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Editorial

Bioavailability and Bioequivalence (BABE) Studies: FDA Guidelines for Industry

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Bioavailability (BA) for a given formulation provides an estimate of the relative fraction of the orally administered dose that is absorbed into the systemic circulation. BA for orally administered drug products can be documented by comparing a systemic exposure profile to that of a suitable reference product.

A profile can be generated by measuring the concentration of active ingredients and/or active moieties over time and, when appropriate, active metabolites over time in samples collected from the systemic circulation. Systemic exposure profiles reflect both release of the drug substance from the drug product and a series of possible presystemic/systemic actions on the drug substance after its release from the drug product.

FDA's regulations at 21 CFR 320.25 set forth guidelines for *in vivo* BA studies. As provided in this regulation, the reference product for BA studies should be a solution, suspension, or intravenous (IV) dosage form (21 CFR 320.25(d)(2) and (3). The purpose of conducting a BA study with an oral solution as a reference is to assess the impact of formulation on BA. Conducting a BA study with an IV reference enables assessment of the impact of route of administration on BA and defines the absolute BA of the drug released from the drug product.

How BA is measured?

- Measure drug concentration in blood over time → plasma concentration-time curve
- Sometimes metabolites are also measured.

Study Design Considers:

Single dose study- CFR 320.26 BABE study/ Multi dose study- FR 320.27 BABE study

MDS may be required when-

1. There is a difference in the rate of absorption but not in the extent of absorption.

2. Excessive inter subject variability in bioavailability

3. The conc. of therapeutic moiety (API) or its metabolite(s), in the blood resulting from a single dose is too low for accurate determination by the analytical method.

4. The drug product is an extended-release dosage form.

Use of Normal Adult Population/ Patients

Benefit-Risk considerations in regard to testing in humans

- No unnecessary human research should be done
- May be done in suitable patients
- Critically ill patients shall not be included-Unless the attending physician determines that there is a potential benefit to the patient

Reference Products for BA Studies

According to 21 CFR 320.25, reference should be:

- Oral solution/suspension
- Or intravenous (IV) formulation
- Oral solution → shows formulation effect
- IV → gives absolute bioavailability (100% reference)

Study Population Considerations

- Usually conducted in healthy adult volunteers
- Sometimes in patients if needed
- Avoid:
- Unnecessary human testing
- Critically ill patients (unless benefit justifies risk)

Concept of "Half Life"

Defined as the time required for drug concentration to reduce to 50%

Types:

Distribution half-life → drug moves into tissues

Elimination half-life → drug is metabolized & excreted

It is usually the elimination ½ life that is used to determine dosing schedules, to decide when it is safe to put patients on a new drug.

Rule of Five

After ~5 half-lives:

- ~97% of drug eliminated
- 5x the elimination ½ life = time at which the drug is "completely" (97%) eliminated from the body

1x ½ life - 50% of the original drug removed, 2x ½ life - 75%, 3x ½ life - 87.5%, 4x ½ life 93.75% and 5x ½ life - 96.875%.

BIOAVAILABILITY ASSESSMENT METHODS:

Pharmacokinetic Methods

Plasma concentration-time studies

Urinary excretion studies

Pharmacodynamic Methods

Acute pharmacologic response

Therapeutic response

Bioequivalence (BE)

Means two drug products show no significant difference in rate and extent of absorption

Difference from BA

BA: Measures drug absorption

BE: Compares two products

BA AND BE FOR VARIOUS DOSAGE FORMS

Solutions and Other Solubilized Dosage Forms

For oral solutions, elixirs, syrups, tinctures, or other solubilized forms, *in vivo* BA and/or BE are generally self-evident and a requirement of *in vivo* data for a product may be waived (21 CFR 320.22(b)(3)). In such instances, the applicant would be deemed to have complied with and fulfilled any requirement for *in vivo* data. Although a comparative study is not necessary, characterization of the pharmacokinetics of the drug is required (21 CFR

314.50(d)(3)). In addition, *in vivo* BE studies that compare different solution formulations are waived based on the assumptions that release of drug substance from the drug product is self-evident and that the solutions do not contain any excipients that significantly affect drug absorption. However, there are certain excipients that may alter the BA (e.g., sorbitol may reduce the BA of drugs, and vitamin E may enhance the BA) in amounts sometimes used in oral liquid dosage forms. In this case, evaluation of *in vivo* BA and/or BE may be required.

Immediate-Release Products

Pre-approval Changes

For BA and BE studies, we recommend a single-dose, fasting study be performed. Under certain circumstances, multiple-dose BA studies (see section III.A.5) and/or food effect studies may be necessary (See the FDA guidance for industry Food-Effect Bioavailability and Fed Bioequivalence). Unconventional dosage forms (buccal, chewable, orally disintegrating, and sublingual dosage forms) should be administered according to intended label use/instructions. In addition, a BA study may be needed with the unconventional dosage form swallowed intact to assess the impact of accidental swallowing of the intact product. Sampling should adequately capture the t_{max} and C_{max} in addition to total exposure.

In vitro dissolution be evaluated for all orally administered products. 501 *In vitro* dissolution test conditions could be the same or different for unconventional 502 compared to conventional dosage forms. If differences in dissolution data exist, they 503 should be discussed with the appropriate review division.

Post approval Changes

Information on the types of *in vitro* dissolution and *in vivo* BE studies needed for approved immediate-release drug products when post approval changes are made is provided in an FDA guidance for industry entitled SUPAC-IR: Immediate Release Solid Oral Dosage Forms Scale-Up and Post approval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation. We recommend that for post approval changes, the *in vitro* or *in vivo* comparison be made between the post-change and pre-change products.

Modified-Release Products

Modified-release (MR) products include extended-release (controlled-release, sustained release)17 and delayed-release products.

Extended-release (ER) products are dosage forms that are designed to extend or prolong the release of active ingredient or active moiety from the drug product and may allow a reduction in dosing frequency as compared to when the drug is administered in an immediate-release (IR) dosage form. These drug products can be developed to reduce fluctuations in plasma concentrations when compared to an IR product. ER products can be capsules, tablets, granules, pellets, or suspensions.

Delayed-release (DR) drug products are dosage forms that release active ingredient or active moiety at a time later than immediately after administration (i.e., these drug products exhibit a lag time in quantifiable plasma concentrations). Typically, coatings (e.g., enteric coatings) are used to delay the release of the drug substance until the dosage form has passed through the acidic medium of the stomach. Generally, DR products are treated as IR products. However, if the DR product has complex release characteristics, the relevant review division should be contacted for additional guidance.

Conclusions:

BA is how much and how fast drug reaches blood, whereas BE is comparison between two drug products. Single-dose studies are standard; multi-dose used in special cases. Half-life determines dosing and elimination. Solutions often don’t need BE studies. Modified-release drugs need special consideration.