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PHARMARON

Radiolabelled Chemistry & Metabolism Strategies

Fully Integrated End-to-End Strategies to Support Market Approval

Driven by Science to Help our Partners Succeed

The Importance of Planning for a Radiolabelled Study

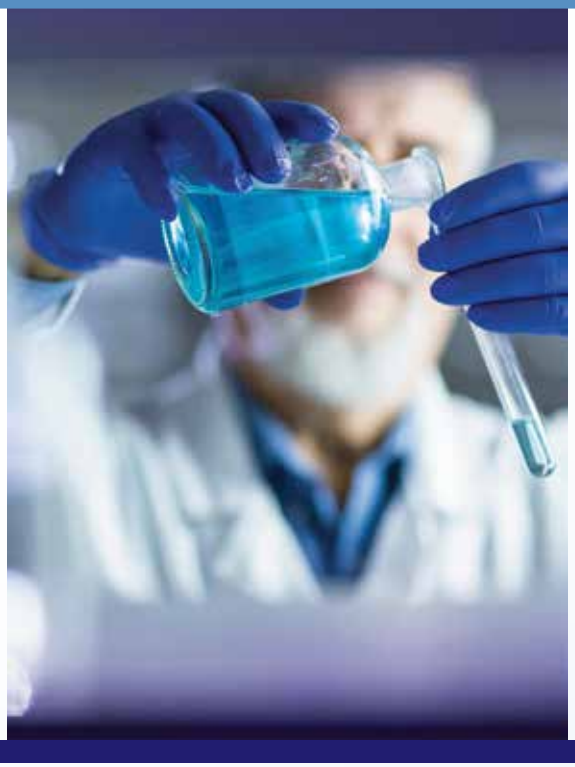
Organising a radiolabelled drug development program requires significant forward planning and in-depth scientific expertise in radiosynthetic chemistry, metabolism, and pharmacokinetics (PK).

Choosing a strong and experienced partner is essential to ensure success and seamless progression to regulatory drug approval.

Pharmaron has a strong track record of supporting our clients' radiolabelled metabolism programs from preclinical to clinical development. Our integrated services for small molecules and biologics offer comprehensive radioisotopic and DMPK expertise enabling us to fully characterize the ADME properties of your compound. These programs have crucial endpoints to meet, and our team has the scientific understanding to guide you through the entire process.

Fully Integrated Support for the Entire Development Program

Pharmaron provides fully integrated ADME services for the entire development program from radiosynthesis through non-clinical and clinical development.



Our team of experienced synthetic and analytical chemists, together with our drug metabolism experts, employ the Carbon-14 (^{14}C) and Tritium (^{3}H) radioisotopes to label a wide variety of compounds to evaluate their ADME (absorption, distribution, metabolism, excretion) characteristics. We also use these radiolabels to study tissue distribution and environmental fate. Tritium can be helpful for lead optimization and biologics in discovery support studies. ^{14}C is the definitive radiolabel for metabolism investigations.

For over 20 years, Pharmaron has developed and utilized AMS (Accelerator Mass Spectrometry) technology for clinical metabolism and PK studies. Our team primarily focuses on employing AMS as a unique, alternative, ultra-sensitive ^{14}C analytical platform to support pharmaceutical and biopharmaceutical R&D.

Integrated Drug Metabolism Program

Radiosynthesis ^{14}C-API

- Determine optimal, metabolically stable, position of ^{14}C label in the molecule
- Determine optimal radiochemistry for synthesis route, yield and number of synthetic steps

Preclinical ADME/QWBA

- Design and execute preclinical ADME program in toxicology species, assess biliary excretion and tissue distribution (QWBA) including human dosimetry

In vitro radiolabelled studies

- Determine comparative metabolism cross-species, enzyme phenotyping, blood partitioning, protein binding and covalent binding

Preparation of GMP or Clinical-Grade ^{14}C-API

- Prepare clinical-grade repurified ^{14}C-API suitable for human administration (microtracer), or synthesize a batch of ^{14}C API to full GMP

Excretion Balance, Profile & ID Metabolites, Tissue Distribution, Dosimetry & Plasma PK

- Establish mass balance rates/routes of excretion, radioprofiles and identity of metabolites seen in toxicology species
- Quantify tissue distribution and elimination half-life including bioanalysis and plasma PK

Phase I hADME for mass balance, rates/routes excretion, identify human metabolites and metabolite safety, PK & biotransformation pathways

- Definitive human mass balance programs to determine all key metabolism parameters in human. Establish metabolite safety and coverage in toxicology species.

Phase I hADME for IVPK, absolute bioavailability, volume distribution, systemic clearance, oral and IV PK using LCMS & LC+AMS bioanalysis

- Include a 2nd cohort for IVPK ^{14}C microtracer for Absolute Bioavailability in human (ABA)

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Integrated End-to-End Radiolabelled Chemistry & Metabolism

Pharmaron provides and coordinates a global portfolio of services in the radiolabelled space, which can simplify and expediate your program with the following benefits:

Consulting, design and execution of a metabolism strategy specific to your molecule.

Access to a **single cross functional team** of experts that will provide guidance, integrated project management, regulatory support and streamlined project delivery.

Extensive scientific expertise, operational know-how and methodologies to optimize ADME investigations including the definitive studies in human for global regulatory submissions.

Continuity of non-clinical and clinical programs that expedites the profiling and identification of metabolites to establish metabolite safety and de-risk your compound.

Pharmaron's Experience in Numbers

20 years proven global track record

>2,000 preclinical ADME studies completed

>70,000 ^{14}C radiolabelled compounds produced

>20,000 tritiated (^{3}H) molecules synthesized

>400 GMP (^{14}C) API batches manufactured & released

>600 QWBA tissue distribution studies completed

>160 ^{14}C clinical studies supported by AMS (since 2018)

66 approved NDAs containing Pharmaron ^{14}C AMS data

96 bed Phase I unit with two ^{14}C human ADME study suites

>40 hADME & hABA clinical studies completed (since 2018)

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Our Radiolabelled Service Capabilities

Radiosynthesis

- Pharmaron's radiochemistry team provide expert advice on radiosynthesis and preparation and release of radiolabelled test compounds for use in non-clinical and clinical drug development and in environmental fate studies. We offer complete management of the radiochemistry process:
  - Selection of label position in the molecule
  - Optimization of the radiosynthetic pathway and yield
  - Stability testing
  - Final product analysis & certification (GMP/GLP)
  - Repurification of ^{14}C APIs

  Additionally, covalent radiolabelling and radiotagging techniques with ^{3}H and ^{14}C for biologics is available.

Non-clinical ADME & QWBA with Radiolabelled Compounds

- Pharmaron conducts a wide range of non-clinical ADME studies, which can include:
  - Pharmacokinetics, biliary excretion & excretion balance
  - *In vitro* profiling of enzyme pathways and drug partitioning /distribution properties
  - Tissue distribution (QWBA, mARG) including disease models
  - Human dosimetry calculations & reports
  - Metabolite profiling & Metabolite Identification (MetID)
  - Placental transfer and milk secretion studies
  - Bioanalytical support (LC-MS/MS)
- Non-clinical ADME studies are typically performed in the appropriate toxicology species in order to establish safety of metabolites identified in human. These studies can also be expanded to cover a wide range of pharmacology models including oncology, CNS, cardiovascular, metabolic disease, inflammation and pain.

Clinical hADME studies with ^{14}C Compounds

- Pharmaron offers comprehensive services to support a wide range of ^{14}C radiolabelled studies in humans
  - Absorption, distribution, metabolism and excretion for mass balance & PK (ADME)
  - IV microtracers for absolute bioavailability (ABA)
  - AMS (Accelerator Mass Spectrometry)
  - High resolution mass spectrometry (HRMS) for MetID
  - Bioanalysis and biomarkers (LC-MS/MS, immunoassay)
- Pharmaron provides fully integrated solutions for human clinical studies by project managing the radiosynthesis, ^{14}C dose formulation, a full-service Phase 0/1 clinical trial and extensive GCP analytical support for radioanalysis, metabolite profiling, MetID and PK.
- The company specializes in clinical protocols utilizing low radioactive dose microtracer approaches. Approximately 1-5 µCi of ^{14}C radioactivity is compounded with a therapeutically relevant mass dose for definitive human ADME studies.
- Absolute bioavailability studies are also conducted which involve IV administration of a microdose containing a ^{14}C microtracer concomitant with an unlabelled extravascular therapeutic mass dose.

Clinical Pharmacology

- Pharmaron's Clinical Pharmacology Center (CPC) provides full-service early phase clinical research for investigational products (IP).
- Our 96-bed facility in Baltimore, US, houses an experienced team, with a facility design supporting operational excellence and efficiency to ensure quality, safety and data integrity at all times, while meeting study timelines.
- Expertise in First-In-Human, micro and macro ^{14}C hADME, DDI, bioavailability, bioequivalence, TQT, cardiac derisking, infectious disease challenge studies as well as outpatient immunobiological and vaccine studies.

Accelerator Mass Spectrometry (AMS)

- Pharmaron's ^{14}C Bioanalysis team is the recognized leader in using the AMS platform for over 20 years, with the AMS and bioanalytical laboratories located nearby to the clinical research unit.
- Advantages of AMS technology:
  - AMS is an ultra-sensitive technique routinely used in hAME and IVPK clinical sample analysis
  - AMS can be used to support both microtracer and macrotracer clinical study designs, and can also be combined with LSC for hybrid sample analysis
  - Both graphite and gaseous AMS instruments are available to clients for rapid ultra-low quantification of the ^{14}C radioisotope
  - The sensitivity of AMS enables the detection and quantitation of low-level metabolites for drugs with complex metabolism profiles
  - AMS data are routinely accepted by the regulatory authorities for human ADME and absolute bioavailability studies

Founded in 2004, Pharmaron is a global life science service provider that offers a broad spectrum of research, development and manufacturing service capabilities throughout the entire drug discovery, preclinical and clinical development process across multiple therapeutic modalities, including small molecules, biologics and CGT products.

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- Laboratory Services
- Chemistry, Manufacturing & Control
- Clinical Development
- Biologics & CGT

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