

Absolute Bioavailability

AMS study design considerations



Purpose Bioavailability is one of the essential tools in pharmacokinetics, as bioavailability must be considered when calculating dosages for non-intravenous routes of administration. Regulatory authorities have provided guidance for those intending to include bioavailability information for orally administered drug products in new drug applications. To date, most of these studies have been conducted using a two-way cross-over design using unlabeled drug product administered at pharmacologic doses by intravenous (IV) and oral routes (or other intended routes of drug administration). The approach requires the preparation of an IV formulation suitable for human administration. This presents a significant challenge in cases where a drug product has poor solubility at pharmacologic concentrations. This can be overcome with the preparation of drug product at subpharmacologic concentrations, such as 100 ug or less. By ^{14}C -labeling the IV formulation, the IV dose can be distinguished isotopically from the unlabeled oral dose. This permits near simultaneous dosing of the unlabeled oral drug with the ^{14}C -labeled IV drug. The subpharmacologic IV dose essentially eliminates any kinetic interference with the oral dose due to its reduced size. Standard LC-MS/MS methods are used to generate the oral area under the curve (AUC) while AMS methods are used to generate the IV AUC. Bioavailability is calculated by normalizing the IV AUC to the oral dose size and calculated the ratio obtained from the oral AUC and the normalized IV AUC. These studies allow an elegant assessment of absolute bioavailability in human subjects, eliminating variability introduced in cross-over design and avoiding the need to develop IV formulations at for drug products that are poorly soluble at pharmacologic concentrations.

Accium has successfully delivered on a wide range of AMS-based absolute bioavailability balance studies. Each study was customized to address particular challenges that were specific to each program. In particular, we employ the use of calibrator and quality controls standards as part of each batch in a manner described in regulatory bioanalytical guidelines. An outline of the various approaches we have employed in the design and conduct of these studies is shown below:

Clinical Design

1. Six to eight subjects.
2. Single dose of unlabeled drug product administered orally at the pharmacologic dose.
3. Single 100 ug dose of 100 nCi ^{14}C -labeled drug product administered by infusion around the oral dose C_{\max} .
4. Collect 1-2 mL plasma for AMS analysis of IV administered drug product.
5. Collect 2-4 mL plasma for LC-MS/MS analysis of orally administered drug product.

Bioanalytical Design

Pre-study Phase

1. Transfer extraction and HPLC procedures to Accium.
2. Transfer unlabeled and ^{14}C -labeled drug reference standards.
3. Demonstrate acceptable chromatographic conditions by UV-HPLC (using spiked unlabeled references).
4. Demonstrate acceptable recovery through extraction and HPLC by AMS (using spiked ^{14}C reference standards).

Study Phase

1. Extract all plasma samples, fractionate by HPLC and quantify by AMS.
2. Incorporate calibrator and quality control standards within each batch of analysis.
3. Calibrator and quality control standards are designed in a manner described in regulatory bioanalytical guidelines.
4. Accept or reject the analysis batch based on established criteria for the quality control samples.
5. Normalize the concentrations of unknown plasma samples using the calibration curve for that batch.
6. Report ng/mL for each plasma sample.

Advantages

- Reduces or eliminates IV dose formulation challenges.
- Concomitant administration of oral and intravenous dose reduces same-subject variability.
- Reduces clinical costs due fewer nights at the clinic.
- Samples are treated as non-radioactive and may be processed in any LC-MS/MS laboratory.

Disadvantages

- Requires ^{14}C -labeled drug product.
- AMS analysis can be more costly than LC-MS/MS.
- Reporting of results may require a longer time.

