

§ 320.32 Procedures for establishing or amending a bioequivalence requirement.

(a) The Food and Drug Administration, on its own initiative or in response to a petition by an interested person, may propose and promulgate a regulation to establish a bioequivalence requirement for a product not subject to section 505(j) of the act if it finds there is well-documented evidence that specific pharmaceutical equivalents or pharmaceutical alternatives intended to be used interchangeably for the same therapeutic effect:

- (1) Are not bioequivalent drug products; or
- (2) May not be bioequivalent drug products based on the criteria set forth in § 320.33; or
- (3) May not be bioequivalent drug products because they are members of a class of drug products that have close structural similarity and similar physicochemical or pharmacokinetic properties to other drug products in the same class that FDA finds are not bioequivalent drug products.

(b) FDA shall include in a proposed rule to establish a bioequivalence requirement the evidence and criteria set forth in § 320.33 that are to be considered in determining whether to issue the proposal. If the rulemaking is proposed in response to a petition, FDA shall include in the proposal a summary and analysis of the relevant information that was submitted in the petition as well as other available information to support the establishment of a bioequivalence requirement.

(c) FDA, on its own initiative or in response to a petition by an interested person, may propose and promulgate an amendment to a bioequivalence requirement established under this subpart.

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§ 320.33 Criteria and evidence to assess actual or potential bioequivalence problems.

The Commissioner of Food and Drugs shall consider the following factors, when supported by well-documented evidence, to identify specific pharmaceutical equivalents and pharmaceutical alternatives that are not or

may not be bioequivalent drug products.

(a) Evidence from well-controlled clinical trials or controlled observations in patients that such drug products do not give comparable therapeutic effects.

(b) Evidence from well-controlled bioequivalence studies that such products are not bioequivalent drug products.

(c) Evidence that the drug products exhibit a narrow therapeutic ratio, e.g., there is less than a 2-fold difference in median lethal dose (LD₅₀) and median effective dose (ED₅₀) values, or have less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and safe and effective use of the drug products requires careful dosage titration and patient monitoring.

(d) Competent medical determination that a lack of bioequivalence would have a serious adverse effect in the treatment or prevention of a serious disease or condition.

(e) Physicochemical evidence that:

(1) The active drug ingredient has a low solubility in water, e.g., less than 5 milligrams per 1 milliliter, or, if dissolution in the stomach is critical to absorption, the volume of gastric fluids required to dissolve the recommended dose far exceeds the volume of fluids present in the stomach (taken to be 100 milliliters for adults and prorated for infants and children).

(2) The dissolution rate of one or more such products is slow, e.g., less than 50 percent in 30 minutes when tested using either a general method specified in an official compendium or a paddle method at 50 revolutions per minute in 900 milliliters of distilled or deionized water at 37° C, or differs significantly from that of an appropriate reference material such as an identical drug product that is the subject of an approved full new drug application.

(3) The particle size and/or surface area of the active drug ingredient is critical in determining its bioavailability.

(4) Certain physical structural characteristics of the active drug ingredient, e.g., polymorphic forms, conformers, solvates, complexes, and crystal