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News Release

Report of the Workshop on Controlled-Release Dosage Forms: Issues and Controversies[1]

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INTRODUCTION

Controlled-release pharmaceutical dosage forms may offer one or several advantages over conventional dosage forms of the same drug, including a reduced dosing frequency, a decreased incidence and/or intensity of adverse effects, greater selectivity of pharmacologic activity, and a more constant therapeutic effect. 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. In some cases, controlled-release products may be therapeutically advantageous primarily for certain subpopulations of patients.

Guidelines for the evaluation of controlled-released 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 drug products that may override the generalities of the guideline.

This paper is an initial attempt to develop guidelines for the design, conduction, and evaluation of studies of controlled-release pharmaceutical dosage forms. No attempt has been made to achieve completeness, and it has been written with the recognition that it can and should be improved. Comments on the proposal are, therefore, solicited and welcome. While this guideline is designed with primarily oral drug delivery systems in mind, many of the general principles are applicable to other sustained-release drug delivery routes, e.g., transdermal, intrauterine, intramuscular, ocular, etc.

Except for the basic design and the need to examine food effects, other details of the bioavailability studies, e.g., subject population, age, dealing with diurnal variation, the volume of solution of the reference dosage form, product standard selection, sampling times for blood or other biological fluids, and criteria for acceptance and stability of dosage form performance, are not addressed except in general terms. It is anticipated that these and other concerns will be addressed in future workshops.

It is desirable to evaluate controlled-release dosage forms in the anticipated typical target population(s). Thus drugs intended for use in a pediatric population should be studied in pediatric subjects. As controlled-release dosage forms contain a relatively large amount of drug compared to conventional dosage forms, it is particularly important to be alert during the postmarketing period for unanticipated effects.

NEED FOR CLINICAL TRIALS

A fundamental question in developing a controlled-release product is whether formal clinical evaluation of the dosage form's safety and effectiveness is needed or whether a pharmacokinetic evaluation will suffice. A rational answer to this question must be based on evaluation of available data on the drug's pharmacodynamics as well as its pharmacokinetics. Where there is a well-defined relationship between plasma concentration of drug and/or active metabolite(s) and 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 is particularly so where the degree of fluctuation $(C_{max} - C_{min})/C_{avg}$ of plasma concentration following administration of the immediate-release product, as administered, is already small. Where the therapeutic effect is indirect, where irreversible toxicity can occur, where there is evidence of functional (pharmacodynamic) tolerance, where peak-to-trough differences of the immediate-release form are very large, or where there is any other reasonable uncertainty 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 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 unexpected decrease in bioavailability by physiological or physicochemical mechanisms, and quantitative alteration in the metabolic fate of the drug due to nonlinear or site-specific disposition.

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Nine of the eleven members of the committee preparing the final report represent the strong interests and input of pharmaceutical scientists whose primary scientific association is the American Association of Pharmaceutical Scientists.

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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.

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.

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

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 Trials, above.) If approval is to be sought without clinical trials it is recommended that there be preconsultation with the FDA to ensure that an adequate data base exists for such approval.

A. A Single-Dose, Three-Way Crossover Study

A single-dose, three-way 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 if previous information indicates that this alternate meal has a potential for causing the maximum perturbation).

If there are no significant differences in AUC and peak concentration in this study as a function of the meal, then no further food-effect studies are necessary.

Although it was not directly addressed at the workshop, the committee felt that if significant biopharmaceutical differences were 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 time 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 alternative meal composition should be considered.

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. Additionally, this will aid in the development of an appropriate *in vitro* dissolution test.

B. 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 case of rhythmic variation in absorption or disposition of the drug) to measure concentrations over an entire day in each leg. The controlled-release product should produce an AUC that is equivalent, using accepted Agency criteria, to that of the immediate-release product and the degree of fluctuation $(C_{max} - C_{min})/C_{avg}$ for the controlled-release product should be similar to, or less than, that for the immediate-release product. 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.)

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 a 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 B.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.

As 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 a specific subpopulation, e.g., a controlled-release product designed for children, it should be tested in that population. For drugs with both linear and nonlinear pharmacokinetics, the basis for approval is not equivalence of the fraction of dose absorbed as such, but rather equivalence of AUC and of the relative 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 this 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: Non-oral 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

For development of a generic equivalent of an approved controlled-release dosage form, the new generic formulation must be comparable with respect to AUC, C_{max}, and C_{min} 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 profile 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.

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 trial, this dosage form should be characterized as described previously. That is, linearity of dose, food effects, absorption characteristics (rate, pattern, and extent), and $(C_{max} - C_{min})/C_{avg}$ fluctuation must be characterized.

BIOPHARMACEUTIC CONSIDERATIONS

It is generally accepted by pharmaceutical scientists that the present state of science and technology does not permit consistently meaningful *in vitro* versus *in vivo* correlations for extended-release dosage forms. Development of such methodology remains a future objective. Nevertheless, adequately validated *in vitro* dissolution testing can be developed to facilitate process control and to enable the determination of some of the final product specifications. To determine the suitability of this *in vitro* test, the relationship of the results obtained with this test to the actual *in vivo* absorption characteristics of the tested products should be established in a small group of human subjects.

The committee believes that an *in vitro* test is desirable for the purposes of (a) providing necessary process control and stability determinations of the relevant release characteristics and (b) facilitating certain regulatory determinations and judgments concerning minor formulation changes, site of manufacturing changes, etc. It recommends, therefore, the following general approach: (a) preparation of at least three 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); (b) development of an appropriate *in vitro* test which can distinguish between these formulations; and (c) determination of the absorption characteristics of these formulations in a small group of human subjects. The *in vitro* drug release kinetics of the dosage form intended to be marketed should be characterized as a function of medium pH, rate of agitation, and possibly also medium composition (such as surfactants and bile salts). Since the knowledge of controlled-release product *in vitro/in vivo* correlation development and testing is still evolving, alternative approaches to this problem should be explored and should be considered by the Agency on their merits.