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FOOD AND DRUG ADMINISTRATION REQUIREMENTS FOR CONTROLLED RELEASE PRODUCTS

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KEY WORDS

Area under the curve (AUC)
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Bioequivalence
Controlled release
Delayed release
Dissolution
Extended release
In vitro in vivo correlation (IVIVC)
Modified release
Peak plasma concentration (C_{max})
Pharmacokinetics

OUTLINE

INTRODUCTION

Controlled-release pharmaceutical dosage forms may offer lease) 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 reduction in drug plasma fluctuation resulting in a more constant or prolonged therapeutic effect. In some cases, controlled-release products may be therapeutically advantageous primarily for certain subpopulations of patients. For example, a controlled-release drug product may allow a child to attend school without drug administration during the school day. In other instances, controlled-release products may have no significant advantages or may actually be less effective or more hazardous than conventional dosage forms of the same drug. Therefore, not all drugs are good candidates for formulation as controlled-release drug products (1). For example, some drugs are more effective if fluctuation in plasma concentrations occur. For such drugs, tolerance to drug effect may develop with the constant levels seen with controlled-release drug products. Ordinarily, oral controlled-release dosage forms result in a longer recommended dosing interval for the controlled-release dosage form, usually twice as long, compared with the dosing interval for the immediate release dosage form. Also, a controlled-release drug product may be warranted if significant clinical advantages for the controlled-release dosage form can be demonstrated, for example, decreased side effects resulting from a lower peak plasma concentration with the controlled-release dosage form relative to the immediate-release dosage form.

TYPES OF CONTROLLED-RELEASE PRODUCTS

The most common type of controlled-release products are oral dosage forms. These products normally provide for a 12- or 24-h dosing interval. Dosing intervals for oral controlled-release products beyond once-a-day dosing are limited by physiologic characteristics of the human gastrointestinal tract. Gastrointestinal transit time, which normally averages 24 h but can vary from a few hours to several days, prevents oral controlled-release products with a dosing interval beyond 24 h. Other types of controlled-release products include transdermal patches that are applied to the skin for periods of 1 day to perhaps 1 week. In addition, controlled-release implants are dosage forms that are implanted below the skin surface and have been developed for continuous therapy for as long as 5 years.

DEFINITIONS

Before beginning a discussion of the regulatory requirements of controlled-release products, it is useful to understand several commonly used definitions for these types of products:

Controlled-release dosage forms. A class of pharmaceuticals or other biologically active products from which a drug is released from the delivery system in a planned, predictable, and slower-than-normal manner (2).

Modified-release dosage form. This refers, in general, to a dosage form for which the drug-release characteristics

therapeutic or convenience objectives not offered by conventional dosage forms (2).

Extended-release dosage form. This is a specific type of modified-release dosage form that allows at least a two-fold reduction in dosage frequency as compared to that drug presented as an immediate- (conventional-) release dosage form (2).

Delayed-release dosage form. This is a specific type of modified-release dosage form that releases a drug at a time other than promptly after administration. An example is enteric-coated tablets (2).

The requirements discussed in this article cover all types of controlled-release dosage forms. The primary focus will be on oral controlled-release drug products, which are most common. Requirements for other types of controlled-release drug products, such as transdermal patches or implants, are similar to those described in this article.

LAWS, REGULATIONS AND GUIDANCES FOR CONTROLLED-RELEASE PRODUCTS

Need for Clinical Studies

Premarketing evaluation of a controlled-release product should include consideration of the possible development of 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 related 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. Where no therapeutic advantage is claimed, the need for clinical studies may be lessened.

An important consideration for the development of controlled-release products as original new drugs is the quantity of evidence needed in particular circumstances to establish substantial proof of effectiveness. The usual practice for all new molecular entities is to accept as proof two or more clinical studies that conclusively define the safety and efficacy of the drug. Within the U.S. Food and Drug Administration (FDA) Modernization Act of 1998 are described situations in which alternative approaches regarding the quantity of evidence to support effectiveness may be possible (3). These include (*1*) situations in which effectiveness of a new use may be extrapolated entirely from existing efficacy studies; (*2*) situations in which a single adequate and well-controlled study of a specific new use can be supported by information from other related adequate and well-controlled studies, such as studies in other phases of a disease; in closely related diseases; or other conditions of use (different dose, duration of use, regimen), (*3*) situations in which a single multicenter study, without supporting information from other adequate and well-controlled studies, may provide evidence that a use is effective. In each of these situations, it is assumed that any studies relied on to support effectiveness meet the requirements for adequate and well-controlled studies in 21 CFR 314.126 (4). It should also be appreciated that reliance on a single study of a given use, whether alone or with substantiation from related trial data, leaves little room for study imperfections or contradictory (nonsupportive) information. In all cases, it is presumed that the single study has been appropriately designed; that the possibility of bias due to baseline imbalance, unblinding, post hoc changes in analysis, or other factors is judged to be minimal; and that the results reflect a clear prior hypothesis documented in the protocol. Moreover, a single favorable study among several similar attempts that failed to support a finding of effectiveness would not constitute persuasive support for a product use unless there were a strong argument for discounting the outcomes in the studies that failed to show effectiveness (e.g., if the study was obviously inadequately powered or there was a lack of assay sensitivity as demonstrated in a three-arm study by failure of the study to show efficacy of a known active agent).

Whether to rely on a single study to support an effectiveness determination is not often an issue in contemporary drug development. In most drug development situations, the need to find an appropriate dose, to study patients of greater and lesser complexity or severity of disease, to compare the drug with other therapy, to study an adequate number of patients for safety purposes, and to otherwise know what needs to be known about a drug before it is marketed will result in more than one adequate and well-controlled study upon which to base an effectiveness determination.

In certain cases, effectiveness of a new controlled-release drug product may be demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen, or dosage form. Controlled-release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form to a previously studied immediate-release dosage form. Because the pharmacokinetic patterns of modified- and immediate-release dosage forms are not identical, it is generally important to have some understanding of the relationship of blood concentration to response, including an understanding of the time course of that relationship, to extrapolate the immediate-release data to the modified-release dosage form (3).

Bioavailability Study Requirements for Controlled Release Products

The bioavailability requirements for controlled-release products are covered in the U.S. Code of Federal Regulations under 21 CFR 320.25(f) (5). The aims of these requirements are to determine that the following conditions

- The drug product meets the controlled-release claims made for it.
- The bioavailability profile established for the drug product rules out the occurrence of clinically significant dose dumping. This is usually achieved by the conduct of a food effect study whereby the drug is administered with and without a high-fat breakfast.
- The drug product's steady-state performance is equivalent to a currently marketed noncontrolled- or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application.
- The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

The reference material for such a bioavailability study shall be chosen to permit an appropriate scientific evaluation of the controlled-release claims made for the drug product. The reference material is normally one of the following:

- A solution or suspension of the active drug ingredient or therapeutic moiety
- A currently marketed immediate-release drug product containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling of immediate-release drug product
- A currently marketed controlled-release drug product subject to an approved full new drug application containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling proposed for the controlled-release drug product

Guidelines for the evaluation of controlled-release pharmaceutical dosage forms provide assistance to those designing, conducting, and evaluating studies. However, a drug may possess inherent properties that require considerations specific to that drug and its dosage form that may override the generalities of these guidelines. Guidances related to the evaluation of controlled-release drug products as well as many other types of guidances are available on the Internet at the Center for Drug Evaluation and Research Web site (*http://www.fda.gov/cder/*).

Controlled-Release New Drug Applications

As mentioned earlier, 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 only a pharmacokinetic evaluation will provide adequate evidence for approval. 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 concentrations of the drug and the clinical response (regarding both safety and efficacy), it may be possible to rely on plasma concentration data alone as a basis for the approval of the controlled-release product. In the following situations, it is expected that clinical data be submitted for the approval of the controlled-release New Drug Application (NDA):

- When the controlled-release product involves a drug that is an unapproved new molecular entity, because there is no approved reference product to which a bioequivalence claim could be made
- When the rate of input has an effect on the drug's efficacy and toxicity profile
- When a claim of therapeutic advantage is intended for the controlled-release product
- When there are safety concerns with regards to irreversible toxicity
- Where there are uncertainties concerning the relationship between plasma concentration and therapeutic and adverse effects or in the absence of a well-defined relationship between plasma concentrations and either therapeutic or adverse clinical response
- Where there is evidence of functional (i.e., pharmacodynamic) tolerance
- Where peak-to-trough differences of the immediate-release form are very large

In all of these instances except for the first, a 505(b)(2) NDA could be submitted for approval to the FDA. The regulations for such application are covered under 21 CFR 314.54. These regulations state that any person seeking approval of a drug product that represents a modification of a listed drug, for example, a new indication or a new dosage form, and for which investigations other than bioavailability or bioequivalence studies are essential to the approval of the changes may submit a 505(b)(2) application. However, such an application may not be submitted under this section of the regulations for a drug product whose only difference from the reference-listed drug is that the extent of absorption or rate of absorption is less than that of the reference-listed drug or if the rate of absorption is unintentionally less than that of the reference-listed drug (6).

INFORMATION TO CHARACTERIZE THE DRUG ENTITY

Physicochemical Characterization

Although 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 related to solubility, dissolution, stability, and other release-controlling variables of the drug under conditions that may mimic the extremes of the physiologic environment experienced by the dosage form is necessary (7).

Pharmacokinetic Characterization

Absorption. It is necessary to characterize the relative bioavailability and the fractional absorption profile versus

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