U.S. FOOD & DRUG ADMINISTRATION

Bioavailability Studies Submitted in NDAs or INDs
General Considerations Final Guidance

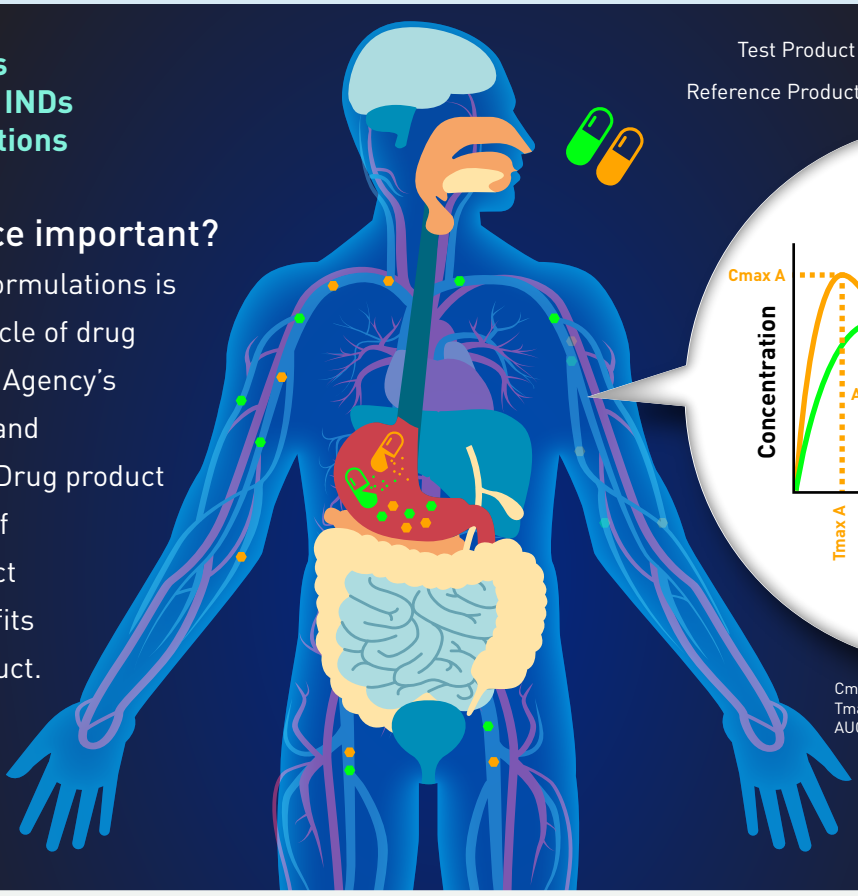
What is covered in this guidance?

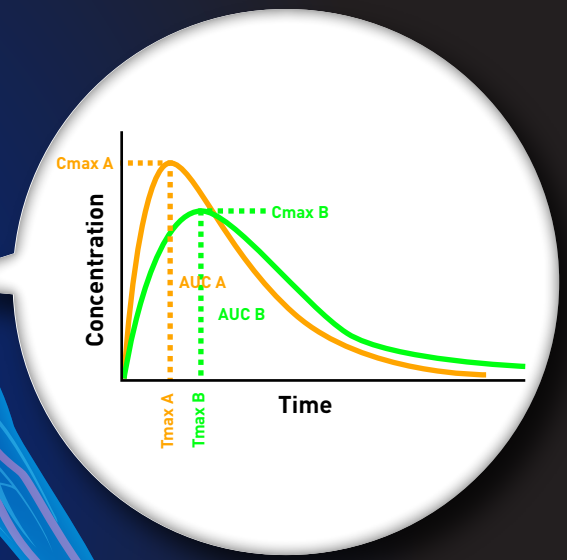
A final guidance has been issued to provide recommendations to sponsors on the conduct of bioavailability (BA) studies for orally administered drug products and certain non-orally administered drug products in investigational new drugs (INDs), new drug applications (NDAs), and supplements.

Bioavailability Studies Submitted in NDAs or INDs — General Considerations

Why is this guidance important?

Determining the BA of formulations is critical during the life cycle of drug products and aids in the Agency's evaluation of the safety and effectiveness of a drug. Drug product formulation, and route of administration may affect BA and impact the benefits and risks of a drug product.





Cmax = maximum plasma concentration
Tmax = time to maximum observed plasma concentration
AUC = area under the curve

Guidance Snapshots are a communication tool and are not a substitute for the guidance document.

To learn more about assessing the bioavailability studies submitted in NDAs or INDs, read the guidance:
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-studies-submitted-ndas-or-inds-general-considerations

ASSESSING BIOAVAILABILITY

WHAT?

BA is defined as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. BA data provide an estimate of the fraction of the drug absorbed as well as information related to the pharmacokinetics of the drug.

HOW?

Sponsors can determine the BA for orally administered drug products by comparing a plasma exposure profile to that of a suitable reference product. Sponsors must use the most accurate, sensitive, and reproducible method available to demonstrate the BA of a drug product.

WHEN?

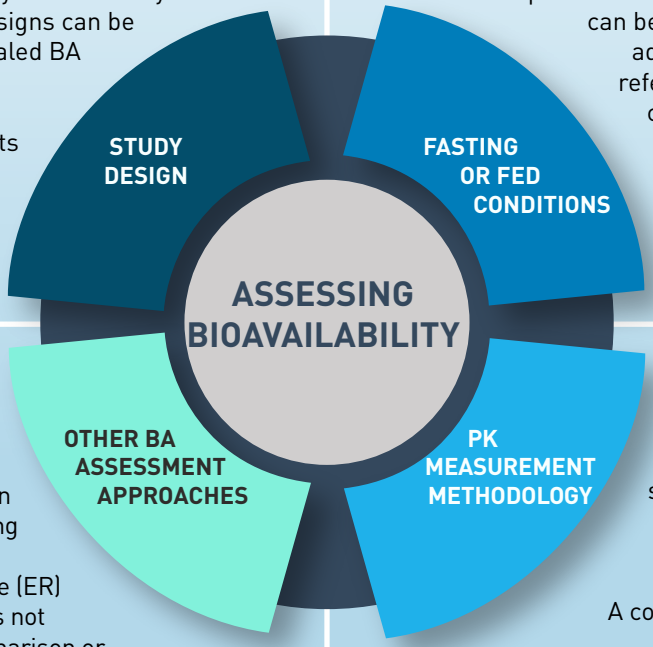
BA should be assessed preapproval and for postapproval changes to drug products. During development, BA comparisons may be needed to compare early versus late clinical trial formulations, clinical trial versus to-be-marketed drug products, and different product strengths, or to support pharmacokinetic (PK) comparison for a 505(b)(2) submission. After approval, major changes in a drug product's components, composition, manufacturing site, or method of manufacture may require a BA assessment to determine bioequivalence (BE).

STUDY DESIGN

Sponsors should use a non-replicate, randomized, single-dose, crossover design to study BA in healthy adult volunteers.* Replicate study designs can be considered for use with reference-scaled BA approaches for products with high intrasubject variability or narrow therapeutic index. For certain products or situations, multiple-dose evaluations may be appropriate.

FASTING OR FED CONDITIONS

Sponsors should determine the BA of the test product under fasting conditions. Fed conditions can be used if tolerability issues or serious adverse events are anticipated or if the reference product is approved under fed conditions. Evaluation of the effect of food on the BA of the test product should be consistent with the expectations outlined in the Food Effect Guidance.



OTHER BA ASSESSMENT APPROACHES

Under certain circumstances, sponsors can determine BA preapproval and postapproval using in vitro approaches (e.g., dissolution, drug-release testing). In addition, an in vitro-in vivo correlation (IVIVC) modeling approach can be used to evaluate formulations such as extended-release (ER) dosage forms. When PK comparison is not possible, pharmacodynamic (PD) comparison or comparative clinical studies can be performed.

PK MEASUREMENT METHODOLOGY

Sponsors should measure the active ingredient or moiety (or active metabolites when appropriate). In general, sponsors should use clinically relevant systemic exposure measures to determine BA, such as area under the curve (AUC) and peak drug concentration (Cmax). A confidence interval approach is used for BA comparisons.

*Sponsors can conduct a pilot trial with a small number of subjects to assess PK variability, determine sample size, and inform sample collection timing before proceeding with a full-scale BA study.

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Background About the Guidance

This guidance finalizes the revised draft guidance published in February 2019 titled "Bioavailability Studies Submitted in NDAs or INDs – General Considerations" that provided recommendations to sponsors planning to include BA information for drug products in INDs, NDAs, and NDA supplements. FDA considered comments received on the revised draft guidance and made technical and editorial changes to address these comments and improve clarity of the document when publishing the final guidance. The technical changes are listed in the Background section of the Notice of Availability published in the Federal Register.

Guidance Recommendations Apply Throughout the Drug Development Timeline

Determining the BA of formulations is important during the entire life cycle of drug products and aids in the FDA's evaluation of the safety and effectiveness of a product in an IND, NDA, or NDA supplement. To determine the safety and efficacy of a drug product for the proposed indication, the FDA uses the totality of information available in the submission, which includes BA data, exposure-response evaluations, and clinical trial results. In the presence of certain major changes in the components, composition, manufacturing site, or method of manufacture of a drug after its approval, the sponsor should demonstrate the in vivo BE for the drug product after the change compared to the drug product before the change.

Guidance Recap Podcast – Hear Highlights Straight From FDA Staff

Speaker: Dakshina Chilukuri, Ph.D., clinical pharmacology reviewer in the Center for Drug Evaluation and Research's Office of Clinical Pharmacology

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To see additional Guidance Snapshots, check out the pilot program:
https://www.fda.gov/drugs/guidances-drugs/guidance-snapshot-pilot