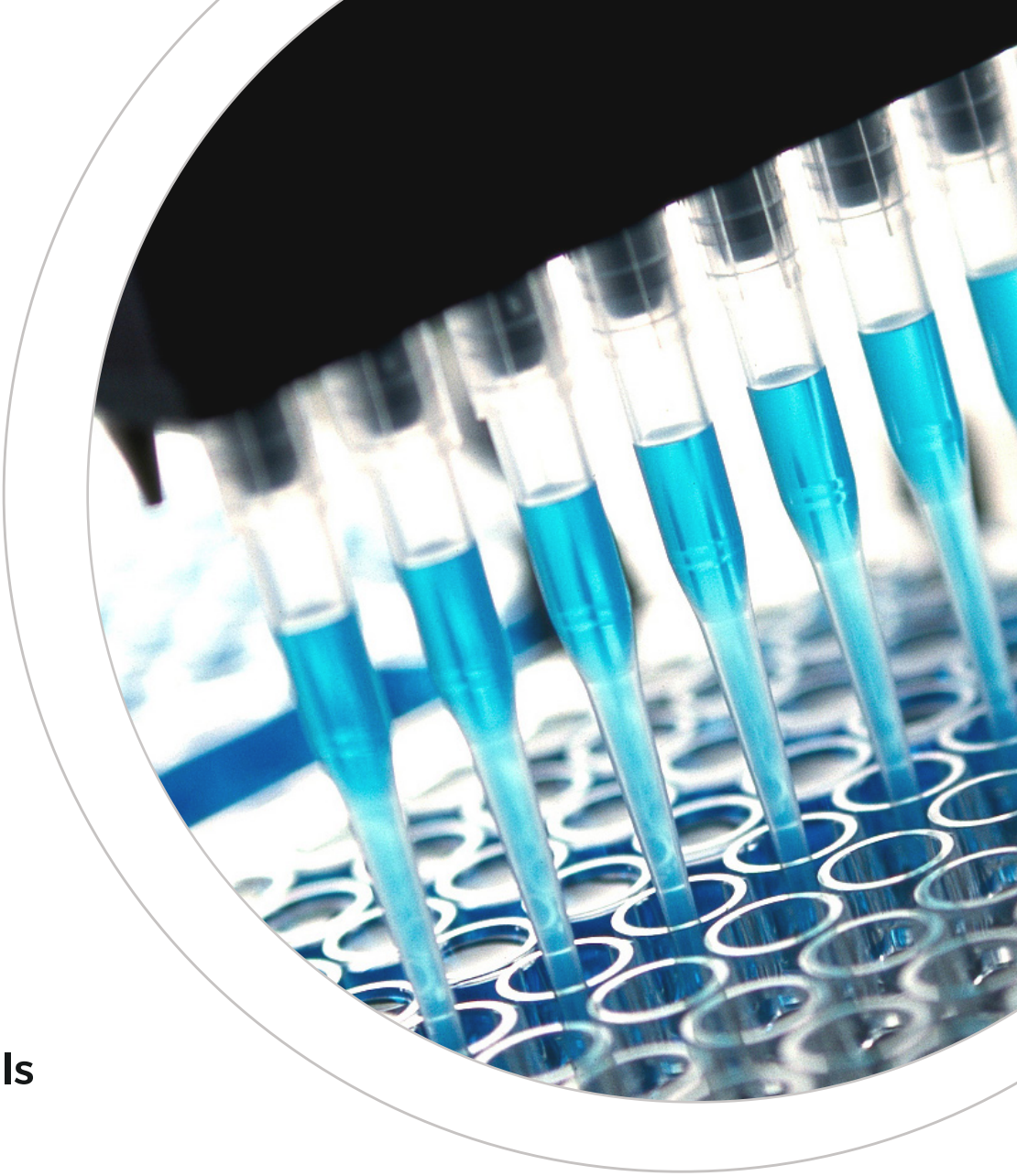

Worldwide Clinical Trials

When the FDA Knocks Answer with AME Study Results for Clinical Trial Success

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Abstract

In general, all new chemical entities (NCEs) require an absorption, metabolism, and excretion (AME) clinical study during development. Resultant data on the AME of the drug product and its metabolites are a critical part of the clinical pharmacology submission package. Also known as a human radiolabeled mass balance study, this study is not only designed to determine overall metabolism and excretion pathways of the NCE but also to identify and quantify circulating metabolites relative to parent or total drug-related exposure.

While AME studies traditionally have been conducted during Phase II clinical development or later, earlier investment in these activities — on the heels of preliminary studies, such as first-in-human, dose escalation, and food effect — often proves worthwhile. AME study results can provide key insights and shed light on the pathway a compound will need to take for approval. This crucial information can also add value to your asset.

Furthermore, the FDA has recently been requesting AME data sooner in the development process. Proactive AME studies will help lay the groundwork for the advanced phases of your study and provide valuable data to satisfy regulators as needed. In May 2022, the FDA issued a document entitled "Clinical Pharmacology Considerations for Human Radiolabeled Mass Balance Studies Guidance for Industry". This document provides valuable recommendations for when to conduct AME studies, design considerations, and data reporting. There are some circumstances where an AME may not be recommended. It is advised that sponsors consult with the appropriate FDA review division when using alternative approaches.

When the FDA Asks for AME Data Sooner Than Expected, Will you be Prepared?

Radioactive tagging of the NCE, quantitative whole body autoradiography (QWBA), and dosimetry calculations to understand where the drug is deposited are activities that require considerable time and expenditure and must take place before radiolabeled NCE studies can be conducted in humans. For this reason, sponsors may be tempted to postpone their AME studies. The most current guidance recommends mass balance studies be "conducted early in drug development, at least before initiating any late-phase clinical trials." Therefore, delay is ill-advised for several reasons:

1. The FDA and other regulatory agencies have been looking for information about the total fate of drug-related material earlier in the clinical pharmacology and drug development process. They want to see an assessment of the parent drug's pharmacokinetics (PK), mass balance, routes and rates of excretion, and metabolic pathways well before larger-scale human testing. This will help to guide whether renal and/or hepatic impairment studies or possibly drug-drug interaction studies need to be conducted.
2. Sponsors benefit from clarifying AME pathways and NCE circulating and excreted metabolites early. Knowledge about multiple metabolites, toxic metabolites, or metabolites occurring only in humanshumans, as well as metabolite and excretion patterns, is crucial for planningfuture studies.

   For example, if most of the radioactivity is found in the urine, excretion is primarily via a renal pathway. In such a case, the sponsor has advance notice that a renal impairment study will likely be needed to develop dosing recommendations for patients with varying degrees of renal impairment (Figure 1).

   Conversely, not conducting an AME study early on can lead to expensive, time-consuming surprises down the road, where the costs are drastically elevated, given the scope and scale of late phase trials.
3. AME studies can also yield critical information on bioavailability (BA), or lack thereof. For example, if most of the radioactivity appears in the stool, the drug is poorly absorbed. The sponsor has a chance to correct this, if possible, at the early stages of clinical development. Determination of the absolute bioavailability of an orally administered drug can be accomplished in a single protocol, two-part AME/BA study.

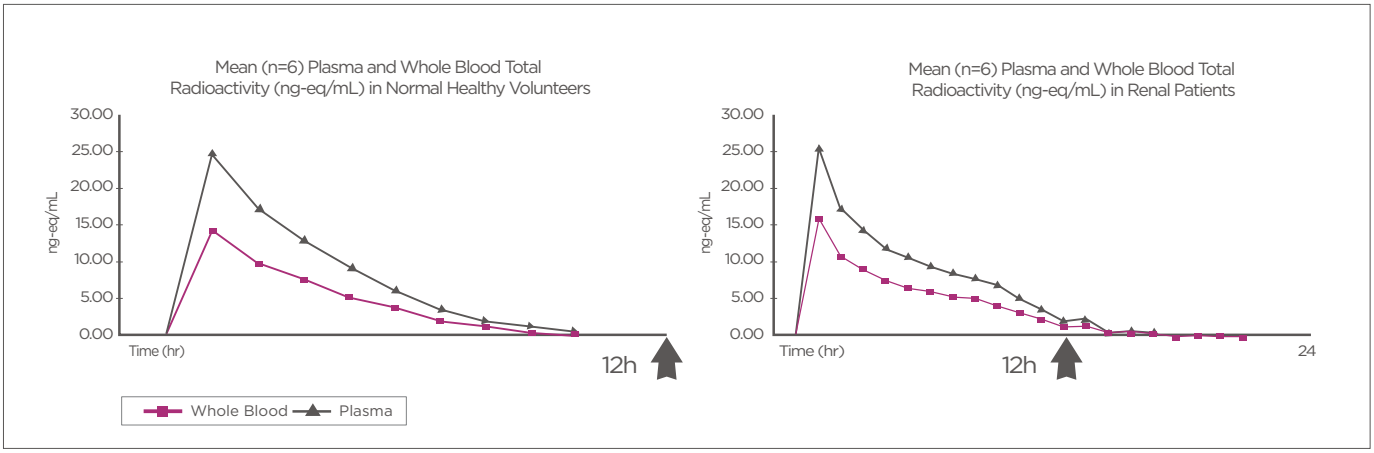

Figure 1. An excretion study showing plasma and whole blood radioactivity in healthy volunteers and renal-impaired patients.

PK in circulation (drug, metabolites, total radioactivity) = Plasma (drug, metabolites, total RA) ± WB partitioning. This is one of the instances where we ran two studies for the same drug: one in normal healthy volunteers and another in renal-impaired patients. Note that the Whole Blood (purple) for both populations has a lower ng-eq/mL value relative to the Plasma (grey). Partitioned primarily in the plasma. Results show it takes longer for the drug to totally eliminate in the renal-impaired (target) patient group.

4. A limited number of CROs offer AME services in the U.S., so wait times can be significant. Sponsors who delay these studies may not be able to meet timelines, which can lead to significant unplanned expenses.

Identify a Partner with a Proven Track Record of Successful AME Clinical Trial Management

Despite the large existing market for AME studies, why is it that so few CROs in the U.S. are able to perform them?

It can be hard to find an AME partner because, for CROs, the necessary setup is time-consuming, labor intensive, and expensive. First, to conduct AME studies, a CRO must have a radiation safety officer (RSO) that is experienced in clinical research trial activities and processes. It must also secure and maintain the appropriate license to handle radioactive materials. This licensure generally involves one or more federal, state, and local governmental agencies.

CROs are required to have the proper standard operating procedures (SOPs) and training procedures in place, and these are reviewed by the relevant authorities for approval in specific radioisotopes, such as carbon-14 and/or tritium. Many clinical pharmacology units (CPUs) and their associated laboratories either don't have the space to devote to a separate radioactive area (i.e., dedicated space for dose preparation, dose administration, subject confinement, and sample collection) or prefer not to undertake the rigorous training necessary for handling radioactive materials safely. Therefore, finding a partner to perform your AME studies in a reasonable time frame, let alone one with an excellent track record, may be a challenge.

At Worldwide, our team can assist throughout your AME clinical trial, from protocol writing through final study report.

Worldwide's Experience and Capabilities for Performing AME Studies

For more than 20 years, Worldwide has been conducting AME studies, working with up to 150 uCi of carbon-14/IP dose to assist in the determination of drug absorption, metabolism, and excretion of parent compound and any metabolites. Over the past three years, our dedicated, controlled-access CPU in San Antonio, Texas, has conducted, on average, four mass balance studies per year, as studies may not overlap to avoid radioactive contamination, or as simultaneous studies are not

permitted to avoid radioactive contamination. Routine matrices for radioactive recovery include blood, urine, and fecal matter, collected over extended time periods (e.g., five days or longer). Procedures have occasionally also included collection of expired air for 14CO2. Without exception, these studies have achieved excellent recovery rates (Figure 2), despite some challenging compounds that demonstrated unexpected pharmacokinetic characteristics.

Radioactive materials licenses are held at both our CPU and our bioanalytical laboratory in nearby Austin, Texas. All necessary SOPs and training documents are in place at both locations. In addition, the Worldwide team has a good working relationship with our central institutional review board, which allows for greater flexibility andsignificant time savings throughout the review process.

Worldwide's CPU goes to great lengths to properly handle AME study samples, including establishing specific procedures for collection, processing, labeling, and shipping. We work with well-established ground couriers that are licensed for transport of radioactive materials. Sample shipments are made daily to our local laboratory, where they are analyzed immediately. This process allows Worldwide to carefully track radiation levels and make informed decisions around radioactive recovery and participant from release our studies.

Best Practices

1. Ensure effective patient and site management

When managing patients and sites, our top priorities include participant comfort and compliance alongside high-quality data. We make every effort using traditional and novel approaches to recruit and retain the right participants for our studies. AME studies are more challenging in this regard and special considerations apply.

From screening with a careful assessment of medical history and daily bowel habits through informed consent and the instructional and dosing phases, our staff ensures that patients fully understand and feel comfortable with the intimate details and importance of total radioactive recovery during these studies. The subjects must be flexible with their time and must provide us with all the samples we need. Proactive management of subject expectations includes information regarding:

- No definitive stopping date
- Dry restrooms
- Dietary requirements: High fiber diet for bowel motility
- 24/7 collection of all urine and fecal matter as well as blood sample collection

2. Prioritize excellence in total radioactive dose recovery rates

As shown in Figure 2, Worldwide has an outstanding track record of 98.9% radioactivity collection. To attain this level of radioactivity recovery requires careful attention to both dosing and sample collection.

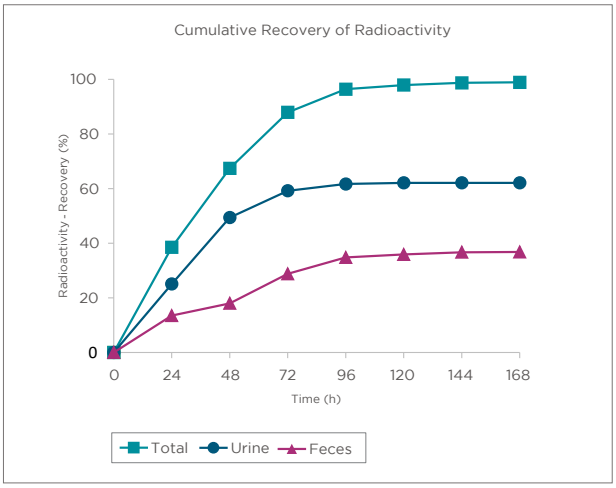

Figure 2. An excretion study showing plasma and whole blood radioactivity in healthy volunteers and renal-impaired patients.

Dosing

It is vital for subjects to take the entire dose, down to the last drop, for liquid doses, and administering the liquids in wide-mouth containers for easy and efficient delivery is best practice. To ensure full dosing, protocols should include steps where trialists rinse bottles with water for the subjects to consume, then follow with more water. Finally, scan the bottles for residual radioactivity.

At Worldwide, a pharmacist with radiolabel product preparation and administration expertise oversees all dosing and is also available to deliver pre- and post-dose instructions and answer questions to ensure uniform, complete dosing across subjects.

Biological sample collection

Staff strategically place reminders around the CPU radiolabel confinement area, especially near the shower, to reinforce the need for collection of all urine and

fecal samples. Diet is modified if needed to promote bowel movements. Collection time is typically five to seven days and subjects cannot miss a collection. Once collections are made each day, they are sent to the lab for measurement of radioactive recovery.

3. Build a specialized team for radiolabeled drug research

The prospective CRO must have a highly trained specialized team to guide the study's safe conduct. Ours includes:

- **Radiation safety officer (RSO):** The RSO engages in staff training, reviews SOPs, oversees sample collection handling and any surface contamination testing as needed and reviews dose calculation, preparation and administration by the pharmacy.
- **Radiologist Sub-Investigator:** A board-certified radiologist is available in addition to the primary physician investigator for protocol review and comments, as well as consultation on study design and to sign off on dose/dosimetry calculations.
- **Pharmacists:** Full-time, specially trained pharmacists handle and prepare the radiolabeled materials. A CPU pharmacist oversees all the dosing.
- **Health physicist:** A health physicist consultant reviews the data from preclinical studies and assists in preparation of dosimetry and radiation exposure reports as needed.

Just-in-time, medic, and technical staff training is performed to ensure facility staff are up-to-date on their understanding of SOPs, processes, and protocol-specific requirements. The RSO covers both the lab and the CPU and is involved in training at both facilities.

4. The on-site cGMP Phase 1 pharmacy must have significant radiolabel drug preparation experience

A CPU used for AME studies must be licensed and experienced in handling radioactive investigational drugs. Our CPU's radiolabel pharmacy is licensed and capable of hot and cold compounding to achieve target investigational product (IP) dose and radioactivity.

We utilize on-site scintillation counting to test investigational drug preparations to see that they conform with the target radioactivity and to confirm full-dose administration.

5. Prioritize custom services suited to the study needs

Due to the complexity and expertise required for successful AME studies, selecting a partner that provides custom-tailored solutions for your IP and study goals, with open, bidirectional communication and flexibility throughout, becomes essential. Worldwide offers true partnerships for Phase I development, with professionals dedicated to fulfilling the needs of sponsors' unique development programs. Our bioanalytical laboratory sets the bar for efficiency and will ensure sponsors receive the AME insights and evaluations they need to make the best possible decisions.

Our bioanalytical lab is flexible and can accommodate analysis based on your study's requirements. State-of-the-art instrumentation and more than 2,400 validated assays make Worldwide an industry leader in bioanalytical method development and validation.

6. Select a CRO that has a streamlined patient-to-lab procedure

A rapid turnaround with accelerated decision-making is vital, as it allows for immediate identification of individual subjects who have met study objectives, saving costs and maintaining the predetermined study time course. The close proximity of Worldwide's bioanalytical lab to our CPU enables streamlined daily ground transport and rapid radioanalysis of AME samples, supporting efficient and informed decision-making.

Our full-service CPU contains 200 beds with flexible procedure space, a cGMP Phase I compounding pharmacy, and a CLIA safety lab. At the bioanalytical lab, in-house bioanalytical scientists engage in LC-MS method development and bioanalysis. In addition, our PK team performs a comprehensive analysis and final study report of radioactive recovery and PK analysis.

The state of Texas defers to federal regulations for licensing and there are no additional state rules with which to comply. Scintillation counting can be conducted daily to provide timely monitoring of cumulative radioactive output.

Collect AME Data Early to Guide Development and Satisfy the FDA

All NCEs require an AME study. Whether, the FDA is calling for AME data early or not, plan for AME studies proactively. Since only a limited number of CROs can perform them in the U.S., reserve ahead. AME data can add valuable insight at the start of a clinical trial journey and can help anticipate later trial expectations, helping sponsors save time and costs.

Worldwide is the ideal partner for AME research. We have significant success and experience conducting AME clinical trials. Sponsors benefit from a highly qualified project team of AME experts. Our integrated lab and clinic facilitate prompt analysis of radioactive samples, allowing for efficient subject dismissal.

At Worldwide, our team can assist throughout your AME clinical trial, from protocol writing to the final study report.

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About Worldwide Clinical Trials

Worldwide Clinical Trials (Worldwide) is a leading full-service global contract research organization (CRO) that works in partnership with biotechnology and pharmaceutical companies to create customized solutions that advance new medications – from discovery to reality.

Anchored in our company's scientific heritage, we are therapeutically focused on cardiovascular, metabolic, neuroscience, oncology, and rare diseases. Our deep therapeutic knowledge enables us to develop flexible plans and quickly solve problems for our customers.

For more information on Worldwide, visit www.worldwide.com or connect with us on LinkedIn.