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Workshop Report

In Vitro and *in Vivo* Testing and Correlation for Oral Controlled/Modified-Release Dosage Forms

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INTRODUCTION

This report is from the second workshop held in Washington, D.C., on controlled/modified-release dosage forms. The consensus of the first workshop (Sept.–Oct. 1985), sponsored by the U.S. Food and Drug Administration (FDA, Agency), Academy of Pharmaceutical Sciences, American Society for Clinical Pharmacology, and Therapeutics and Drug Information Association, was published in *Pharmaceutical Research,* Vol. 4, No. 1, pp. 75–77, 1987. This report is a synthesis of the first workshop report and the recommendations of the second workshop.

The objectives of this second workshop were to determine the optimum information needed to characterize the drug entity and the drug dosage form and to explore the *in vitro–in vivo* relationship so as to determine the criteria for establishing an *in vitro–in vivo* correlation as well as the usefulness of *in vitro* data in the drug approval/regulatory process. Since this report is directed primarily toward oral

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controlled-release dosage forms, designated modified release by the United States Pharmacopeia (USP), the terms controlled release and modified release are used interchangeably.

Controlled-release pharmaceutical dosage forms may offer one or more advantages over conventional or immediate-release dosage forms of the same drug, including a reduced dosing frequency, a decreased incidence and/or intensity of adverse effects, a greater selectivity of pharmacologic activity, and a more constant or prolonged therapeutic effect. In some cases, controlled-release products may be therapeutically advantageous primarily for certain subpopulations of patients. In other instances, controlled-release products may have no significant advantages or they may actually be less effective and/or more hazardous than conventional dosage forms of the same drug. Ordinarily, oral controlled-release dosage forms should not be developed unless the recommended dosage interval for the controlled-release dosage form is longer than that for the immediate-release dosage form or unless significant clinical advantages for the controlled release dosage form can be justified (for example, decreased side effects resulting from a lower C_{max} with the controlled-release dosage form relative to the immediate-release dosage form).

Guidelines for the evaluation of controlled-release pharmaceutical dosage forms may provide assistance to those designing, conducting, and evaluating studies. However, it is important at the outset to recognize that each drug may possess inherent properties that require considerations specific to that drug and its dosage forms which may override the generalities of these guidelines.

This paper revises the informal guidelines published in 1987 for the design, conduct, and evaluation of studies of controlled-release pharmaceutical dosage forms. As was the case previously, no attempt has been made to achieve completeness. The report has been written with the recognition that it can and should be improved. Comments on the proposal are, therefore, solicited and are welcomed. While this guideline is designed primarily with oral drug delivery systems in mind, the general principles are applicable to other controlled-release drug delivery routes, e.g., transdermal, intramuscular, intranasal, etc.

In some cases, it is desirable to evaluate controlled-release dosage forms in the anticipated target population(s). Thus, drugs intended for use in pediatric patients should be studied in children, whereas products intended for geriatric patients should be studied in geriatric subjects. Since controlled-release dosage forms may contain a relatively large amount of drug compared to conventional dosage forms, postmarket surveillance for unanticipated effects is essential.

NEED FOR CLINICAL STUDIES

A fundamental question in evaluating a controlled-release product is whether formal clinical studies of the dosage form's safety and efficacy are needed or whether a pharmacokinetic evaluation will suffice. A rational answer to this question must be based on evaluation of the pharmacokinetic properties and plasma concentration–effect relationship of the drug. Where there is a well-defined predictive relationship between the plasma concentration(s) of the drug and/or active metabolite(s) and the clinical response (therapeutic and adverse), it may be possible to rely on plasma concentration data alone as a basis for the approval of the controlled-release product. This may be true, for example, where the degree of fluctuation $[(C_{max} - C_{min}/\overline{C}]$ (see Glossary) of the plasma concentration following dosing of the immediate-release product, as generally administered, is small. Where the therapeutic or toxic effects are indirectly related to plasma concentrations, where irreversible toxicity can occur, where there is evidence of functional (i.e., pharmacodynamic) tolerance, where peak-to-trough differences of the immediate-release form are very large, or where there are uncertainties concerning the relationship between plasma concentration and therapeutic and adverse effects, it will probably be necessary to carry out clinical studies.

Premarketing evaluation of a controlled-release product should include consideration of the possible development of functional tolerance to the drug, the occurrence of sensitivity reactions or local tissue damage due to dosage form-dependent persistence or localization of the drug, the clinical implications of dose dumping or of an unexpected decrease in bioavailability by physiological or physicochemical mechanisms, and a quantitative alteration in the metabolic fate of the drug due to nonlinear, or site-specific disposition.

Specific claims for all therapeutic advantages of a controlled-release product over the conventional dosage forms should be based on adequate clinical studies, the results of which should be available to health professionals upon request.

OPTIMUM INFORMATION TO CHARACTERIZE THE DRUG ENTITY

Physicochemical Characterization

While the required physicochemical information to characterize the drug entity in a controlled-release dosage form should generally be no different from that for the drug entity in an immediate-release dosage form, additional physicochemical information on solubility, dissolution, stability, and other release-controlling variables of the drug under conditions which may mimic the extremes of the physiologic environment experienced by the dosage form is necessary.

Pharmacokinetic Characterization

Input (Absorption)

It is necessary to characterize the oral input profile of the drug entity from a rapidly available dosage form which serves as a reference to evaluate the input profile of the controlled or modified release dosage form. This information together with the disposition characteristics for the drug entity can be used to characterize and predict changes in the bioavailability of the drug entity when input is modified following administration of the controlled-release dosage form. (For example, the drug may exhibit saturable first-pass hepatic metabolism, which could result in decreased systemic availability when the input rate is decreased.)

In designing a controlled-release dosage form, it may be useful to determine the absorption characteristics of the drug

entity in various segments of the gastrointestinal tract (particularly the colon for dosage forms that may release drug in the colon). Such information may not be required for regulatory submission if an appropriate determination of controlled-release is provided via pharmacokinetic or pharmacodynamic measurements.

Disposition

The information required to characterize the disposition processes for the drug entity in a controlled-release dosage form should include those generally determined for the drug entity in an immediate-release dosage form. This may include the following:

(1) disposition parameters—clearance, volume of distribution, half-life, mean residence time, or model dependent or noncompartmental parameters;
(2) linearity or characterization of nonlinearity over the dose and/or concentration range which could possibly be encountered;
(3) accumulation;
(4) metabolic profile and excretory organ dependence with special attention to the active metabolite(s) and active enantiomers of racemic mixtures;
(5) enterohepatic circulation;
(6) protein binding parameters and dialyzability;
(7) the effect of age, gender, race, and relevant disease states; and
(8) plasma/blood ratio.

In addition, in cases where the drug has a narrow therapeutic index, or where there is evidence that the clinical response varies significantly as a function of the time of the day, it is recommended that circadian variability in the drug's disposition parameters (ADME) and pharmacodynamics be characterized to determine whether changes in the rate of drug input with time are essential to ensure adequate safety and efficacy.

Pharmacodynamic Characterization

For the drug entity a concentration–response relationship over a sufficiently wide dose range should be available for important therapeutic and adverse responses. In addition, the equilibration time (see Glossary) characteristics between plasma concentration and effect should have been evaluated. These concentration–response relationships should be sufficiently characterized so that a reasonable prediction can be made of the safety margin, if dose dumping from the controlled-release dosage form should occur. As defined under Need for Clinical Studies, the clinical performance of a new controlled-release dosage form could be characterized by plasma concentration–time data, if there is a well-defined relationship between the plasma concentration of the drug and/or active metabolite(s) and the clinical response (therapeutic and adverse). If such data are not available, then clinical trials of the controlled-release dosage form must be carried out with concurrent pharmacokinetic/pharmacodynamic measurements.

OPTIMUM INFORMATION TO CHARACTERIZE THE DOSAGE FORM

Physicochemical Characterization

The variables employed to characterize the physicochemical properties of the dosage form should be the same as employed to characterize the drug entity. Solubility and dissolution profiles from pH 1 to pH 7.4 should be obtained, with particular attention to the effect of the formulation (as compared to the drug entity). Characterization of formulations which are highly insoluble in purely aqueous systems may require the addition of sodium lauryl sulfate or another suitable surfactant to more closely mimic *in vivo* conditions.

Pharmacokinetic Studies

The type of pharmacokinetic studies that need to be carried out depends upon how much is known about the drug, its clinical pharmacokinetics and biopharmaceutics, and whether pharmacokinetic studies are intended to be the sole basis for product approval. There should be a sufficient number of dosage strengths of the controlled-release dosage form to allow flexibility for the clinician to titrate the patient over the recommended therapeutic dose range of the immediate-release dosage form.

As a minimum, a single-dose crossover study for each strength of the controlled-release dosage form and a multiple-dose, steady-state study using the highest strength of controlled-release dosage form is required for New Drug Application/Abbreviated New Drug Application (NDA/ANDA) approval. (Appropriate single-dose crossover and multiple-dose steady-state studies are described below.)

In the case of a controlled-release capsule dosage form, where the strengths differ from each other only in the amount of *identical beaded material* each capsule contains, a single-dose and a multiple-dose steady-state study at the highest dosage strength will be sufficient for NDA/ANDA approval. Other strengths may be approved solely on the basis of comparative *in vitro* dissolution data.

The types of studies needed can be categorized as follows.

Case I: Controlled-Release Oral Dosage Form of a Marketed Immediate-Release Drug for Which Extensive Pharmacodynamic–Pharmacokinetic Data Exist.

The following pharmacokinetic studies would be needed for most controlled-release dosage forms. They may, for this case, constitute the sole basis for approval of a controlled-release dosage form. (See Need For Clinical Studies, above.) If approval is to be sought without clinical trials, it is recommended that there be preconsultation with the regulatory authorities to ensure that an adequate data base exists for such approval.

A Single-Dose Crossover Study. A single-dose crossover study would include the following treatments: the controlled-release dosage form administered under fasting conditions, a rapidly available dosage form (an iv solution and/or oral solution or a well-characterized FDA approved immediate-release drug product) administered under fasting conditions, and the controlled-release dosage form administered at the same time as a high-fat meal (and/or another type of meal that has a potential for causing maximum perturbation).

The study of food effects should include provision for control of the fluid intake (e.g., 6 to 8 oz) and temperature (e.g., ambient), at the time of drug administration. The dos-

age form should be administered within 5 min after completion of the breakfast or meal.

If there are no significant differences in the rate of extent of bioavailability (most of the time AUC and peak concentration) in this study as a function of the meal, then no further food effect studies are necessary.

If significant differences in bioavailability are found, it would be necessary to define the cause of the food effect on the controlled-release dosage form, as well as the effect of time on the food–drug effect.

1. If no well-controlled studies have previously defined the effects of a concurrent high-fat meal on the immediate-release dosage form, studies should be carried out to determine whether a food effect is present and to define whether this food effect is a result of (a) problems with the dosage form, i.e., food-related changes in release, or (b) food effects that are unrelated to the dosage form, such as changes in the drug's absorption from the gastrointestinal tract and/or changes in the drug's disposition (i.e., distribution and/or elimination) that are independent of absorption. The cause of the food effect, i.e., a or b, should be determined by conducting a single-dose crossover study comparing the solution (or immediate-release dosage form) under fed and fasting conditions. If there is no effect of food, then conclude a; if there is an effect of food, then conclude b.
2. The effect of timing on the food–drug effect should be tested by performing a four-way crossover study with the controlled-release product under the following treatment conditions: fasting, drug with a high-fat meal, drug 1 hr before a high-fat meal, and drug 2 hr after a high-fat meal.
3. If the food effect on the immediate-release dosage form is determined to result from changes in the dissolved drug's absorption from the gastrointestinal tract or from changes in drug disposition, studies should be designed, in consultation with the FDA, to define the appropriate relationship between drug dosing and meals.
4. Alternative appropriate studies could be conducted if the applicant wanted to label the drug for administration with a meal which is not fat loaded. In this case an alternative meal composition should be considered.
5. The entire single-dose controlled-release absorption profile should be monitored. Where appropriate (e.g., in a multiple-dose study) for specific drugs and drug delivery systems, blood samples should be taken following breakfast on the second day, before the second dose is administered. This sampling schedule is particularly important for once a day products.
6. For delayed-release (enteric-coated) dosage forms, bioavailability studies adequately characterizing the food effects to support the dosing claims stated in the labeling need to be performed.

The purpose of these studies is twofold: first, to determine whether there is any need for labeling specifications of special conditions for administration with respect to meals and, second, to provide information concerning the pattern of absorption of the controlled-release dosage form compared to the rapidly available dosage form. The drug input function should be defined for controlled-release dosage forms by an appropriate method, e.g., Wagner-Nelson, Loo Riegelman, or other deconvolution methods. Additionally, this will aid in the development of an appropriate *in vitro* dissolution test. For dosage forms that exhibit a high variability, replicate studies are recommended.

Multiple-Dose, Steady-State Studies (Either 1 or 2 Below).

1. When data exist for the immediate release product establishing linear pharmacokinetics, a steady-state study with the controlled-release product at one dose rate (preferably at the high end of the usual dose-rate range) using an immediate-release formulation as a control should be conducted. At least three trough concentrations (C_{min}), over a period equal to or greater than two times the biological half-life of the drug, should be measured to ascertain that the subjects are at steady-state. Concentrations over at least one dosage interval of the controlled-release product should be measured in each leg of the crossover, although it may be preferable (in the case of rhythmic variation in absorption or disposition of the drug) to measure concentrations over an entire day in each leg. The presence or absence of circadian variation should be verified. The controlled-release product should produce an AUC that is equivalent, using accepted Agency critieria, to the immediate-release product and the degree of fluctuation, $[(C_{max} - C_{min})/\bar{C}]$, for the controlled release product should be the same as, or less than, that for the immediate-release dosage form given by the approved regimen. This is predicated on the knowledge that the FDA requires the C_{min} of the controlled-release dosage form to be higher than the C_{min} of the immediate-release dosage form and that the C_{max} of the controlled-release dosage form be below the C_{max} of the immediate-release dosage form unless it can be shown that the deviations are not therapeutically significant. Appropriate concentration measurements should include unchanged drug and/or major active metabolites. For racemic products, consideration should be given to measurement of the active enantiomer(s).
2. Where comparisons of pharmacokinetics of the immediate-release product at different dose rates are not available, or where the data show nonlinearity, steady-state crossover studies comparing the controlled-release product with the immediate-release formulation at two different dose rates should be conducted (one at the low end of the recommended dosing range and the second at the high end of the dosing range). For each of the comparisons, the controlled-release product must meet the criteria with respect to AUC and fluctuation stated in Study 1 above. If there are significant differences between the controlled-release product and the immediate-release product at either the low or the high dosing rate, these data alone would not serve as a basis for approval.

Since the data could be misleading if obtained from subjects with atypical drug disposition or physiologic characteristics, relative to the target population, subject selection should be randomized or from an appropriate target population. If the controlled-release product is aimed at the specific subpopulation, e.g., a controlled-release product designed for children, it should be tested in that population. Independent of whether a drug exhibits linear or nonlinear pharmacokinetics, the basis for approval is not equivalence of fraction of dose absorbed as such, but rather equivalence of AUC and of the relative degree of fluctuation of concentrations of the controlled-release and immediate-release products as administered. The controlled-release dosage form is not necessarily required to contain the same amount of drug as several doses of the immediate-release dosage form administered in the same dosing interval, e.g., if first-pass metabolism was greater for the controlled-release dosage form, it might contain more drug than the total of immediate-release doses.

Steady-state studies in selected patient population groups and/or drug interaction studies may also be necessary, depending upon the therapeutic use of the drug and the type of individuals for which the controlled-release product will be recommended. For drugs with narrow therapeutic indices it may be necessary to carry out more extensive plasma concentration measurements to determine the potential for unusual drug release patterns in certain subpopulations. In such studies, it may be advisable to carry out more than one AUC measurement per patient to assess variability with both the controlled-release and the immediate-release dosage forms.

Case II: Nonoral Controlled-Release Dosage Forms of Drugs Meeting the Criteria in Case I

The studies described previously (omitting the food effect studies) would be appropriate for the evaluation of a controlled-release formulation designed for an alternate route of administration unless an altered biotransformation pattern of active metabolites is observed. In that event a clinical efficacy study would be required. In addition to bioavailability studies, special studies should be concerned with specific risk factors, e.g., irritation and/or sensitization at the site of application, etc.

Case III: Generic Equivalent of an Approved Controlled-Release Product

The same bioequivalence requirements apply to (a) the establishment of the equivalence of the formulation used in efficacy trials if it is different from the formula intended for marketing and (b) the generic product approval. For development of a generic equivalent of an approved controlled-release form, the new generic formulation must be comparable with respect to rate and extent of availability (usually using AUC, C_{max}, C_{min}, and the degree of fluctuation as criteria) in a crossover steady-state study vs the standard controlled-release product using the accepted Agency criteria for equivalence. In some cases it may also be necessary to match the concentration–time profle of the approved controlled-release dosage form.

The food studies described previously are also needed (generic product with or without high-fat meal). Other special studies mentioned in previous paragraphs may also be indicated.

Statistical Analysis. (i) Any appropriate statistical method should be considered; (ii) where bioequivalence is to be demonstrated, the statistical test should be such that the null hypothesis states inequivalence and the alternative states equivalence.

The currently accepted Agency criteria for equivalence for most products require that the mean pharmacokinetic parameters of the test product should be shown to be within 80–120% of the reference product using the 90% confidence interval (or, equivalently, the two one-sided test procedure, $P = 0.05$).

Case IV: Controlled-Release Pharmaceutical Dosage Form as a New Drug Application

Independent of whether a controlled-release dosage form is evaluated by a clinical study, this dosage form should be characterized as described previously. That is, linearity of dose, food effects, absorption characteristics (rate, pattern, and extent), and fluctuation $[(C_{max} - C_{min})/\overline{C}]$ must be characterized.

IN VITRO–IN VIVO CORRELATIONS

The *in vitro* dissolution test is important for the purposes of (a) providing necessary process control, (b) determining stability of the relevant release characteristics of the product, and (c) facilitating certain regulatory determinations and judgments concerning minor formulation changes, change in site of manufacture, etc.

The present state of the science and technology does not always permit meaningful correlations between *in vitro* dissolution rates and the rate and extent of availability as determined by blood concentrations and/or urinary excretion of drug or metabolites (referred to as *in vitro–in vivo* correlations). Development of such correlations is an important objective and should be vigorously and systematically pursued on a product-by-product basis. Such correlations allow one to develop product specifications with bioavailability implications providing maximum assurance and predictability. Indeed, the value of *in vitro* dissolution specifications as a quality control measure is dependent primarily upon a relationship to bioavailability. The current state of the art is such that it is unlikely that a single *in vitro–in vivo* correlation for different products of the same drug can be accomplished at this time. Rather, it is likely that a separate *in vitro–in vivo* correlation will have to be developed for each manufacturer's product. The issue of *in vitro–in vivo* correlations was addressed in a Stimuli Article in the July–August 1988 issue of *Pharmacopeial Forum*. There is an agreement in principle with the approaches given there, but also a recognition that alternative approaches are possible.

RELATIONSHIP BETWEEN CRITICAL MANUFACTURING VARIABLES AND *IN VITRO* DISSOLUTION

The *in vitro* dissolution procedure and operating param-

eters must be optimized to be sensitive to critical manufacturing variables within the acceptable range of values expected during the manufacturing process. Critical manufacturing variables are those materials and methods used in the manufacturing processes that can significantly affect release of drug from the product (e.g., coating thickness, excipient concentrations, tablet hardness, compression pressure, etc.). The *in vitro* dissolution specifications (range of values permitted) should correspond to the range of values of the critical manufacturing variables that might be expected during normal manufacturing procedures using an *in vitro* procedure that has been developed and optimized to detect differences in critical manufacturing variables.

DEVELOPING AN *IN VITRO–IN VIVO* CORRELATION

Currently, dissolution specifications are usually defined by either of two methods: (1) the range of dissolution values found in the lot used in the pivotal bioavailability study or (2) the range of values from different lots produced during the development phase. Neither procedure necessarily provides *in vivo* validation.

The *in vitro* dissolution procedure used for quality control should be validated by appropriate *in vivo* bioavailability studies. To accomplish validation, the following procedures are suggested as possible approaches.

Correlation Approaches

These procedures validate the *in vitro* process by testing one or more products with altered rate characteristics or evaluating alternative dissolution procedures until a "correlation" can be established to an acceptable degree. The following process might be used. (a) Prepare two or more dosage formulations with different biopharmaceutic characteristics. Changes in *in vitro* dissolution of these test dosage forms should be accomplished by changing only those process and component variables that are likely to be varied under normal manufacturing conditions, i.e., the critical manufacturing variables. (b) Develop an appropriate *in vitro* test that can distinguish between these formulations. (c) Determine the absorption characteristics of these formulations in a small group of human subjects.

Correlation Approach Where the Dissolution Rate Is Independent of the Testing Conditions

When the dissolution rate is independent of the testing conditions (i.e., pH, surfactant, osmotic pressure, agitation, etc.), a single curve will define the dissolution rate. This *in vitro* dissolution curve is compared to the input function resulting from deconvolution of the plasma concentration–time curve of the definitive bioavailability/bioequivalence study. If these curves are superimposable, there is a 1:1 relationship which is defined as a Level A correlation (see Glossary).

It is also possible, through appropriate use of time corrections or other mathematical functions, to obtain reproducible correlations between *in vitro* dissolution curves and input functions. Although not 1:1 correlations, these procedures provide point-to-point relationships and can be considered Level A correlations.

Further validation of this correlation may be done by preparing one or more batches of product which release at different rates and determining the absorption characteristics of these batches in a small group of human subjects. Corresponding correlation at this other rate(s) may be considered to validate the *in vitro–in vivo* correlation for that dosage form. Modifying the *in vitro* dissolution of these test dosage forms should be accomplished by changing only those process and component variables that are likely to be varied under normal manufacturing conditions, i.e., the critical manufacturing variables.

If Level A correlation is not demonstrated with a product, one should attempt Level B or C correlation. Correlation at the B and C levels requires *in vivo* testing of three or more formulations having different release rates.

Correlation Approach Where the Dissolution Rate Is Dependent on the Testing Conditions

Under such conditions, the curve obtained by deconvolution of the plasma concentration–time curve obtained from the bioavailability/bioequivalence study is compared to the *in vitro* dissolution curve obtained under various dissolution conditions. Once the dissolution conditions which correlate best with the deconvolution curve are found, validation of these conditions should be performed. This may be accomplished by preparing one or more batches of product with different dissolution rates (usually one faster and one slower than the definitive bioavailability/bioequivalence batch) measured using the dissolution conditions that correlated with the *in vivo* data and determining the absorption characteristics of these formulations in a small (e.g., six) panel of human subjects. If the correlation is consistent, it may be considered to be validated. As in the previous case, this represents a Level A correlation. Furthermore, the test dosage forms are subject to the same caveats that apply when the dissolution rate is independent of testing conditions.

Again, if Level A correlation is not demonstrated, one should attempt to correlate at Level B or C. As in the case above it is necessary to test at least three dosage forms for a Level B or C correlation.

Specification Validation

In this case the upper and lower dissolution specifications are validated by a bioavailability study in normal subjects, using the currently accepted statistical criteria, showing that the products exhibiting the lower and higher dissolution specifications are bioequivalent. This would assure that the lot-to-lot variation permitted in the marketplace would not result in bioinequivalence.

It is important to validate the procedure of relating the upper and lower dissolution specifications to bioavailability parameters.

TYPE OF APPARATUS

The current Agency policy of allowing alternative dissolution methods and apparati is necessary to assure further

technological development. However, since it is also important that needless proliferation of methods be discouraged, the official *in vitro* dissolution methods described in the current U.S. Pharmacopeia should be utilized unless shown to be unsatisfactory. Alternative *in vitro* procedures such as the flow-through filter method, modified rotating bottle, or rotating flask methods might be considered, since all have some merit. Other methods should be considered on the basis of their proven superiority for a particular product. In other words, alternative approaches should not be discouraged. It is important to allow experimentation because of the diversity of biological and formulation variables and the evolving nature of our understanding and methodologies in this area.

DISSOLUTION CONDITIONS AND SAMPLING TIMES

(1) Characterization of the dosage form over the full range of physiological pH values is essential, e.g., pH 1, 4, 6, and 7.4.

(2) It is recommended that different agitation rates be used. This evaluation should include the standard operating conditions of 50 rpm for the paddle and 100 rpm for the basket. For solid dosage forms where particles result from disintegration, visual observation of the dosage form is recommended to detect changes due to increased agitation such as physical effects or changes in particle location and shape in the dissolution vessel.

(3) In general, it is recommended that the media be confined to only aqueous systems rather than hydroorganic, e.g., hydroalcoholic systems. For water-insoluble drugs, aqueous systems containing surfactant (e.g., sodium lauryl sulfate) should first be explored. For poorly soluble drugs where sink conditions cannot be achieved with the basket or paddle methods, the flow-through apparatus may serve as an appropriate alternative.

(4) At a minimum, at least three time points are recommended, but more are strongly encouraged: a 1-hr time point to assure that there is no dose dumping, a second time point at about 50% dissolution, and a third time point at about 80% dissolution. However, generally it is best to characterize the entire *in vitro* release profile.

EXAMPLES OF APPLICATION OF *IN VITRO–IN VIVO* CORRELATIONS

Interlot Variation

Based on an *in vitro–in vivo* correlation, the relevance of interlot dissolution variability can be assessed and appropriate specifications defined. If a valid *in vitro–in vivo* correlation does not exist, then appropriate studies in humans may be required to access interlot variability.

Product Shelf Life

Product shelf-life specifications can be defined in terms of *in vitro* dissolution tests using accepted stability studies if an *in vitro–in vivo* correlation has been established. If a valid *in vitro–in vivo* correlation does not exist, then appropriate human studies may be required to establish that product storage for the stated shelf life has no significant influence on expected performance of the dosage form.

Minor Formulation and Process Changes

When the relationships between the critical manufacturing variables and *in vitro* dissolution rates have been clearly defined for controlled release preparations and an *in vitro–in vivo* correlation has been established, it may be possible to use *in vitro* dissolution data to justify minor formulation and processes changes. These might include minor changes in color, size, shape, preservatives, flavor, coating procedure, amount and composition of materials, source of inactive and active (if adequately characterized) ingredients, equipment or site of manufacture. In the absence of a clearly defined relationship between the manufacturing variable in question and the dissolution rate, or if a valid *in vitro–in vivo* correlation does not exist, then appropriate testing in humans may be required.

GLOSSARY

C_{max}
: Observed maximum drug plasma concentration achieved after dosage form administration.

C_{min}
: Observed minimum drug plasma concentration at steady state.

$\overline{C}$ *(C Average)*
: $\overline{C} = \text{AUC}/\mathcal{T}$, where AUC is the area under the concentration time curve from time t to time $t + \mathcal{T}$, and $\mathcal{T}$ is the dosing interval.

Degree of Fluctuation
: $(C_{max}-C_{min})/\overline{C}$.

Correlation
: To show a relationship between two parameters. Typically a relationship is sought between *in vitro* dissolution rate and *in vivo* input rate. This initial relationship may be expanded to critical formulation parameters and *in vivo* input rate.

Equilibration Time
: A measure of the time-dependent discontinuity between measured plasma concentrations and measured effects. The discontinuity is most often characterized by the degree of hysteresis observed when the effect–concentration plot for increasing concentrations is compared with that for decreasing concentrations. Where the equilibration time is very short (i.e., rapid equilibration) and no active metabolites are generated, there will be little or no hysteresis. That is, the same effect will be observed for a given concentration independent of the time after dosing when measurements are made.

*Levels A–C Correlations (*Pharmacopeial Forum, *July–Aug. 1988, p. 1460).*

Level A: In this level of correlation, the *in vitro* dissolution

curve of the product is compared with the *in vivo* dissolution curve generated by deconvolution of the plasma-level data.

Level B: In this level of of correlation, the mean *in vitro* dissolution time of the product is compared to either the mean *in vivo* residence time or the mean *in vivo* dissolution time of the product derived by using principles of statistical moment analysis.

Level C: In this level of correlation, the mean *in vitro* dissolution time of the product is compared to one mean pharmacokinetic parameter. This does not reflect the complete dissolution profile or the blood-level profile, which is important for controlled-release products.

Modified-Release Dosage Forms

Those products that release a drug other than immediately. These dosage forms include extended release (sustained) and delayed release (enteric coated).