U.S. FOOD & DRUG ADMINISTRATION

Guidance Snapshot

Clinical Pharmacology Considerations For Human Radiolabeled Mass Balance Studies

Guidance for Industry

What is Recommended in This Guidance?

This guidance provides the FDA's recommendations on clinical pharmacology considerations for conducting human radiolabeled mass balance studies of investigational drugs, these include:
1) whether and when to do the study,
2) designing the study, and
3) reporting results.

Why Is This Guidance Important?

This guidance is critical because it provides recommendations to ensure a comprehensive understanding of the investigational drug's absorption, distribution, metabolism, and excretion (ADME) in humans. Human radiolabeled mass studies are pivotal in identifying metabolic and excretory pathways, identifying circulating metabolites, and determining the need for additional studies like renal or hepatic impairment studies and drug-drug interaction evaluations. This knowledge is instrumental for the safe and effective development of new drugs and in making informed decisions during drug development processes.

What are Human Radiolabeled Mass Balance Studies?

Human radiolabeled mass balance studies administer a radiolabeled investigational drug to volunteers and then measure the radioactivity in various biological matrices such as plasma, urine, and feces. By tracking the radioactivity, researchers can obtain detailed information on the drug's pharmacokinetics, including how it is absorbed, distributed, metabolized, and excreted from the body. This allows for the understanding of the drug's overall metabolism and excretion pathways in the human body and the identification of metabolites.

Considerations for Designing Mass Balance Studies

The FDA offers recommendations to ensure that human radiolabeled mass balance studies yield critical insights into the ADME properties of investigational drugs, these include:

- **Study Design:** Mass balance studies are non-randomized and open label studies.
- **Study Participants:** Mass balance studies can generally be conducted in healthy adult volunteers and should include at least six evaluable volunteers.
- **Administered Radioactivity Dose and Radiolabel Position:** The absorbed dose of radioactivity should be estimated via dosimetry calculations based on data from animal studies. The position of the radioisotope should be chemically and metabolically stable such that the radionuclide is not lost during metabolism, and both the parent drug and metabolites can be detected and quantified.
- **Investigational Drug Dose:** The dose of the non-radiolabeled investigational drug used should be the final intended dose, or at least in the anticipated therapeutic dose range or in the pharmacokinetic linearity range. Generally, a single-dose study is sufficient. In some instances, a multiple-dose study can be considered.
- **Route of Administration and Formulation:** The routes of administration should include the final intended routes, unless precluded by practical considerations. The fit-for-purpose formulation used in the mass balance study contains both radiolabeled and non-radiolabeled drug materials.
- **Determination of Absolute Bioavailability for Orally Administered Investigational Drugs:** When only the oral formulation is being developed, an absolute bioavailability study can be combined with the mass balance study in a single protocol in a two-part study. Information on the absolute bioavailability can help interpret mass balance data.
- **Recovery:** Preferably, the total recovery of radioactivity in the urine and feces should exceed 90 percent of the administered dose.
- **Sample Collection and Handling:** Plasma, urine, feces, and other matrices should be collected for quantitative analysis. Sample collection should continue until specific recovery criteria are met.
- **Parent and Metabolites:** In addition to the parent drug, metabolite profiling should be performed in plasma, urine, and feces samples. Ideally, more than 80 percent of the radioactivity recovered in the excreta should be identified to assess the metabolic pathways of the parent drug.
- **Bioanalysis:** The choice of bioanalytical quantification techniques and any associated method validation depends on the objective of the mass balance study.

Reporting of Human Radiolabeled Mass Balance Study Results

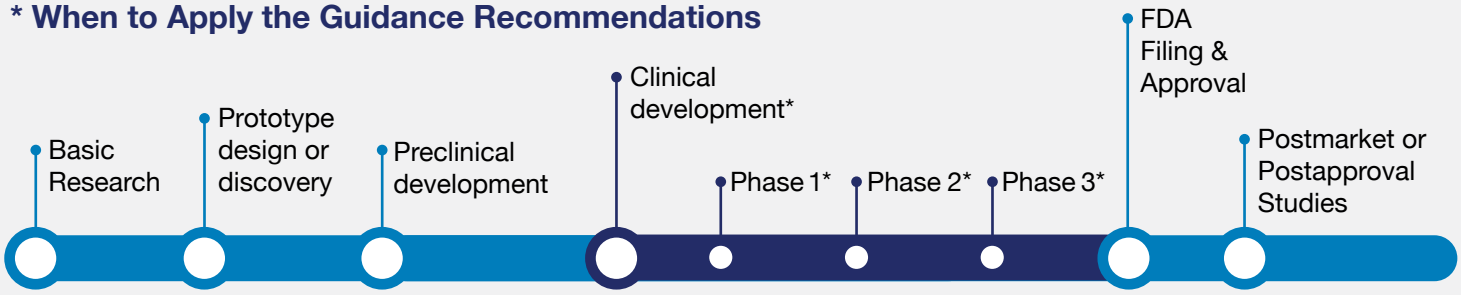
The study report(s) should include the following:

- Plasma and whole blood concentration versus time profiles of total radioactivity.
- Plasma concentration versus time profiles for the parent drug and metabolites of interest.
- Descriptive statistics of pharmacokinetic parameters for total radioactivity, the parent drug, and metabolites of interest in plasma (e.g., the area under the concentration time curve (AUC), the maximum concentration (Cmax), the time to maximum concentration (Tmax), terminal half-life).
- The cumulative percentage of the administered radioactivity dose recovered in urine, feces, and total excreta (urine and feces combined) versus time profiles.
- Quantitative information on the radioactivity associated with the parent drug and each identified metabolite in collected matrices (e.g., plasma, urine, feces).
- A biotransformation scheme with the structures or descriptions of the metabolites, if available.

Results from mass balance studies are generally included in Subsection 12.3 Pharmacokinetics of the approved prescribing information.

Drug Development Timeline

*** When to Apply the Guidance Recommendations**



Recommendations from this guidance typically apply during clinical development.

Guidance Recap Podcast

Hear highlights straight from FDA staff

Speakers: Suresh Doddapaneni, PhD, Deputy Director of the Division of Inflammation and Immune Pharmacology, Zhixia (Grace) Y. Danielsen, PhD, Deputy Director of the Division of Infectious Disease Pharmacology, and Anuradha Ramamoorthy, PhD, Master Scientist in the Office of Clinical Pharmacology located within the Office of Translational Sciences in the Center for Drug Evaluation and Research.

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Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about clinical pharmacology considerations for human radiolabeled mass balance studies, **read the guidance**. To see additional Guidance Snapshots, **check out the pilot program**.