90% CI of the geometric mean test/reference AUC and C_{max} ratios must fall within the limits of 80% to 125%.

The FDA presently requests fed bioequivalence studies for all immediate- and modified-release oral dosage forms, with few exceptions. Generally, if the labeling warns that the product should be taken only on an empty stomach for reasons of safety or efficacy, then fed bioequivalence studies are not recommended; in such cases, it is necessary to evaluate bioequivalence only under fasting conditions.[50–52] In very few cases, bioequivalence is evaluated only under fed conditions because there are safety concerns associated with administration of the product on an empty stomach.[53]

Study Population in Bioequivalence Studies

The FDA recommends that in vivo bioequivalence studies be conducted in individuals that are representative of the general population, taking into account age, sex, and race factors.[26] For example, if a drug product is to be used in both sexes, the sponsor should attempt to include similar proportions of males and females in the study; if the drug product is to be used predominantly in the elderly, the applicant should attempt to include as many subjects of 60 years of age or older as possible. Restrictions on admission into the study should generally be based solely on safety considerations.

Bioequivalence studies should be conducted in the intended patient population when there are significant safety concerns associated with use in healthy subjects. For example, bioequivalence studies of drugs used for cancer chemotherapy are generally conducted in cancer patients.[54,55] These studies should be conducted in patients who are already stabilized on the medication of interest.

TYPES OF EVIDENCE TO ESTABLISH BIOAVAILABILITY AND BIOEQUIVALENCE

Subpart B of the *Bioavailability and Bioequivalence Requirements* in 21 CFR Part 320 lists the following in vivo and in vitro approaches to determining bioequivalence in descending order of accuracy, sensitivity, and reproducibility:[32]

- In vivo measurement of active moiety or moieties in biological fluid
- In vivo pharmacodynamic comparison
- In vivo limited clinical comparison
- In vitro comparison
- Any other approach deemed appropriate by FDA

Bioequivalence Studies with Pharmacokinetic Endpoints

Figure 10.3 illustrates, for a model of oral dosage form performance, why the most sensitive approach is to measure the drug in biological fluids, such as blood, plasma, or serum. The active ingredient leaves the solid dosage form and dissolves in the