process, including a change in product formulation or dosage strength, beyond the variations provided for in the approved application.

(2) A change in the labeling to provide for a new indication for use of the drug product, if clinical studies are required to support the new indication for use.

(3) A change in the labeling to provide for a new dosage regimen or for an additional dosage regimen for a special patient population, e.g., infants, if clinical studies are required to support the new or additional dosage regimen.

(d) FDA may approve a full new drug application, or a supplemental application proposing any of the changes set forth in paragraph (c) of this section, that does not contain evidence of in vivo bioavailability or information to permit waiver of the requirement for in vivo bioavailability data, if all of the following conditions are met.

(1) The application is otherwise approvable.

(2) The application agrees to submit, within the time specified by FDA, either:

(i) Evidence measuring the in vivo bioavailability and demonstrating the in vivo bioequivalence of the drug product that is the subject of the application; or

(ii) Information to permit FDA to waive measurement of in vivo bioavailability.

(e) Evidence measuring the in vivo bioavailability and demonstrating the in vivo bioequivalence of a drug product shall be obtained using one of the approaches for determining bioavailability set forth in § 320.24.

(f) Information to permit FDA to waive the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence shall meet the criteria set forth in § 320.22.

(g) Any person holding an approved full or abbreviated new drug application shall submit to FDA a supplemental application containing new evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of the drug product that is the subject of the application if notified by FDA that:

(1) There are data demonstrating that the dosage regimen in the labeling is based on incorrect assumptions or facts regarding the pharmacokinetics of the drug product and that following this dosage regimen could potentially result in subtherapeutic or toxic levels; or

(2) There are data measuring significant intra-batch and batch-to-batch variability, e.g., plus or minus 25 percent, in the bioavailability of the drug product.

(h) The requirements of this section regarding the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence apply only to a full or abbreviated new drug application or a supplemental application for a finished dosage formulation.

[57 FR 17998, Apr. 28, 1992, as amended at 67 FR 77672, Dec. 19, 2002]

§ 320.22 Criteria for waiver of evidence of in vivo bioavailability or bioequivalence.

(a) Any person submitting a full or abbreviated new drug application, or a supplemental application proposing any of the changes set forth in § 320.21(c), may request FDA to waive the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of the drug product that is the subject of the application. An applicant shall submit a request for waiver with the application. Except as provided in paragraph (f) of this section, FDA shall waive the requirement for the submission of evidence of in vivo bioavailability or bioequivalence if the drug product meets any of the provisions of paragraphs (b), (c), (d), or (e) of this section.

(b) For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

(1) The drug product:

(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

(2) The drug product:

(i) Is administered by inhalation as a gas, e.g., a medicinal or an inhalation anesthetic; and

(ii) Contains an active ingredient in the same dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

(3) The drug product:

(i) Is a solution for application to the skin, an oral solution, elixir, syrup, tincture, a solution for aerosolization or nebulization, a nasal solution, or similar other solubilized form; and

(ii) Contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application; and

(iii) Contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application or abbreviated new drug application that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed, or that may significantly affect systemic or local availability for products intended to act locally.

(c) FDA shall waive the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of a solid oral dosage form (other than a delayed release or extended release dosage form) of a drug product determined to be effective for at least one indication in a Drug Efficacy Study Implementation notice or which is identical, related, or similar to such a drug product under §310.6 of this chapter unless FDA has evaluated the drug product under the criteria set forth in §320.33, included the drug product in the Approved Drug Products with Therapeutic Equivalence Evaluations List, and rated the drug product as having a known or potential bioequivalence problem. A drug product so rated reflects a determination by FDA that an in vivo bioequivalence study is required.

(d) For certain drug products, bioavailability may be measured or bioequivalence may be demonstrated by evidence obtained in vitro in lieu of in vivo data. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of the drug product if the drug product meets one of the following criteria:

(1) [Reserved]

(2) The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval and the conditions in paragraphs (d)(2)(i) through (d)(2)(iii) of this section are met:

(i) The bioavailability of this other drug product has been measured;

(ii) Both drug products meet an appropriate in vitro test approved by FDA; and

(iii) The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients.

(iv) Paragraph (d) of this section does not apply to delayed release or extended release products.

(3) The drug product is, on the basis of scientific evidence submitted in the application, shown to meet an in vitro test that has been correlated with in vivo data.

(4) The drug product is a reformulated product that is identical, except for a different color, flavor, or preservative that could not affect the bioavailability of the reformulated product, to another drug product for which the same manufacturer has obtained approval and the following conditions are met:

(i) The bioavailability of the other product has been measured; and

(ii) Both drug products meet an appropriate in vitro test approved by FDA.

(e) FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability or bioequivalence if waiver is compatible with the protection of the public health. For full new drug applications, FDA may defer a requirement for the submission of evidence of in vivo bioavailability if deferral is compatible with the protection of the public health.

(f) FDA, for good cause, may require evidence of in vivo bioavailability or bioequivalence for any drug product if the agency determines that any difference between the drug product and a listed drug may affect the bioavailability or bioequivalence of the drug product.

[57 FR 17998, Apr. 28, 1992, as amended at 67 FR 77673, Dec. 19, 2002]

§ 320.23 Basis for measuring in vivo bioavailability or demonstrating bioequivalence.

(a)(1) The in vivo bioavailability of a drug product is measured if the product's rate and extent of absorption, as determined by comparison of measured parameters, e.g., concentration of the active drug ingredient in the blood, urinary excretion rates, or pharmacological effects, do not indicate a significant difference from the reference material's rate and extent of absorption. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

(2) Statistical techniques used shall be of sufficient sensitivity to detect differences in rate and extent of absorption that are not attributable to subject variability.

(3) A drug product that differs from the reference material in its rate of absorption, but not in its extent of absorption, may be considered to be bioavailable if the difference in the rate of absorption is intentional, is appropriately reflected in the labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug product.

(b) Two drug products will be considered bioequivalent drug products if they are 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 active 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, and are considered medically insignificant for the particular drug product studied.

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

§ 320.24 Types of evidence to measure bioavailability or establish bioequivalence.

(a) Bioavailability may be measured or bioequivalence may be demonstrated by several in vivo and in vitro methods. FDA may require in vivo or in vitro testing, or both, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products. Information on bioequivalence requirements for specific products is included in the current edition of FDA's publication ''Approved Drug Products with Therapeutic Equivalence Evaluations'' and any current supplement to the publication. The selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of measuring bioavailability or establishing bioequivalence, as appropriate, for the product being tested.