

methods are not available for measurement of the concentration of the moiety, and, when appropriate, its active metabolite(s), in biological fluids or excretory products but a method is available for the measurement of an appropriate acute pharmacological effect. This approach may be particularly applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution.

(4) Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence. This approach is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence. For dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution, this approach may be considered acceptable only when analytical methods cannot be developed to permit use of one of the approaches outlined in paragraphs (b)(1)(i) and (b)(2) of this section, when the approaches described in paragraphs (b)(1)(ii), (b)(1)(iii), and (b)(3) of this section are not available. This approach may also be considered sufficiently accurate for measuring bioavailability or demonstrating bioequivalence of dosage forms intended to deliver the active moiety locally, e.g., topical preparations for the skin, eye, and mucous membranes; oral dosage forms not intended to be absorbed, e.g., an antacid or radiopaque medium; and bronchodilators administered by inhalation if the onset and duration of pharmacological activity are defined.

(5) A currently available *in vitro* test acceptable to FDA (usually a dissolution rate test) that ensures human *in vivo* bioavailability.

(6) Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence.

(c) FDA may, notwithstanding prior requirements for measuring bioavailability or establishing bioequivalence, require *in vivo* testing in hu-

mans of a product at any time if the agency has evidence that the product:

(1) May not produce therapeutic effects comparable to a pharmaceutical equivalent or alternative with which it is intended to be used interchangeably;

(2) May not be bioequivalent to a pharmaceutical equivalent or alternative with which it is intended to be used interchangeably; or

(3) Has greater than anticipated potential toxicity related to pharmacokinetic or other characteristics.

[57 FR 17999, Apr. 28, 1992; 57 FR 29354, July 1, 1992, as amended at 67 FR 77673, Dec. 19, 2002]

§ 320.25 Guidelines for the conduct of an *in vivo* bioavailability study.

(a) *Guiding principles.* (1) The basic principle in an *in vivo* bioavailability study is that no unnecessary human research should be done.

(2) An *in vivo* bioavailability study is generally done in a normal adult population under standardized conditions. In some situations, an *in vivo* bioavailability study in humans may preferably and more properly be done in suitable patients. Critically ill patients shall not be included in an *in vivo* bioavailability study unless the attending physician determines that there is a potential benefit to the patient.

(b) *Basic design.* The basic design of an *in vivo* bioavailability study is determined by the following:

(1) The scientific questions to be answered.

(2) The nature of the reference material and the dosage form to be tested.

(3) The availability of analytical methods.

(4) Benefit-risk considerations in regard to testing in humans.

(c) *Comparison to a reference material.* *In vivo* bioavailability testing of a drug product shall be in comparison to an appropriate reference material unless some other approach is more appropriate for valid scientific reasons.

(d) *Previously unmarketed active drug ingredients or therapeutic moieties.* (1) An *in vivo* bioavailability study involving a drug product containing an active drug ingredient or therapeutic moiety that has not been approved for marketing can be used to measure the following pharmacokinetic data:

(i) The bioavailability of the formulation proposed for marketing; and

(ii) The essential pharmacokinetic characteristics of the active drug ingredient or therapeutic moiety, such as the rate of absorption, the extent of absorption, the half-life of the therapeutic moiety in vivo, and the rate of excretion and/or metabolism. Dose proportionality of the active drug ingredient or the therapeutic moiety needs to be established after single-dose administration and in certain instances after multiple-dose administration. This characterization is a necessary part of the investigation of the drug to support drug labeling.

(2) The reference material in such a bioavailability study should be a solution or suspension containing the same quantity of the active drug ingredient or therapeutic moiety as the formulation proposed for marketing.

(3) The reference material should be administered by the same route as the formulation proposed for marketing unless an alternative or additional route is necessary to answer the scientific question under study. For example, in the case of an active drug ingredient or therapeutic moiety that is poorly absorbed after oral administration, it may be necessary to compare the oral dosage form proposed for marketing with the active drug ingredient or therapeutic moiety administered in solution both orally and intravenously.

(e) *New formulations of active drug ingredients or therapeutic moieties approved for marketing.* (1) An in vivo bioavailability study involving a drug product that is a new dosage form, or a new salt or ester of an active drug ingredient or therapeutic moiety that has been approved for marketing can be used to:

(i) Measure the bioavailability of the new formulation, new dosage form, or new salt or ester relative to an appropriate reference material; and

(ii) Define the pharmacokinetic parameters of the new formulation, new dosage form, or new salt or ester to establish dosage recommendation.

(2) The selection of the reference material(s) in such a bioavailability study depends upon the scientific questions to be answered, the data needed to es-

tablish comparability to a currently marketed drug product, and the data needed to establish dosage recommendations.

(3) The reference material should be taken from a current batch of a drug product that is the subject of an approved new drug application and that contains the same active drug ingredient or therapeutic moiety, if the new formulation, new dosage form, or new salt or ester is intended to be comparable to or to meet any comparative labeling claims made in relation to the drug product that is the subject of an approved new drug application.

(f) *Extended release formulations.* (1) The purpose of an in vivo bioavailability study involving a drug product for which an extended release claim is made is to determine if all of the following conditions are met:

(i) The drug product meets the extended release claims made for it.

(ii) The bioavailability profile established for the drug product rules out the occurrence of any dose dumping.

(iii) The drug product's steady-state performance is equivalent to a currently marketed nonextended release or extended release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application.

(iv) The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

(2) The reference material(s) for such a bioavailability study shall be chosen to permit an appropriate scientific evaluation of the extended release claims made for the drug product. The reference material shall be one of the following or any combination thereof:

(i) A solution or suspension of the active drug ingredient or therapeutic moiety.

(ii) A currently marketed noncontrolled release drug product containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling of the noncontrolled release drug product.

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(iii) A currently marketed extended 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 extended release drug product.

(iv) A reference material other than one set forth in paragraph (f)(2) (i), (ii) or (iii) of this section that is appropriate for valid scientific reasons.

(g) *Combination drug products.* (1) Generally, the purpose of an in vivo bioavailability study involving a combination drug product is to determine if the rate and extent of absorption of each active drug ingredient or therapeutic moiety in the combination drug product is equivalent to the rate and extent of absorption of each active drug ingredient or therapeutic moiety administered concurrently in separate single-ingredient preparations.

(2) The reference material in such a bioavailability study should be two or more currently marketed, single-ingredient drug products each of which contains one of the active drug ingredients or therapeutic moieties in the combination drug product. The Food and Drug Administration may, for valid scientific reasons, specify that the reference material shall be a combination drug product that is the subject of an approved new drug application.

(3) The Food and Drug Administration may permit a bioavailability study involving a combination drug product to determine the rate and extent of absorption of selected, but not all, active drug ingredients or therapeutic moieties in the combination drug product. The Food and Drug Administration may permit this determination if the pharmacokinetics and the interactions of the active drug ingredients or therapeutic moieties in the combination drug product are well known and the therapeutic activity of the combination drug product is generally recognized to reside in only one of the active drug ingredients or therapeutic moieties, e.g., ampicillin in an ampicillin-probenecid combination drug product.

(h) *Use of a placebo as the reference material.* Where appropriate or where necessary to demonstrate the sensi-

tivity of the test, the reference material in a bioavailability study may be a placebo if:

(1) The study measures the therapeutic or acute pharmacological effect of the active drug ingredient or therapeutic moiety; or

(2) The study is a clinical trial to establish the safety and effectiveness of the drug product.

(i) *Standards for test drug product and reference material.* (1) Both the drug product to be tested and the reference material, if it is another drug product, shall be shown to meet all compendial or other applicable standards of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and dissolution rates.

(2) Samples of the drug product to be tested shall be manufactured using the same equipment and under the same conditions as those used for full-scale production.

[42 FR 1648, Jan. 7, 1977, as amended at 67 FR 77674, Dec. 19, 2002]

§ 320.26 Guidelines on the design of a single-dose in vivo bioavailability or bioequivalence study.

(a) *Basic principles.* (1) An in vivo bioavailability or bioequivalence study should be a single-dose comparison of the drug product to be tested and the appropriate reference material conducted in normal adults.

(2) The test product and the reference material should be administered to subjects in the fasting state, unless some other approach is more appropriate for valid scientific reasons.

(b) *Study design.* (1) A single-dose study should be crossover in design, unless a parallel design or other design is more appropriate for valid scientific reasons, and should provide for a drug elimination period.

(2) Unless some other approach is appropriate for valid scientific reasons, the drug elimination period should be either:

(i) At least three times the half-life of the active drug ingredient or therapeutic moiety, or its metabolite(s), measured in the blood or urine; or

(ii) At least three times the half-life of decay of the acute pharmacological effect.