

As part of the process of developing this

[1] *This guidance has been prepared by the Extended Release Dissolution Working Group of the Biopharmaceutics Coordinating Committee (BCC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). This guidance represents the Agency's current thinking on in vitro/in vivo correlations for extended release oral dosage forms. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the applicable statute, regulations, or both.*

FDA Extended Release Guidance...continued

guidance, the Agency conducted several surveys of NDA submissions for ER drug products to find out the number of times that IVIVCs were developed. The first survey included NDA submissions from 1982-1992 and found 9 IVIVCs in 60 submissions. A more recent survey included NDA submissions from October 1994 to October 1995 and found 9 IVIVCs in 12 submissions.

This guidance is based on these prior deliberations and publications as well as on current understanding at the FDA and elsewhere on approaches to developing reliable and useful IVIVCs. This guidance describes the levels of correlations that can be established with varying degrees of usefulness, important considerations for in vivo and in vitro experimentation, evaluation of the correlation by focusing on the critical feature of predictability, and practical applications that can be achieved using the IVIVC. With the availability of this guidance, sponsors are encouraged to develop IVIVCs for ER products in the expectation that the information will be useful in establishing dissolution specifications and will permit certain formulation and manufacturing changes without an in vivo bioequivalence study.

CATEGORIES OF IN VITRO/IN VIVO CORRELATIONS

A. Level A

A Level A correlation[2] is usually estimated by a two-stage procedure: deconvolution followed by comparison of the fraction of drug absorbed to the fraction of drug dissolved. A correlation of this type is generally linear and represents a point-to-point relationship between in vitro dissolution and the in vivo input rate (e.g., the in vivo dissolution of the drug from the dosage form). In a linear correlation, the in vitro dissolution and in vivo input curves may be directly superimposable or may be made to be superimposable by the use of a scaling factor. Nonlinear correlations, while uncommon, may also be appropriate.

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 plasma concentration in a single step. Plasma concentrations predicted from the model and those observed are compared directly. For these methods, a reference treatment is desirable, but the lack of one does not preclude the ability to develop an IVIVC.

Whatever the method used to establish a Level A IVIVC, the model should predict the entire in vivo time course from the in vitro data. In this context, the model refers to the relationship between in vitro dissolution of an ER dosage form and an in vivo response such as plasma drug concentration or amount of drug absorbed.

B. Level B

A Level B IVIVC uses the principles of statistical moment analysis. The mean in vitro dissolution time is compared either to the mean residence time or to the mean in vivo dissolution time. A Level B correlation, like a Level A, uses all of the in vitro and in vivo data, but is not considered to be a point-to-point correlation. A Level B correlation does not uniquely reflect the actual in vivo plasma level curve, because a number of different in vivo curves will produce similar mean residence time values.

C. Level C

A Level C IVIVC establishes a single point relationship between a dissolution parameter, for example, $t_{50\%}$, percent dissolved in 4 hours and a pharmacokinetic parameter (e.g., AUC, C_{max}, T_{max}). A Level C correlation does not reflect the complete shape of the plasma concentration time curve, which is the critical factor that defines the performance of ER products.

D. Multiple Level C

A multiple Level C correlation relates one or several pharmacokinetic parameters of interest to the amount of drug dissolved at several time points of the dissolution profile.

GENERAL CONSIDERATIONS:

The following general statements apply in the development of an IVIVC in an NDA or ANDA/AADA:

- Human data should be supplied for regulatory consideration of an IVIVC.

- Bioavailability studies for IVIVC development should be performed with enough subjects to characterize adequately the performance of the drug product under study. In prior acceptable data sets, the number of subjects has ranged from 6 to 36. Although crossover studies are preferred, parallel studies or cross-study analyses may be acceptable. The latter may involve normalization with a common reference treatment. The reference product in developing an IVIVC may be an intravenous solution, an aqueous oral solution, or an immediate release product.

- IVIVCs are usually developed in the fasted state. When a drug is not tolerated in the fasted state, studies may be conducted in the fed state.

- Any in vitro dissolution method may be used to obtain the dissolution characteristics of the ER dosage form. The same system should be used for all formulations tested.

- The preferred dissolution apparatus is USP apparatus I (basket) or II (paddle), used at compendially recognized rotation speeds (e.g., 100 rpm for the basket and 50-75 rpm for the paddle). In other cases, the dissolution properties of some ER formulations may be determined with USP apparatus III (reciprocating cylinder) or IV (flow through cell).

Appropriate review staff in CDER should be consulted before using any other type of apparatus.

- An aqueous medium, either water or a buffered solution prefer-

[2] *Level A correlations are the most common type of correlation developed in NDAs submitted to the FDA. Level B correlations are rarely seen in NDAs; multiple Level C correlations are seen infrequently.*

ably not exceeding pH 6.8, is recommended as the initial medium for development of an IVIVC. Sufficient data should be submitted to justify pH greater than 6.8. For poorly soluble drugs, addition of surfactant (e.g., 1% sodium lauryl sulfate) may be appropriate. In general, nonaqueous and hydroalcoholic systems are discouraged unless all attempts with aqueous media are unsuccessful. Appropriate review staff in CDER should be consulted before using any other media.

• The dissolution profiles of at least 12 individual dosage units from each lot should be determined. A suitable distribution of sampling points should be selected to define adequately the profiles. The coefficient of variation (CV) for mean dissolution profiles of a single batch should be less than 10%.

• A Level A IVIVC is considered to be the most informative and is recommended, if possible.

• Multiple Level C correlations can be as useful as Level A correlations. However, if a multiple Level C correlation is possible, then a Level A correlation is also likely and is preferred.

• Level C correlations can be useful in the early stages of formulation development when pilot formulations are being selected.

• Level B correlations are least useful for regulatory purposes.

• Rank order correlations are qualitative and are not considered useful for regulatory purposes.

DEVELOPMENT AND EVALUATION OF A LEVEL A IN VITRO/IN VIVO CORRELATION

A. Developing the Correlation

The most commonly seen process for developing a Level A IVIVC is to (1) develop formulations with different release rates, such as slow, medium, fast, or a single release rate if dissolution is condition independent; (2) obtain in vitro dissolution profiles and in vivo plasma concentration profiles for these formulations; (3) estimate the in vivo absorption or dissolution time course using an appropriate deconvolution technique for each formulation and subject (e.g., Wagner-Nelson, numerical deconvolution). These three steps establish the IVIVC model. Alternative approaches to developing Level A IVIVCs are possible. Further general information follows:

• The IVIVC relationship should be demonstrated consistently with two or more formulations with different release rates to 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. Exceptions to this approach (i.e., use of only one formulation) may be considered for formulations for which in vitro dissolution is independent of the dissolution test conditions (e.g., medium, agitation, pH).

• Ideally, formulations should be compared in a single study with a crossover design.

• If one or more of the formulations (highest or lowest release rate formulations) does not show the same relationship between in vitro dissolution and in vivo performance compared with the other formulations, the correlation may still be used within the range of release rates encompassed by the remaining formulations.

• The in vitro dissolution methodology should adequately discriminate among formulations. Dissolution testing can be carried out during the formulation screening stage using several methods. Once a discriminating system is developed, dissolution conditions should be the same for all formulations tested in the biostudy for development of the correlation and should be fixed before further steps towards correlation evaluation are undertaken.

• During the early stages of correlation development, dissolution conditions may be altered to attempt to develop a 1-to-1 correlation between the in vitro dissolution profile and the in vivo dissolution profile.

• Time scaling may be used as long as the time scaling factor is the same for all formulations. Different time scales for each formulation indicate absence of an IVIVC.

B. Evaluating the Predictability of a Level A Correlation

An IVIVC should be evaluated to demonstrate that predictability of in vivo performance of a drug product from its in vitro dissolution characteristics is maintained over a range of in vitro dissolution release rates and manufacturing changes. Since the objective of developing an IVIVC is to establish a predictive mathematical model describing the

relationship between an in vitro property and a relevant in vivo response, the proposed evaluation approaches focus on the estimation of predictive performance or, conversely, prediction error. Depending on the intended application of an IVIVC and the therapeutic index of the drug, evaluation of prediction error internally and/or externally may be appropriate. Evaluation of internal predictability is based on the initial data used to define the IVIVC model. Evaluation of external predictability is based on additional test data sets. Application of one or more of these procedures to the IVIVC modeling process constitutes evaluation of predictability.

An important concept is that the less data available for initial IVIVC development and evaluation of predictability, the more additional data may be needed to define completely the IVIVC's predictability. Some combination of three or more formulations with different release rates is considered optimal.

Another significant factor is the range of release rates studied. The release rates, as measured by percent dissolved, for each formulation studied, should differ adequately (e.g., by 10%). This should result in in vivo profiles that show a comparable difference, for example, a 10% difference in the pharmacokinetic parameters of interest (C_{max} or AUC) between each formulation.

Methodology for the evaluation of IVIVC predictability is an active area of investigation and a variety of methods are possible and potentially acceptable. A correlation should predict in vivo performance accurately and consistently. Once this relationship has been achieved, in vitro dissolution can be used confidently as a surrogate for in vivo bioequivalence of ER drug products in the situations described below.

1. Experimental Data Considerations

a. Dosage Form Properties: Dependence of In Vitro Release on Experimental Conditions

Condition independent dissolution: If in vitro dissolution is shown to be independent of dissolution conditions (e.g., pH and agitation) and if the in vitro dissolution profile is shown to be equal to the in vivo absorption or in vivo dissolution profile, then the results for a single formulation (one release rate) may be sufficient. Evaluation of data for this formulation and evaluation of additional test data sets, as appropriate, for the purpose of estimation of internal and/or external predictability are recommended.

Condition dependent dissolution: In all other instances where an IVIVC model is presented, results from a single formulation (one release rate) should be considered insufficient. To estimate internal and/or external predictability, evaluation of data from two or more formulations with different release rates is recommended.

b. Internal and External Predictability

Two distinct aspects of predictability can be considered. However, both aspects are not recommended in all instances.

Estimation of prediction error internally: The first aspect relates to evaluating how well the model describes the data used to define the IVIVC and is appropriate in all instances.

If formulations with three or more release rates are used to develop the IVIVC model, no further evaluation beyond this initial estimation of prediction error may be necessary for non-narrow therapeutic index drugs (Category 2 a and b applications, see page 28). However, depending on the results of this internal prediction error calculation, determination of prediction error externally may be appropriate.

If only two formulations with different release rates are used, the application of the IVIVC is further limited to Category 2a applications (see page 28). In this circumstance, determination of prediction error externally is recommended for complete evaluation and subsequent full application of the IVIVC.

Estimation of prediction error externally: The second aspect relates to how well the model predicts data when one or more additional test data sets are used that differ from those used to define the correlation. This is appropriate in some situations, particularly when only two formulations with different release rates are used to develop the IVIVC model, when calculation of prediction error internally is inconclusive, or when a narrow therapeutic index drug is studied.

The additional test data sets used for external prediction error calculation may have several differing characteristics compared to the data sets used in IVIVC development. Although formulations with different release rates provide the optimal test of an IVIVC's predictability, a formulation need not be prepared solely for this purpose. In the absence of such a formulation, data from other types of formulations may be considered. In each case, bioavailability data should be available for the data set under consideration.

The following represent, in decreasing order of preference, formulations that may be used to estimate prediction error externally:

- A formulation with a different release rate than those used in IVIVC development. The release rate of the test formulation may be either within or outside the range used to define the IVIVC relationship.

- A formulation with the same or similar release rate, but involving some change in manufacture of this batch (e.g., composition, process, equipment, manufacturing site).

- A formulation with the same or similar release rate obtained from another batch/lot with no changes in manufacturing.

c. Pharmacologic Properties of the Drug (Therapeutic Index)

Narrow therapeutic index drugs: If an IVIVC model is to be used in estimating the in vivo performance of formulations of narrow therapeutic index drugs, the model's predictability should be tested further with a data set that differs from those data sets used to define the correlation. In other words, the external predictability of the correlation should be evaluated.

Non-narrow therapeutic index drugs: If an IVIVC model is to be used in estimating the in vivo performance of formulations of non-narrow therapeutic index drugs, testing the model's predictability with a data set that differs from those data sets used to define the cor-

relation may be desirable, but is not considered as important as for a narrow therapeutic index drug.

Note — If the classification of a drug as a narrow therapeutic index drug is uncertain, appropriate review staff in CDER should be consulted.

2. Methods for Evaluation of Predictability

The objective of IVIVC evaluation is to estimate the magnitude of the error in predicting the in vivo bioavailability results from in vitro dissolution data. This objective should guide the choice and interpretation of evaluation methods. Any appropriate approach related to this objective may be used for evaluation of predictability.

Internal predictability: All IVIVCs should be studied regarding internal predictability. One recommended approach involves the use of the IVIVC model to predict each formulation's plasma concentration profile (or C_{max} and/or AUC for a multiple Level C IVIVC) from each respective formulation's dissolution data. This is performed for each formulation used to develop the IVIVC model. The predicted bioavailability is then compared to the observed bioavailability for each formulation and a determination of prediction error is made.

Criteria

- Average absolute percent prediction error (% PE) of 10% or less for C_{max} and AUC establishes the predictability of the IVIVC. In addition, the % PE for each formulation should 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.

External predictability: Most important when using an IVIVC as a surrogate for bioequivalence is confidence that the IVIVC can predict in vivo performance of subsequent lots of the drug product. Therefore, it may be important to establish the external predictability of the IVIVC. This involves using the IVIVC to predict the in vivo performance for a formulation with known bioavailability that was not used in developing the IVIVC model.

Criteria

- % PE of 10% or less for C_{max} and AUC establishes the external predictability of an IVIVC.

- % PE between 10 - 20% indicates inconclusive predictability and the need for further study using additional data sets. Results of estimation of PE from all such data sets should be evaluated for consistency of predictability.

- % PE greater than 20% generally indicates inadequate predictability, unless otherwise justified.

With the exception of narrow therapeutic index drugs, the external predictability step in the IVIVC evaluation process may be omitted if the evaluation of internal predictability indicates acceptable % PE. However, when the evaluation of internal predictability is inconclusive, evaluation of external predictability is recommended.

DEVELOPMENT AND EVALUATION OF A LEVEL C IN VITRO/IN VIVO CORRELATION

A single point Level C correlation allows a dissolution specification to be set at the specified time point. While the information may be useful in formulation development, waiver of an in vivo bioequivalence study (biowaiver) is generally not possible if only a single point correlation is available. A multiple point Level C correlation may be used to justify a biowaiver, provided that the correlation has been established over the entire dissolution profile with one or more pharmacokinetic parameters of interest. This could be achieved by correlating the amount dissolved at various time points with C_{max}, AUC, or any other suitable parameter. A relationship should be demonstrated at each time point with the same parameter such that the effect on the in vivo performance of any change in dissolution can be assessed. If such a multiple Level C correlation is achievable, then the development of a Level A correlation is likely. A multiple Level C correlation should be based on at least three dissolution time points covering the early, middle, and late stages of the dissolution profile. The recommendations for assessing the predictability of Level C correlations will depend on the type of application for which the correlation is to be used. These methods and criteria are the same as those for a Level A correlation (see "Methods for Evaluation of Predictability," column one, this page).

APPLICATIONS OF AN IVIVC

In vitro dissolution testing is important for (1) providing process control and quality assurance; (2) determining stable release characteristics of the product over time; and (3) facilitating certain regulatory determinations (e.g., absence of effect of minor formulation changes or of change in manufacturing site on performance). In certain cases, especially for ER formulations, the dissolution test can serve not only as a quality control for the manufacturing process but also as an indicator of how the formulation will perform in vivo. Thus, a main objective of developing and evaluating an IVIVC is to establish the dissolution test as a surrogate for human bioequivalence studies, which may reduce the number of bioequivalence studies performed during the initial approval process as well as with certain scale-up and postapproval changes. However, for the applications outlined below, the adequacy of the in vitro dissolution method to act as a surrogate for in vivo testing should be shown through an IVIVC for which predictability has been established.

A. Biowaivers for Changes in the Manufacturing of a Drug Product

1. Category 1: Biowaivers Without an IVIVC

For formulations consisting of beads in capsules, with the only difference between strengths being the number

of beads, approval of lower strengths without an IVIVC is possible, provided bioavailability data are available for the highest strength.

Where the guidance for industry *SUPAC-MR: Modified Release Solid Oral Dosage Forms; Scale-Up and Postapproval changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* recommends a biostudy, biowaivers for the same changes made on lower strengths are possible without an IVIVC if (1) all strengths are compositionally proportional or qualitatively the same, (2) in vitro dissolution profiles of all strengths are similar, (3) all strengths have the same release mechanism, (4) bioequivalence has been demonstrated on the highest strength (comparing changed and unchanged drug product), and (5) dose proportionality has been demonstrated for this ER drug product. In the last circumstance (5), documentation of dose proportionality may not be necessary if bioequivalence has been demonstrated on the highest and lowest strengths of the drug product, comparing changed and unchanged drug product for both strengths, as recommended in SUPAC-MR.

For the above situations, waivers can be granted without an IVIVC if dissolution data are submitted in the application/compendial medium and in three other media (e.g., water, 0.1N HCl, and USP buffer at pH 6.8, comparing the drug product after the change to the drug product before the change).

Biowaivers, as defined in SUPAC-MR, that do not necessitate either bioequivalence testing or an IVIVC will likely be granted in preapproval situations for both narrow and non-narrow therapeutic index ER drug products if dissolution data, as described in SUPAC-MR, are submitted.

Comparison of dissolution profiles: Dissolution profiles can be compared using model independent or model dependent methods. A model independent approach using a similarity factor, and comparison criteria are described in SUPAC-MR.

2. Category 2: Biowaivers Using an IVIVC: Non-Narrow Therapeutic Index Drugs

a. Two Formulations/Release Rates

A biowaiver will likely be granted for an ER drug product using an IVIVC developed with two formulations/release rates for (1) Level 3 manufacturing site changes as defined in SUPAC-MR; (2) Level 3 nonrelease controlling excipient changes as defined in SUPAC-MR, with the exception of complete removal or replacement of excipients (see below).

b. Three Formulations/Release Rates

A biowaiver will likely be granted for an ER drug product using an IVIVC developed with three formulations/release rates (or developed with two formulations/release rates with establishment of external predictability) for (1) Level 3 process changes as defined in SUPAC-MR; (2) complete removal of or replacement of nonrelease controlling excipients as defined in SUPAC-MR; and (3) Level 3 changes in the release controlling excipients as defined in SUPAC-MR.

c. Biowaivers for Lower Strengths

If an IVIVC is developed with the highest strength, waivers for changes made on the highest strength and any lower strengths may be granted if these strengths are compositionally proportional or qualitatively the same, the in vitro dissolution profiles of all the strengths are similar, and all strengths have the same release mechanism.

d. Approval of New Strengths

This biowaiver is applicable to strengths lower than the highest strength, within the dosing range that has been established to be safe and effective, if the new strengths are compositionally proportional or qualitatively the same; have the same release mechanism; have similar in vitro dissolution profiles; and are manufactured using the same type of equipment and the same process at the same site as other strengths that have bioavailability data available.

For generic products to qualify for this biowaiver, one of the following situations should exist:

- Bioequivalence has been established for all strengths of the reference listed product.

- Dose proportionality has been established for the reference listed product, and all reference product strengths are compositionally proportional or qualitatively the same, have the same release mechanism, and the in vitro dissolution profiles of all strengths are similar.

- Bioequivalence is established between the generic product and the reference listed product at the highest and lowest strengths and, for the reference listed product, all strengths are compositionally proportional or qualitatively the same, have the same release mechanism, and the in vitro dissolution profiles are similar.

Obtaining category 2d biowaivers: The difference in predicted means of C_{max} and AUC should be no more than 10%, based on dissolution profiles of the highest strength and the lower strength product.

e. Changes in Release Controlling Excipients

Changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation.

f. Obtaining Category 2a, 2b, and 2c Biowaivers:

The difference in predicted means of C_{max} and AUC should be no more than 20% from that of the reference product and, where appropriate, the new formulation should meet the application/compendial dissolution specifications.

3. Category 3: Biowaivers Using an IVIVC: Narrow Therapeutic Index Drugs

If external predictability of an IVIVC is established, the following waivers will likely be granted if at least two formulations/release rates have been studied for the development of the IVIVC.

a. Situations in Which Biowaivers May Be Granted

A biowaiver will likely be granted for an ER drug product using

an IVIVC for (1) Level 3 process changes as defined in SUPAC-MR; (2) complete removal of or replacement of non-release controlling excipients as defined in SUPAC-MR; and (3) Level 3 changes in the release controlling excipients as defined in SUPAC-MR.

b. Biowaivers for Lower Strengths

If an IVIVC is developed with the highest strength, waivers for changes made on the highest strength and any lower strengths may be granted, if these strengths are compositionally proportional or qualitatively the same, the in vitro dissolution profiles of all the strengths are similar, and all strengths have the same release mechanism.

c. Approval of New Strengths

This biowaiver is applicable to strengths lower than the highest strength, within the dosing range that has been established to be safe and effective, provided that the new strengths are compositionally proportional or qualitatively the same, have the same release mechanism, have similar in vitro dissolution profiles, and are manufactured using the same type of equipment, and the same process at the same site as other strengths that have bioavailability data available.

For generic products to qualify for this biowaiver, one of the following situations should exist:

- Bioequivalence has been established for all strengths of the reference listed product.

- Dose proportionality has been established for the reference listed product, all reference product strengths are compositionally proportional or qualitatively the same and have the same release mechanism, and the in vitro dissolution profiles of all strengths are similar.

- Bioequivalence is established between the generic product and the reference listed product at the highest and lowest strengths and, for the reference listed product, all strengths are compositionally proportional or qualitatively the same and have the same release mechanism, and the in vitro dissolution profiles are similar.

Obtaining category 3c biowaivers: The difference in predicted means of C_{max} and AUC should be no more than 10%, based on dissolution profiles of the highest strength and the lower strength product.

d. Changes in Release Controlling Excipients

- Changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation.

e. Obtaining Category 3a and 3b Biowaivers:

The difference in predicted means of C_{max} and AUC should be no more than 20% from that of the reference product and, where appropriate, the new formulation meets the application/compendial dissolution specifications.

4. Category 4: Biowaivers When In Vitro Dissolution Is Independent of Dissolution Test Conditions

Situations in which biowaivers are likely to be granted for both narrow and non-narrow therapeutic index drugs:

a. Category 2 and Category 3 biowaivers are likely to be granted with an IVIVC established with one formulation/release rate.

Biowaivers may be granted if dissolution data are submitted in application/compendial medium and in three other media (e.g., water, 0.1 N HCl, USP buffer at pH 6.8) and the following conditions apply:

- In vitro dissolution should be shown to be independent of dissolution test conditions after change is made in drug product manufacturing.

- Comparison of dissolution profiles

Dissolution profiles can be compared using model independent or model dependent methods. A model independent approach using a similarity factor and comparison criteria is described in SUPAC-MR.

b. Obtaining Category 4 Biowaivers

The difference in predicted means of C_{max} and AUC should be no more than 20% from that of the reference product and, where appropriate, the new formulation should meet the application/compendial dissolution specifications.

5. Category 5: Situations for which an IVIVC Is Not Recommended

a. Approval of a new formulation of an approved ER drug product when the new formulation has a different release mechanism.

b. Approval of a dosage strength higher or lower than the doses that have been shown to be safe and effective in clinical trials.

c. Approval of another sponsor's ER product even with the same release controlling mechanism.

d. Approval of a formulation change involving a nonrelease controlling excipient in the drug product that may significantly affect drug absorption.

B. Setting Dissolution Specifications

In vitro dissolution specifications should generally be based on the performance of the clinical/bioavailability lots. These specifications may sometimes be widened so that scale-up lots, as well as stability lots, meet the specifications associated with the clinical/bioavailability lots. This approach is based on the use of the in vitro dissolution test as a quality control test without any in vivo significance, even though in certain cases (e.g., ER formulations, the rate limiting step in the absorption of the drug is the dissolution of the drug from the formulation). An IVIVC adds in vivo relevance to in vitro dissolution specifications, beyond batch-to-batch quality control. In this approach, the in vitro dissolution test becomes a meaningful predictor of in vivo performance of the formulation, and dissolution specifications may be used to minimize the possibility of releasing lots that would be different in in vivo performance.

FDA Extended Release Guidance...continued

1. Setting Dissolution Specifications Without an IVIVC

• The recommended range at any dissolution time point specification is ± 10% deviation from the mean dissolution profile obtained from the clinical/bioavailability lots.

• In certain cases, reasonable deviations from the ± 10 % range can be accepted provided that the range at any time point does not exceed 25%. Specifications greater than 25% may be acceptable based on evidence that lots (side batches) with mean dissolution profiles that are allowed by the upper and lower limit of the specifications are bioequivalent.

• Specifications should be established on clinical/bioavailability lots. Widening specifications based on scale-up, stability, or other lots for which bioavailability data are unavailable is not recommended.

• A minimum of three time points is recommended to set the specifications. These time points should cover the early, middle, and late stages of the dissolution profile. The last time point should be the time point where at least 80% of drug has dissolved. If the maximum amount dissolved is less than 80%, the last time point should be the time when the plateau of the dissolution profile has been reached.

• Specifications should be established based on average dissolution data for each lot under study, equivalent to USP Stage 2 testing. Specifications allow that all lots to pass at Stage 1 of testing may result in lots with less than optimal in vivo performance passing these specifications at USP Stage 2 or Stage 3.

• USP acceptance criteria for dissolution testing are recommended unless alternate acceptance criteria are specified in the ANDA/NDA.

2. Setting Dissolution Specifications Where an IVIVC Has Been Established

Optimally, specifications should be established such that all lots that have dissolution profiles within the upper and lower limits of the specifications are bioequivalent. Less optimally but still possible, lots exhibiting dissolution profiles at the upper and lower dissolution limits should be bioequivalent to the clinical/bioavailability lots or to an appropriate reference standard.

a. Level A Correlation Established

• Specifications should be established based on average data.

• A minimum of three time points is recommended to establish the specifications. These time points should cover the early, middle and late stages of the dissolution profile. The last time point should be the time point where at least 80% of drug has dissolved. If the maximum amount dissolved is less than 80%, then the last time point should be the time where the plateau of the dissolution profile has been reached.

• Calculate the plasma concentration time profile using convolution techniques or other appropriate modeling techniques and determine whether the lots with the fastest and slowest release rates that are allowed by the dissolution specifications result in a maximal difference of 20% in the predicted C_{max} and AUC.

• An established IVIVC may allow setting wider dissolution specifications. This would be dependent on the predictions of the IVIVC (i.e., 20% differences in the predicted C_{max} and AUC).

• USP acceptance criteria for dissolution testing are recommended unless alternate acceptance criteria are specified in the ANDA/NDA.

b. Multiple Level C Correlation Established

• If a multiple point Level C correlation has been established, establish the specifications at each time point such that there is a maximal difference of 20% in the predicted C_{max} and AUC.

• Additionally, the last time point should be the time point where at least 80% of drug has dissolved.

c. Level C Correlation Based on Single Time Point Established

This one time point may be used to establish the specification such that there is not more than a 20% difference in the predicted AUC and C_{max}. At other time points, the maximum recommended range at any dissolution time point specification should be ± 10% of label claim deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Reasonable deviations from ± 10% may be acceptable if the range at any time point does not exceed 25%.

3. Setting Specifications Based on Release Rate

If the release characteristics of the formulation can be described by a zero-order process for some period of time (e.g., 5%/hr from 4 to 12 hours), and the dissolution profile appears to fit a linear function for that period of time, a release rate specification may be established to describe the dissolution characteristics of that formulation. A release rate specification may be an addition to the specifications established on the cumulative amount dissolved at the selected time points. Alternatively, a release rate specification may be the only specification except for the specification for time when at least 80% of drug has dissolved.

REFERENCES

1. Gillespie, W. R., Office of Clinical Pharmacology and Biopharmaceutics, FDA, "Convolution-Based Approaches for In Vivo-In Vitro Correlation Modeling."
2. FDA, September 1997, Guidance for Industry: *SUPAC-MR: Modified Release Solid Oral Dosage Forms; Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation.*
3. Moore, J. W., and H. H. Flanner, November 1994, "Mathematical Comparison of Curves with an Emphasis on Dissolution Profiles," presented at the AAPS National Meeting, Personal Communication from AAI Inc., Wilmington, NC 28405.

4. Skelly, J. P., et al., 1987, "Report of the Workshop on CR Dosage Forms: Issues and Controversies," *Pharmaceutical Research*, 4(1):75-78.
5. United States Pharmacopeial Convention, Inc., July 1988, "In Vitro-In Vivo Correlation for Extended Release Oral Dosage Forms," *Pharmacopeial Forum* Stimuli Article, 4160-4161.
6. Skelly, J. P., et al., September 1990, "Report of Workshop on In Vitro and In Vivo Testing and Correlation for Oral Controlled/Modified-Release Dosage Forms," *Journal of Pharmaceutical Sciences*, 79(9):849-854.
7. United States Pharmacopeial Convention, Inc., "In Vitro In Vivo Evaluation of Dosage Forms", USP XXIII<1088>, 1927-1929.
8. Skelly, J. P., et al., 1993, Workshop II Report "Scale-up of Oral Extended Release Dosage Forms," *Pharmaceutical Research*, 10(12):1800-1805.

DEFINITION OF TERMS

Batch: A specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits *(21 CFR 210.3(b)(2))*.

Batch formula (composition): A complete list of the ingredients and their amounts to be used for the manufacture of a representative batch of the drug product. All ingredients should be included in the batch formula whether or not they remain in the finished product *(Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products, FDA, February 1987)*.

Bioavailability: The rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action *(21 CFR 320.1(a))*.

Biobatch: A lot of drug product formulated for purposes of pharmacokinetic evaluation in a bioavailability/bioequivalency study. This lot should be 10% or greater than the proposed commercial production batch or at least 100,000 units, whichever is greater.

Bioequivalent drug products: Pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied *(21 CFR 320.1(e))*.

Convolution: Prediction of plasma drug concentrations using a mathematical model based on the convolution integral. For example, the following convolution integral equation may be used to predict the plasma concentration ($c(t)$) resulting from the absorption rate time course (r_{abs}):

$$c(t) = \int_0^t c_\delta\,(t-u)\, r_{abs}(u)\, du$$

The function c_δ represents the concentration time course that would result from the instantaneous absorption of a unit amount of drug and can be

See **Extended Release** ... *continued page 32*

FDA Extended Release Guidance...continued

estimated from either i.v. bolus data, oral solution, suspension or rapidly releasing (in vivo) immediate release dosage forms.

Correlation: As used in this guidance, a relationship between in vitro dissolution rate and in vivo input (absorption) rate.

Deconvolution: Estimation of the time course of drug input (usually in vivo absorption or dissolution) using a mathematical model based on the convolution integral. For example, the absorption rate time course (r_{abs}) that resulted in the plasma concentrations ($c(t)$) may be estimated by solving the following convolution integral equation for r_{abs}:

$$c(t) = \int_0^t c_\delta(t-u)\, r_{abs}(u)\, du$$

The function c_δ represents the concentration time course that would result from the instantaneous absorption of a unit amount of drug and is typically estimated from either i.v. bolus data, oral solution, suspension or rapidly releasing (in vivo) immediate release dosage forms.

Development: Establishing an in vitro/in vivo correlation.

Drug product: A finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients *(21 CFR 314.3(b))*.

Extended release dosage form: A dosage form that allows a reduction in dosing frequency as compared to that presented by a conventional dosage form, e.g., a solution or an immediate release dosage form.

Evaluation: In the context of in vitro/in vivo correlation, a broad term encompassing experimental and statistical techniques used during development and evaluation of a correlation which aid in determining the predictability of the correlation.

Formulation: A listing of the ingredients and composition of the dosage form.

In vitro/in vivo correlation: A predictive mathematical model describing the relationship between an in vitro property of an extended release dosage form (usually the rate or extent of drug dissolution or release) and a relevant in vivo response, e.g., plasma drug concentration or amount of drug absorbed.

In vivo dissolution: The process of dissolution of drug in the gastrointestinal tract.

In vitro release: Drug dissolution (release) from a dosage form as measured in an in vitro dissolution apparatus.

In vivo release: In vivo dissolution of drug from a dosage form as determined by deconvolution of data obtained from pharmacokinetic studies in humans (patients or healthy volunteers).

Level A correlation: A predictive mathematical model for the relationship between the entire in vitro dissolution/release time course and the entire in vivo response time course, e.g., the time course of plasma drug concentration or amount of drug absorbed.

Level B correlation: A predictive mathematical model for the relationship between summary parameters that characterize the in vitro and in vivo time courses, e.g., models that relate the mean in vitro dissolution time to the mean in vivo dissolution time, the mean in vitro dissolution time to the mean residence time in vivo, or the in vitro dissolution rate constant to the absorption rate constant.

Level C correlation: A predictive mathematical model of the relationship between the amount dissolved in vitro at a particular time (or the time required for in vitro dissolution of a fixed percent of the dose, e.g., $T_{50}\%$) and a summary parameter that characterizes the in vivo time course (e.g., C_{max} or AUC).

Lot: A batch, or a specific identified portion of a batch, having uniform character and quality within specified limits or, in the case of a drug product produced by continuous process, a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits *(21 CFR 210.3(b)(10))*.

Mean absorption time: The mean time required for drug to reach systemic circulation from the time of drug administration. This term commonly refers to the mean time involved in the in vivo release and absorption processes as they occur in the input compartment and is estimated as MAT = $MRT_{oral} - MRT_{i.v.}$

Mean in vitro dissolution time: The mean time for the drug to dissolve under in vitro dissolution conditions. This is calculated using the following equation:

$$MDT_{vitro} = \frac{\int_0^\infty (M_\infty - M(t))\, dt}{M_\infty}$$

Mean in vivo dissolution time: For a solid dosage form: $MDT_{solid} = MRT_{solid} - MRT_{solution}$. This reflects the mean time for drug to dissolve in vivo.

Mean residence time: The mean time that the drug resides in the body. MRT may also be the mean transit time. MRT = AUMC/AUC.

Narrow therapeutic index drugs: Drugs having, for example, less than a two-fold difference in the minimum toxic concentrations and the minimum effective concentrations *(21 CFR 320.33 (c))*.

Nonrelease controlling excipient (noncritical compositional variable): An inactive ingredient in the final dosage form that does not significantly affect the release of the active drug substance from the dosage form.

Predictability: Verification of the model's ability to describe in vivo bioavailability results from a test set of in vitro data (external predictability) as well as from the data that was used to develop the correlation (internal predictability).

Percent prediction error:

% PE = [(Observed value-Predicted value)/Observed value] x 100

Release controlling excipient (critical compositional variable): An inactive ingredient in the final dosage form that functions primarily to extend the release of the active drug substance from the dosage form.

Release mechanism: The process by which the drug substance is released from the dosage form.

Release rate: Amount of drug released per unit of time as defined by in vitro or in vivo testing.

Statistical moments: Parameters that describe the characteristics of the time courses of plasma concentration (area, mean residence time, and variance of mean residence time) and of urinary excretion rate.